PRODUCT MONOGRAPH

NASACORT® (CFC-FREE)
(Triamcinolone Acetonide)

Nasal Inhaler - 100 mcg/Metered Spray

Corticosteroid for Nasal Use

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PRODUCT MONOGRAPH

NAME OF DRUG

NASACORT® (CFC-FREE)
(Triamcinolone Acetonide)

Nasal Inhaler - 100 mcg/Metered Spray

THERAPEUTIC CLASSIFICATION

Corticosteroid for Nasal Use

ACTIONS AND CLINICAL PHARMACOLOGY

Triamcinolone acetonide is a potent anti-inflammatory steroid with strong topical and weak systemic activity. Triamcinolone acetonide is a more potent derivative of triamcinolone. Although triamcinolone itself is approximately one to two times as potent as prednisone in animal models of inflammation, triamcinolone acetonide is approximately 8 times more potent than prednisone.

When administered intranasally in therapeutic doses, it has a direct anti-inflammatory action on the nasal mucosa, the mechanism of which is not yet completely defined. The minute amount absorbed in therapeutic doses has not been shown to exert any apparent clinical systemic effects.

Corticosteroids are very effective. However, when allergic symptoms are very severe, local treatment with recommended doses (microgram) of any available topical corticosteroid are not as effective as treatment with larger doses (milligram) of oral or parenteral formulations. Corticosteroids do not have an immediate effect on allergic signs and symptoms. An improvement of symptoms may be seen as early as the first day after initiation of treatment and full benefit may be expected in 3 to 4 days. However, symptomatic relief may not occur in some patients for as long as two weeks. NASACORT® should not be continued beyond three weeks in the absence of significant symptomatic improvement.

Pharmacokinetics

Based upon intravenous dosing of triamcinolone acetonide phosphate ester, the half-life of triamcinolone acetonide was reported to be 88 minutes. The volume of distribution (Vd) reported was 99.5 L (SD ± 27.5) and clearance was 45.2 L/ hour (SD ± 9.1) for triamcinolone acetonide. The plasma half-life of corticosteroids does not correlate well with the biologic half-life.

When a single 800 mcg dose of NASACORT® was administered intranasally to normal healthy subjects, the mean maximum plasma concentration was 0.196 ng/mL and was observed on average at 3.8 hours postdosing. The terminal elimination half-life was 4.1 hours.

INDICATIONS AND CLINICAL USE

NASACORT® (CFC-free) (triamcinolone acetonide) nasal inhaler is indicated for the topical treatment of the symptoms of perennial and seasonal allergic rhinitis unresponsive to conventional treatment.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients of NASACORT® (CFC-free) (triamcinolone acetonide) nasal inhaler (see AVAILABILITY), and in patients with active or quiescent tuberculosis, or untreated fungal, bacterial and viral infection, or ocular herpes simplex.

WARNINGS

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; in severe cases, adrenal insufficiency may occur, necessitating the temporary resumption of systemic steroid therapy. These patients should be carefully monitored for acute adrenal insufficiency in response to stress. 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.

The use of NASACORT® (CFC-free) (triamcinolone acetonide) nasal inhaler with alternate day systemic prednisone could increase the likelihood of hypothalamic-pituitary-adrenal (HPA) suppression compared to a therapeutic dose of either one alone. Therefore, NASACORT® should be used with caution in patients already receiving alternate-day prednisone treatment for any disease.

Patients who are on immunosuppressant drugs are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have a more serious or even fatal course in children or adults on immunosuppressant doses of corticosteroids. In such children, or in adults who have not had these diseases, particular care should be taken to avoid exposure. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If chickenpox develops, treatment with antiviral agents may be considered.

Pregnancy: See PRECAUTIONS.

PRECAUTIONS

1) The replacement of a systemic steroid with NASACORT® (CFC-free) (triamcinolone acetonide) nasal inhaler has to be gradual and carefully supervised by the physician (see WARNINGS). The guidelines under "DOSAGE AND ADMINISTRATION" should be followed in all such cases.

2) During long-term therapy pituitary-adrenal function and hematological status should be assessed.

3) Patients should be informed that relief of some symptoms may occur within the first day of treatment but full benefit of NASACORT® may not be achieved until 3 to 4 days of regular daily treatment have been completed. However, symptomatic relief may not occur in some patients for as long as two weeks after starting treatment. NASACORT® should not be continued beyond three weeks in absence of significant symptomatic improvement.

4) Treatment with NASACORT® 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 NASACORT®. If localized fungal infection of the nose or pharynx develops such as with *Candida albicans*, discontinue NASACORT® treatment. Persistence of nasopharyngeal irritation may be an indication for discontinuing NASACORT®.

6) Glaucoma and osteoporosis are possible adverse effects associated with a long term use of large doses of corticosteroids. 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) As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances. Cases of nasal septum perforation among pediatric patients using Nasacort® (CFC formulation) have been reported in rare instances. It is important to use the inhaler correctly to minimize the potential for nasal septum perforation (i.e., pointing it slightly towards outside nostril wall). See INSTRUCTIONS FOR USE.

10) Following the use of intranasal aerosolized corticosteroids, instances of increased intraocular pressure have been reported in rare instances.

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

12) Until greater clinical experience has been gained, the continuous, long-term treatment of children under age 4 is not recommended.

13) Pregnancy:
The safety of NASACORT®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, triamcinolone acetonide is teratogenic to rodents and non-human primates (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.

14) Lactation:
Glucocorticosteroids are excreted in human milk. It is not known whether triamcinolone acetonide would be secreted in human milk, but it is suspected to be likely. The use of NASACORT® in nursing mothers, requires that the possible benefits of the drug be weighed against the potential hazards to the infant.

15) Children:
NASACORT® is not presently recommended for children younger than 4 years of age due to limited clinical data in this age group. Oral corticosteroids have been shown to cause growth suppression in children and teenagers, particularly with higher doses over extended periods. If a child or teenager on any corticosteroids appears to have growth suppression, the possibility that they are particularly sensitive to this effect of steroids should be considered.

16) To ensure the proper dosage and administration of the drug, the patient should be instructed by a physician or other health professional in the use of NASACORT® (see Patient Instructions).

ADVERSE REACTIONS

A total of 1200 patients were enrolled in placebo-controlled and open-label clinical studies of NASACORT® (CFC-free) . In the controlled trial described below, 333 patients were treated with NASACORT® for an average of 15 days (range 1-19 days). Of the 396 patients enrolled in open label studies, 75% received treatment for greater than six months. No changes in mucous membranes were noted from physical and visual examinations during these trials.

The most commonly reported adverse reactions included those involving mucous membranes of the nose and throat. The three most prevalent adverse reactions considered to be at least possibly drug-related were rhinitis (3.0%), headache (1.8%) and epistaxis (1.5%).

The incidence of specific nasopharyngeal-related adverse reactions considered drug related is summarized as follows:

ADVERSE EVENTS	Placebo (N=111)	Nasacort® 25 mcg (N=113)	Nasacort® 200 mcg (N=107)	Nasacort® 800 mcg (N=113)	Nasacort® Total (N=333)
Naso-Pharyngeal AEs	13 (11.7%)	18 (15.9%)	20 (18.7%)	21 (18.6%)	5.9 (17.7%)
Dry Mucous Membrane	0 (0.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.3%)
Epistaxis	1 (0.9%)	1 (0.9%)	2 (1.9%)	2 (1.8%)	5 (1.5%)
Nasal Irritation	4 (3.6%)	9 (8.0%)	8 (7.5%)	7 (6.2%)	24 (7.2%)
Naso-Sinus Congestion	0 (0.0%)	1 (0.9%)	0 (0.0%)	1 (0.9%)	2 (0.6%)
Sneezing	8 (7.2%)	13 (11.5%)	15 (14.0%)	18 (15.9%)	46 (13.8%)
Throat Discomfort	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Nasal adverse events do not usually interfere with treatment and in the controlled and open-label studies only 2% of patients receiving recommended doses discontinued due to nasal adverse effects.

The following table summarizes the adverse events (% of patients) present in at least 5% of patients in the double-blind and open label phase studies.

ADVERSE EVENTS	Double-blind			Open Label
	Placebo (N=111)	Nasacort® 200 mcg (N=107)	Nasacort® 800 mcg (N=113)	Nasacort® 800 mcg (N=396)
Headache	8.1%	10.3%	6.2%	6.8%
Rhinitis	1.8%	4.7%	3.5%	11.6%
Epistaxis	1.8%	1.9%	1.8%	19.4%

In the event of accidental overdose, an increased potential for these adverse experiences may be expected, but systemic adverse experiences are unlikely (see OVERDOSAGE section).

Hypersensitivity reactions including skin rash and edema of the face or tongue have been reported with other intranasal corticosteroids.

When patients are transferred to NASACORT® from a systemic steroid, allergic conditions such as asthma or eczema may be unmasked (see WARNINGS).

Cases of nasal septum perforation among pediatric users have been reported in post-marketing surveillance of Nasacort® (CFC formulation) (See PRECAUTIONS).

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. In the event that the entire contents of the bottle were administered all at once, via either oral or nasal application, clinically significant systemic adverse events would most likely not result. The patient may experience some gastrointestinal upset.

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 occur, the dosage of NASACORT® (CFC-free) (triamcinolone acetonide) nasal inhaler should be discontinued slowly consistent with accepted procedures for discontinuation of chronic steroid therapy. (see 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

See WARNINGS.

Careful attention must be given to patients previously treated for prolonged periods with systemic corticosteroids when transferred to NASACORT® (CFC-free). Initially, NASACORT®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 NASACORT® 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 NASACORT® therapy. Patients should be instructed on the correct method of use, which is to blow the nose, then insert the nozzle firmly into the nostril, compress the opposite nostril and actuate the spray while inspiring through the nose, with the mouth closed.

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. NASACORT®should not be continued beyond three weeks in the absence of significant symptomatic improvement. Treatment with NASACORT® should not be stopped abruptly but tapered off gradually.

When possible, treatment of seasonal rhinitis should be started before the exposure of allergens.

Adults and children 12 years of age and older:
The recommended starting dose of NASACORT® (triamcinolone acetonide) nasal inhaler is 400 mcg per day given as two sprays (100 mcg/spray) in each nostril once a day. If needed, the dose may be increased to 800 mcg per day (100 mcg/spray) either as once a day dosage or divided up to four times a day , i.e., twice a day (two sprays/nostril), or four times a day (one spray/nostril).
After the desired effects are obtained, patients may be maintained on a dose of one spray (100 mcg) in each nostril once a day (total daily dose: 200 mcg per day).

Children 4 through 11 years of age:
The recommended starting dose of NASACORT® is 200 mcg per day given as one spray (100 mcg/spray) in each nostril once a day. Patients who do not achieve maximum symptom control may benefit from a dose of 400 mcg given as two sprays (100 mcg/spray) in each nostril once a day. Once symptoms are controlled, patients can be maintained on 200 mcg (one spray in each nostril) once daily.

NASACORT® is not recommended for children below 4 years of age since adequate numbers of patients have not been studied in this age group.

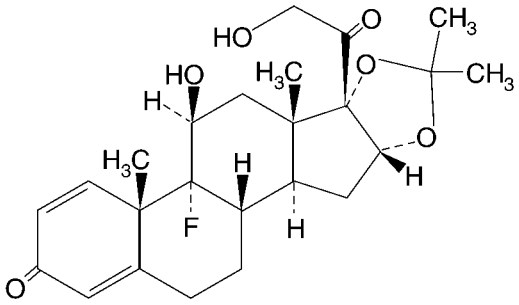
PHARMACEUTICAL INFORMATION

(i) Drug Substance

Proper Name: Triamcinolone acetonide

Chemical Name: Pregna-1,4-diene-3,20-dione, 9-fluoro-11,21-dihydroxy-16,-17- [(1-methyethylidene) bis(oxy)] -,(11β,16α)-

Structural Formula:



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

Molecular Weight: 434.49

Physical Form: white crystalline powder

Solubility: sparingly soluble in methanol, acetone, ethyl acetone

Melting Point: 292 - 294 ˚C

(ii) Composition

NASACORT® (CFC-free) is an unscented, taste-free metered-dose aerosol unit containing a microcrystalline suspension of triamcinolone acetonide in tetrafluoroethane (HFA-134a) and dehydrated alcohol USP 0.7% w/w. Each actuation releases approximately 100 mcg triamcinolone of which approximately 55 mcg are delivered from the nasal actuator to the patient (estimated from *in vitro* testing) after an initial priming of 3 actuations. The canister will remain primed for 3 days. If the product is not used for more than 3 days, then it should be reprimed with 3 actuations. Each canister contains 15 mg triamcinolone acetonide.

(iii) Stability and Storage Recommendations

Store at controlled room temperature (15 - 30˚C).

Caution: Container may explode if heated. Contents under pressure. Do not place in hot water or near radiators, stoves or other sources of heat. When empty do not puncture or incinerate containers or store at temperature over 50°C.

AVAILABILITY OF DOSAGE FORMS

Each NASACORT® (CFC-free) (triamcinolone acetonide) canister contains sufficient amount for either 100 actuations. The canister should not be used after 100 actuations, since the amount delivered thereafter per actuation may not be consistent. In the Information for Patients, patients are provided with a check-off form to track usage.

The NASACORT® canister and accompanying nasal actuator are designed to be used together. The NASACORT® canister should not be used with other nasal actuators and the supplied nasal actuator should not be used with other products' canisters. NASACORT® is supplied with a white plastic nasal actuator and patient instructions.

INFORMATION FOR THE PATIENT

NASACORT® (CFC-free)
(Triamcinolone Acetonide)
Nasal Inhaler

Please read this leaflet carefully before you start to take your medication. For further information or advice, ask your doctor or pharmacist.

About Your Medicine

The name of this product is NASACORT® nasal inhaler. It contains triamcinolone acetonide, a corticosteroid that is used to treat seasonal allergic rhinitis (including hayfever) and perennial rhinitis. Symptoms of these conditions include itching, nasal congestion and excessive sneezing. NASACORT® relieves the nasal congestion, runny nose, itching and sneezing by reducing the irritation and inflammation in the lining of the nose and nasal passages.

Before Using This Medication

Tell your doctor or pharmacist (if you have not already done so) any of the following before you start taking the medication:

- If you have already taken NASACORT®or any other corticosteroids and developed an allergy or intolerance to any of them;

- If you are allergic to any other substances, such as food, preservatives or dyes;

- If you are pregnant or breast feeding, or likely to become pregnant or breast feed. Your doctor may decide not to prescribe this medication in these circumstances;

- If you are taking any other prescription or nonprescription (over-the-counter) medicines;

- If you suffer from any other medical problems or if you have had a recent injury or surgery to your nose.

Proper Use of This Medication

Follow the INSTRUCTIONS FOR USE described below. If you have any problems tell your doctor or pharmacist.

- It is important that you inhale each dose through the nose as instructed. The label will usually tell you how many doses to take. If it does not, ask your doctor or pharmacist;

- DO NOT inhale more doses or use your nasal inhaler more often than your doctor advises.

- The effects of NASACORT® are not immediate. It takes a few days for this medicine to work. IT IS VERY IMPORTANT THAT YOU USE IT REGULARLY, not as you feel necessary. DO NOT STOP treatment even if you feel better, unless told to do so by your doctor.

- If your symptoms have not improved after three weeks of daily treatment with NASACORT®or your symptoms worsen, tell your doctor.

- Adults and children 12 years of age and older: The usual dose is two sprays into each nostril once daily (400 mcg per day).

- Children 4 through 11 years of age: The recommended dose is 200 mcg per day given as one spray into each nostril once daily. Children should be using NASACORT® under adult supervision.

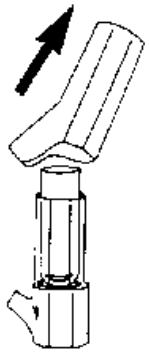
- NASACORT® is not recommended for children under 4 years of age.

Instructions for Use

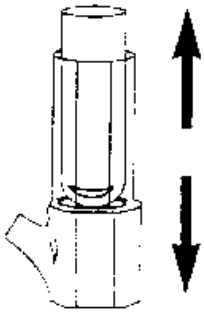
It is important to shake the inhaler well before each use. Also, the inhaler should be discarded after 100 sprays.

Before each use of your NASACORT®nasal inhaler, gently blow your nose, making sure your nostrils are clear. Then follow these steps:

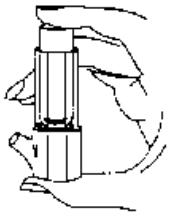
1. Remove the white protective cap from the nasal inhaler.



2. Shake the canister well.



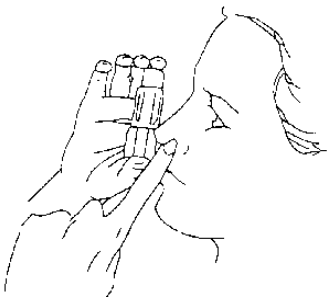
3. The canister must be primed **prior to the first use**. To prime, point away from face, hold the canister between your thumb and forefinger and press down on the canister to release one spray. Repeat this until you have released a total of 3 sprays. Now your canister is primed and ready for use.



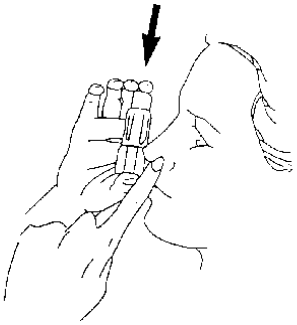
Repriming is only necessary when the canister has not been used for more than 3 days. To reprime, shake the canister and release three sprays. Now the canister is reprimed. There is no need to reprime the canister between more frequent usage.

4. Hold the inhaler between your thumb and forefinger.

5. Tilt your head back slightly and insert the end of the inhaler into one nostril, pointing it slightly toward the outside nostril wall, while holding your other nostril closed with one finger.



6. Press down on the canister to release one dose and, at the same time, inhale gently, with your mouth closed.



7. Hold your breath for a few seconds, then breathe out slowly through your mouth.

8. Withdraw the nasal inhaler from your nostril.

9. **Repeat the process in your other nostril.**

   Note: When the physician prescribes more than one puff per nostril, for each puff repeat steps 4 through 8.

10. Replace the white protective inhaler cap on the nasal inhaler.

    Note: Avoid blowing your nose for the next 15 minutes.

We have included a convenient check-off chart to assist you in keeping track of medication sprays used. This will help assure that you receive the 100 "Full Sprays" of medication present. Please note that the bottle has been filled with extra solution to accomodate the initial priming activity. Please, note that any additional repriming (i.e. other than the initial priming) should be accounted for as a full spray.

NASACORT® 100-Spray Check-off
Check off one circle per spray (include treatment inhalations and repriming sprays) :

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
61	62	63	64	65	66	67	68	69	70	71	72	73	74	75
76	77	78	79	80	81	82	83	84	85	86	87	88	89	90
91	92	93	94	95	96	97	98	99	100					

What to do if you miss a dose

If you miss a dose do not worry; take a dose if you remember within an hour or so. However, if you do not remember until later, skip the missed dose and go back to your regular dosing schedule. Do not double up doses.

What to do if an overdose is taken

Tell your doctor if you use more than you were told.

What to do if you stop your medicine

If your doctor decides to stop your treatment, do not keep any left over medicine unless your doctor tells you to.

Storage of your medicine

Keep out of the reach of children.

Store at controlled room temperature (15 - 30°C).

Side Effects of this medication

Along with its needed effects, a medicine may cause some unwanted effects. Contact your physician as soon as possible if any of the following occur:

- If you notice that any discharge from your nose is yellow or green;
- If you experience an unpleasant taste or smell;
- If nasal irritation, burning or stinging occurs;
- If your nose or throat becomes painful or if you have a severe nose bleed after using the nasal spray;
- If you feel unwell or have any other problems;

Other side effects may occur that usually do not need medical attention. They may go away as your body adjusts to the medicine. However, check with your doctor if any of the following side effects continue or are bothersome:

- Sneezing;
- Headaches;
- Burning, dryness or other irritation inside the nose (lasting only a short time after applying the medication).

Other side effects not listed above may also occur in some patients. If you notice any other effects, check with your doctor.

A Reminder

REMEMBER this medicine is for YOU. Only a doctor can prescribe it for you. Never give it to others. It may harm them even if their symptoms are the same as yours.

Keep all medicines out of the reach of children.

If you have questions or are not sure about anything, then you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

Cleaning instructions

Your NASACORT® nasal inhaler should be cleaned weekly. Remove the canister from the nasal adapter. Clean the nasal adapter thoroughly in lukewarm water. Allow the adapter to dry completely before inserting canister for the next use.

Caution

Container may explode if heated. Contents under pressure. Do not place in hot water or near radiators, stoves, or other sources of heat. When empty do not puncture or incinerate containers or store at temperatures over 50°C.

PHARMACOLOGY AND PHARMACOKINETICS

Pharmacokinetics studies with radiolabelled triamcinolone acetonide have been carried out by the oral, pulmonary, and intravenous routes in several species. The pharmacokinetic behaviour of the triamcinolone acetonide was similar in all species within each route of administration. The results of studies in which triamcinolone acetonide was administered as an aerosol showed rapid disappearance of radioactivity from lungs, comparable to that observed following oral administration.

Peak blood levels occurred in one to two hours. Virtually no radioactivity was present in the lungs and trachea 24 hours after dosing. Three major metabolites of triamcinolone acetonide have been identified. They are 6-hydroxy-triamcinolone acetonide (much less biologically active than triamcinolone acetonide), 21-carboxytriamcinolone acetonide and 21-carboxy-6-hydroxytriam-cinolone acetonide. The latter two metabolites would also be expected to be substantially less active than the parent compound due to:

a) the dependence of anti-inflammatory activity on the presence of the 21-hydroxyl group,

b) the decreased activity observed upon 6-hydroxylation, and

c) the markedly increased water solubility that favours rapid elimination.

There appeared to be some qualitative differences in the metabolites among the species. No differences were detected in the metabolic pattern as a function of route of administration.

Excretion

Studies completed utilizing radiolabelled triamcinolone acetonide given via oral and intravenous routes in several species show the major portion of the drug is eliminated in the feces, irrespective of the route of administration, with only one species (rabbit) showing significant urinary excretion of radioactivity.

Glucocorticoid Effects

Triamcinolone acetonide is a potent derivative of triamcinolone. Although triamcinolone itself is approximately 1-2 times as potent as prednisone in animal models of inflammation, triamcinolone acetonide is much more potent. In croton oil-induced ear inflammation, triamcinolone acetonide topically applied was 59 times more active than hydrocortisone when given by mouth in equivalent doses. Comparable effects were obtained in rats with cotton and asbestos pellet induced granuloma.

Thymolytic potency was essentially equivalent, when given by the subcutaneous, intramuscular, intravenous and intraperitoneal routes. It was, however, 3-4 times more potent when given orally. Neither triamcinolone nor triamcinolone acetonide produced sodium retention in adrenalectomized rats or androgenic effects in castrated rats.

HUMAN PHARMACOLOGY

The precise mechanism of action of the intranasal drug is unknown. However, clinical studies utilizing nasal administration have demonstrated effective local steroid activity with no evidence of systemic effects. Smears of the nasal mucosa obtained during clinical studies demonstrated marked reductions in nasal eosinophils, which are known to release highly active chemical mediators.

In order to determine if systemic absorption plays a role in triamcinolone acetonide nasal inhaler treatment of allergic rhinitis symptoms, a two week double-blind placebo-controlled clinical study was conducted comparing triamcinolone acetonide nasal inhaler, orally ingested triamcinolone acetonide, and placebo in 297 patients with seasonal allergic rhinitis. The study demonstrated that the therapeutic efficacy of triamcinolone acetonide nasal inhaler can be attributed to the topical effects of triamcinolone acetonide.

In order to evaluate the effects of systemic absorption on the Hypothalmic-Pituitary-Adrenal (HPA) axis, a clinical study was performed comparing 400 mcg or 800 mcg triamcinolone acetonide nasal inhaler, or 10 mg prednisone to placebo for 42 days. Adrenal response to a 6-hour cosyntropin stimulation test clearly indicated that triamcinolone acetonide nasal inhaler administered at doses of 400 mcg and 800 mcg had no effect on HPA activity versus placebo. Conversely, oral prednisone at 10 mg/day significantly reduced the response to ACTH.

Pharmacokinetic characterization with NASACORT® (CFC-free) Nasal Inhaler was determined in 24 healthy adult subjects. After single 800 mcg dose of NASACORT®, the mean peak plasma concentration was approximately 0.196 ng/mL. The maximum mean plasma triamcinolone acetonide concentrations occurred between 2-4 hours post dose.

Clinical Trials

The safety and efficaty of NASACORT®Nasal Inhaler has been evaluated in adults and children 12 years and older with seasonal or perennial allergic rhinitis. In these clinical trials, 333 patients were treated with NASACORT®for seasonal allergic rhinitis and 396 patients were treated for perennial allergic rhinitis.

The efficacy of NASACORT®was assessed using the classical mean change from baseline in primary nasal symptoms (stuffiness, discharge, sneezing and nasal index). Overall, NASACORT®treatment resulted in prompt, consistent reductions in nasal symptoms of seasonal allergy. NASACORT®treatment resulted in moderate to complete symptom relief from perennial allergens within two weeks after initiation of treatment and this relief was maintained throughout the long-term treatment period.

TOXICOLOGY

Animal

Acute toxicity studies in mice and rats and subacute toxicity studies in rats, rabbits and dogs were done by conventional routes of administration. The findings in these studies were typically those seen following the administration of potent glucocorticosteroids. Subacute toxicity studies in rats and dogs and chronic studies in rats and monkeys were conducted by inhalation of aerosolized triamcinolone acetonide. A one-month intranasal toxicity study in dogs with triamcinolone acetonide aqueous nasal formulation revealed no toxicity other than that expected from triamcinolone acetonide. The findings in these studies generally were minimal and the same as in studies carried out by conventional routes of administration, with changes typical of those seen with potent glucocorticoids. There were no gross histopathological or ultrastructural findings suggestive of untoward effects on the respiratory tract.

An eye irritation study conducted in rabbits with triamcinolone acetonide aqueous nasal formulation revealed only a slight reversible irritation of the conjunctiva and iris.

Teratogenic Tests

Teratology studies have been conducted in rats and rabbits by the subcutaneous route and by aerosol inhalation. The known teratogenic effects of glucocorticoids were found to occur following both routes of administration. Triamcinolone acetonide has been shown to be teratogenic in rats and rabbits. Teratogenic effects in both species at 0.02, 0.04 and 0.08 mg/kg/day (approximately 135, 270 and 540 mcg/m^2/day in the rat and 320, 640 and 1280 mcg/m^2/day in the rabbit, as calculated on a surface area basis), included low incidence of cleft palate and/or internal hydrocephaly and axial skeletal defects. Teratogenic effects, including CNS and cranial malformation have also been observed in non-human primates at 0.5 mg/kg/day (approximately 6.7 mg/m^2/day). The doses of 0.02, 0.04, 0.08 and 0.5 mg/kg/day used in these toxicology studies are approximately 12.8, 25.5, 51 and 318.2 times the minimum recommended dose of 200 mcg of NASACORT® (CFC-free) (triamcinolone acetonide) nasal inhaler per day and 6.4, 12.7, 25.5 and 159.1 times the maximum recommended dose of 400 mcg of NASACORT® per day based on a patient body weight of 70 kg.

Administration by aerosol inhalation to pregnant rats and rabbits produced embryotoxic and fetotoxic effects which were comparable to those produced by administration by other routes.

Carcinogenesis, Mutagenesis

A recent literature report of a chronic bioassay conducted with several corticosteroids (budenoside, prednisolone, triamcinolone acetonide) indicated that all caused slightly increased incidence of liver tumors at toxic doses over a two-year study period. However, no evidence of treatment-related carcinogenicity was demonstrated after two years of once daily oral administration of triamcinolone acetonide at a maximum daily dose of

1.0 mcg/kg/day (6.1 mcg/m^2/day) in male or female rats and 3.0 mcg/kg/day (12.9 mcg/m^2/day) in male or female mice.

Impairment of Fertility

Male and female rats which were administered oral triamcinolone acetonide at doses as high as 15 mcg/kg/day (110 mcg/m^2/day, as calculated on a surface area basis) exhibited no evidence of impaired fertility. The maximum human dose, for comparison, is 6.3 mcg/kg/day (240 mcg/m^2/day). However, a few female rats which received maternally toxic doses of 8 or 15 mcg/kg/day (60 mcg/m^2/day or 110 mcg/m^2/day, respectively, as calculated on a surface area basis) exhibited dystocia and prolonged delivery. Developmental toxicity, which included increases in fetal resorptions and stillbirths and decreases in pup body weight and survival, also occurred at the maternally toxic doses (2.5-15.0 mcg/kg/day or 20-110 mcg/m^2/day, as calculated on a surface area basis). Reproductive performance of female rats and effects on fetuses and offspring were comparable between groups that received placebo and nontoxic or marginally toxic doses (0.5 and 1.0 mcg/kg/day or 3.8 mcg/m^2/day and 7.0 mcg/m^2/day).

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