

Rx only

Nasacort[®] AQ

Rev. XXXX

Nasacort[®] AQ

[na' za-cort]

(triamcinolone acetonide)

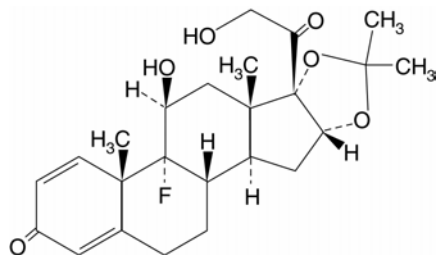
Nasal Spray

For intranasal use only.

Shake Well Before Using

DESCRIPTION

Triamcinolone acetonide, USP, the active ingredient in **Nasacort[®] AQ** Nasal Spray, is a corticosteroid with a molecular weight of 434.51 and with the chemical designation 9-Fluoro-11 β ,16 α ,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with acetone (C₂₄H₃₁FO₆).



Nasacort AQ Nasal Spray is an unscented, thixotropic, water-based metered-dose pump spray formulation unit containing a microcrystalline suspension of triamcinolone acetonide in an aqueous medium. Microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80, dextrose, benzalkonium chloride, and edetate disodium are contained in this aqueous medium; hydrochloric acid or sodium hydroxide may be added to adjust the pH to a target of 5.0 within a range of 4.5 and 6.0.

Each actuation delivers 55 mcg triamcinolone acetonide from the nasal actuator after an initial priming of 5 sprays. It will remain adequately primed for 2 weeks. If the product is not used for more than 2 weeks, then it can be adequately reprimed with one spray. The contents of one 6.5 gram sample bottle provide 30 actuations, and the contents of one 16.5 gram bottle provide 120 actuations. **After either 30 actuations or 120 actuations, the amount of triamcinolone acetonide delivered per actuation may not be consistent and the unit should be discarded.** Each 30 actuation sample bottle contains 3.575 mg of triamcinolone acetonide and each 120 actuation bottle contains 9.075 mg of triamcinolone acetonide.

In the **Information for Patients** tear-off sheet, patients are provided with a check-off form to track usage.

CLINICAL PHARMACOLOGY

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.

Although the precise mechanism of corticosteroid antiallergic action is unknown, corticosteroids are very effective. However, when allergic symptoms are very severe, local treatment with recommended doses (microgram) of any available topical corticosteroid is not as effective as treatment with larger doses (milligram) of oral or parenteral formulations.

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

Pharmacokinetic characterization of the **Nasacort AQ** Nasal Spray formulation was determined in both normal adult subjects and patients with allergic rhinitis. Single dose intranasal administration of 220 mcg of **Nasacort AQ** Nasal Spray in normal adult subjects and patients demonstrated minimal absorption of triamcinolone acetonide. The mean peak plasma concentration was approximately 0.5 ng/mL (range: 0.1 to 1.0 ng/mL) and occurred at 1.5 hours post dose. The mean plasma drug concentration was less than 0.06 ng/mL at 12 hours, and below the assay detection limit at 24 hours. The average terminal half-life was 3.1 hours. The range of mean AUC_{0-∞} values was 1.4 ng•hr/mL to 4.7 ng•hr/mL between doses of 110 mcg to 440 mcg in both patients and healthy volunteers. Dose proportionality was demonstrated in both normal adult subjects and in allergic rhinitis patients following single intranasal doses of 110 mcg or 220 mcg **Nasacort AQ** Nasal Spray. The C_{max} and AUC of the 440 mcg dose increased less than proportionally when compared to 110 and 220 mcg doses. Following multiple doses in pediatric patients receiving 440 mcg/day, plasma drug concentrations, AUC, C_{max} and T_{max} were similar to those values observed in adult patients.

In animal studies using rats and dogs, three metabolites of triamcinolone acetonide have been identified. They are 6β-hydroxytriamcinolone acetonide, 21-carboxytriamcinolone acetonide and 21-carboxy-6β-hydroxytriamcinolone acetonide. All three metabolites are expected to be substantially less active than the parent compound due to (a) the dependence of anti-inflammatory activity on the presence of a 21-hydroxyl group, (b) the decreased activity observed upon 6-hydroxylation, and (c) the markedly increased water solubility favoring rapid elimination. There appeared to be some quantitative differences in the metabolites among species. No differences were detected in metabolic pattern as a function of route of administration.

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

In order to evaluate the effects of systemic absorption on the Hypothalamic-Pituitary-Adrenal (HPA) axis, a clinical study was performed in adults comparing 220 mcg or 440 mcg **Nasacort AQ** per day, or 10 mg prednisone per day with placebo for 42 days. Adrenal response to a six-hour cosyntropin stimulation test showed that **Nasacort AQ** administered at doses of 220 mcg

and 440 mcg had no statistically significant effect on HPA activity versus placebo. Conversely, oral prednisone at 10 mg/day significantly reduced the response to ACTH.

A study evaluating plasma cortisol response thirty and sixty minutes after cosyntropin stimulation in 80 pediatric patients who received 220 mcg or 440 mcg (twice the maximum recommended daily dose) daily for six weeks was conducted. No abnormal response to cosyntropin infusion (peak serum cortisol <18 mcg/dL) was observed in any pediatric patient after six weeks of dosing with **Nasacort AQ** at 440 mcg per day.

CLINICAL TRIALS

The safety and efficacy of **Nasacort AQ** Nasal Spray have been evaluated in 10 double-blind, placebo-controlled clinical trials of two- to four-weeks duration in adults and children 12 years and older with seasonal or perennial allergic rhinitis. The number of patients treated with **Nasacort AQ** Nasal Spray in these studies was 1266; of these patients, 675 were males and 591 were females.

Overall, the results of these clinical trials in adults and children 12 years and older demonstrated that **Nasacort AQ** Nasal Spray 220 mcg once daily (2 sprays in each nostril), when compared to placebo, provides statistically significant relief of nasal symptoms of seasonal or perennial allergic rhinitis including sneezing, stuffiness, discharge, and itching.

The safety and efficacy of **Nasacort AQ** Nasal Spray, at doses of 110 mcg or 220 mcg once daily, have also been adequately studied in two double-blind, placebo-controlled trials of two- and twelve-weeks duration in children ages 6 through 12 years with seasonal and perennial allergic rhinitis. These trials included 341 males and 177 females. **Nasacort AQ** administered at either dose resulted in statistically significant reductions in the severity of nasal symptoms of allergic rhinitis.

INDICATIONS AND USAGE

Nasacort AQ Nasal Spray is indicated for the treatment of the nasal symptoms of seasonal and perennial allergic rhinitis in adults and children 6 years of age and older.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients of this preparation contraindicates its use.

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency and, in addition, some patients may experience symptoms of withdrawal; *e.g.*, joint and/or muscular pain, lassitude and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chickenpox and measles, for example, can have a more serious or even fatal course in children 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.

PRECAUTIONS

General: In clinical studies with triamcinolone acetonide nasal spray, the development of localized infections of the nose and pharynx with *Candida albicans* has rarely occurred. When such an infection develops it may require treatment with appropriate local or systemic therapy and discontinuance of treatment with **Nasacort AQ** Nasal Spray.

Nasacort AQ Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infection of the respiratory tract or in patients with untreated fungal, bacterial, or systemic viral infections or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids, in patients who have experienced recent nasal septal ulcers, nasal surgery, or trauma, a corticosteroid should be used with caution until healing has occurred. As with other nasally inhaled corticosteroids, nasal septal perforations have been reported in rare instances.

When used at excessive doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, **Nasacort AQ** Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral steroid therapy.

Information for Patients: Patients being treated with **Nasacort AQ** Nasal Spray should receive the following information and instructions. Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to obtain medical advice.

Patients should use **Nasacort AQ** Nasal Spray at regular intervals since its effectiveness depends on its regular use. (See **DOSAGE AND ADMINISTRATION**.)

An improvement in some patient symptoms may be seen within the first day of treatment, and generally, it takes one week of treatment to reach maximum benefit. Initial assessment for response should be made during this time frame and periodically until the patient's symptoms are stabilized.

The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after three weeks, or if the condition worsens. Patients who experience recurrent episodes of epistaxis (nose bleeds) or nasal septum discomfort while taking this medication should contact their physician. For the proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully.

It is important to shake the bottle well before each use. **Also, the bottle should be discarded after 120 actuations since the amount of triamcinolone acetonide delivered thereafter per actuation may be substantially less than 55 mcg of drug.** Do not transfer any remaining suspension to another bottle.

Carcinogenesis, Mutagenesis, and Impairment Of Fertility: In a two-year study in rats, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 1.0 mcg/kg (approximately 1/30 and 1/50 of the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis, respectively). In a two-year study in mice, triamcinolone acetonide caused no treatment-related carcinogenicity at oral doses up to 3.0 mcg/kg (approximately 1/12 and 1/30 of the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis, respectively).

No evidence of mutagenicity was detected from *in vitro* tests (a reverse mutation test in *Salmonella* bacteria and a forward mutation test in Chinese hamster ovary cells) conducted with triamcinolone acetonide.

In male and female rats, triamcinolone acetonide caused no change in pregnancy rate at oral doses up to 15.0 mcg/kg (approximately 1/2 of the maximum recommended daily intranasal dose in adults on a mcg/m² basis). Triamcinolone acetonide caused increased fetal resorptions and stillbirths and decreases in pup weight and survival at doses of 5.0 mcg/kg and above (approximately 1/5 of the maximum recommended daily intranasal dose in adults on a mcg/m² basis). At 1.0 mcg/kg (approximately 1/30 of the maximum recommended daily intranasal dose in adults on a mcg/m² basis), it did not induce the above mentioned effects.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Triamcinolone acetonide was teratogenic in rats, rabbits, and monkeys. In rats, triamcinolone acetonide was teratogenic at inhalation doses of 20 mcg/kg and above (approximately 7/10 of the maximum recommended daily intranasal dose in adults on a mcg/m² basis). In rabbits, triamcinolone acetonide was teratogenic at inhalation doses of 20 mcg/kg and above (approximately 2 times the maximum recommended daily intranasal dose in adults on a mcg/m² basis). In monkeys, triamcinolone acetonide was teratogenic at an inhalation dose of 500 mcg/kg (approximately 37 times the maximum recommended daily intranasal dose in adults on a mcg/m² basis). Dose-related teratogenic effects in rats and rabbits included cleft palate and/or internal hydrocephaly and axial skeletal defects, whereas the effects observed in the monkey were cranial malformations.

There are no adequate and well-controlled studies in pregnant women. ~~Therefore, triamcinolone acetonide—~~ **Nasacort AQ Nasal Spray, like other corticosteroids,** should be used ~~in~~ during pregnancy only if the potential benefit justifies the potential risk to the fetus. Since their introduction, experience with oral corticosteroids in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in glucocorticoid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether triamcinolone acetonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when **Nasacort AQ** Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 6 years have not been established.

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 corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered.

ADVERSE REACTIONS

In placebo-controlled, double-blind, and open-label clinical studies, 1483 adults and children 12 years and older received treatment with triamcinolone acetonide aqueous nasal spray. These patients were treated for an average duration of 51 days. In the controlled trials (2-5 weeks duration) from which the following adverse reaction data are derived, 1394 patients were treated with **Nasacort AQ** Nasal Spray for an average of 19 days. In a long-term, open-label study, 172 patients received treatment for an average duration of 286 days.

Adverse events occurring at an incidence of 2% or greater and more common among **Nasacort AQ**-treated patients than placebo-treated patients in controlled adult clinical trials were:

Adverse Events	Patients treated with 220 mcg triamcinolone acetonide (n=857) %	Vehicle Placebo (n=962) %
Pharyngitis	5.1	3.6
Epistaxis	2.7	0.8
Increase in cough	2.1	1.5

A total of 602 children 6 to 12 years of age were studied in 3 double-blind, placebo-controlled clinical trials. Of these, 172 received 110 mcg/day and 207 received 220 mcg/day of **Nasacort AQ** Nasal Spray for two, six, or twelve weeks. The longest average durations of treatment for patients receiving 110 mcg/day and 220 mcg/day were 76 days and 80 days, respectively. Only 1% of those patients treated with **Nasacort AQ** were discontinued due to adverse experiences. No patient receiving 110 mcg/day discontinued due to a serious adverse event and one patient receiving 220 mcg/day discontinued due to a serious event that was considered not drug related. Overall, these studies found the adverse experience profile for **Nasacort AQ** to be similar to placebo. A similar adverse event profile was observed in pediatric patients 6-12 years of age as compared to older children and adults with the exception of epistaxis which occurred in less than 2% of the pediatric patients studied.

Adverse events occurring at an incidence of 2% or greater and more common among adult patients treated with placebo than **Nasacort AQ** were: headache, and rhinitis. In children aged 6 to 12 years these events included: asthma, epistaxis, headache, infection, otitis media, sinusitis, and vomiting.

In clinical trials, nasal septum perforation was reported in one adult patient although relationship to **Nasacort AQ** Nasal Spray has not been established.

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

DOSAGE AND ADMINISTRATION

Recommended Doses: *Adults and children 12 years of age and older:* The recommended starting and maximum dose is 220 mcg per day as two sprays in each nostril once daily.

Children 6 to 12 years of age: The recommended starting dose is 110 mcg per day given as one spray in each nostril once daily. The maximum recommended dose is 220 mcg per day as two sprays per nostril once daily.

Nasacort AQ Nasal Spray is not recommended for children under 6 years of age since adequate numbers of patients have not been studied in this age group.

Individualization of Dosage: It is always desirable to titrate an individual patient to the minimum effective dose to reduce the possibility of side effects. In adults, when the maximum benefit has been achieved and symptoms have been controlled, reducing the dose to 110 mcg per day (one spray in each nostril once a day) has been shown to be effective in maintaining control of the allergic rhinitis symptoms in patients who were initially controlled at 220 mcg/day.

In children six to twelve years of age, the recommended starting dose is 110 mcg per day given as one spray in each nostril once daily. The maximum recommended daily dose in children 6 to 12 years of age is 220 mcg per day (two sprays in each nostril once daily). Some patients who do not achieve maximum symptom control at a dose of 110 mcg per day may benefit from a dose of 220 mcg given as two sprays in each nostril once daily. The minimum effective dose should be

used to ensure continued control of symptoms. Once symptoms are controlled, pediatric patients may be able to be maintained on 110 mcg per day (1 spray in each nostril once daily).

An improvement in some patient symptoms may be seen within the first day of treatment, and generally, it takes one week of treatment to reach maximum benefit. Initial assessment for response should be made during this time frame and periodically until the patient's symptoms are stabilized. If adequate relief of symptoms has not been obtained after 3 weeks of treatment, **Nasacort AQ** Nasal Spray should be discontinued. (See **WARNINGS**, **PRECAUTIONS**, **Information for Patients**, and **ADVERSE REACTIONS**.)

Directions For Use: Illustrated Patient's Instructions for use accompany each package of **Nasacort AQ** Nasal Spray.

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.

HOW SUPPLIED

Nasacort AQ Nasal Spray is a nonchlorofluorocarbon (non-CFC) containing metered-dose pump spray. The contents of one 6.5 gram sample bottle provide 30 actuations, and the contents of one 16.5 gram bottle provide 120 actuations. The bottle should be discarded when the labeled number of actuations have been reached even though the bottle is not completely empty.

It is supplied in a white high-density polyethylene container with a metered-dose pump unit, white nasal adapter, and patient instructions.

NDC 0075-1506-16

Keep out of reach of children.

Store at Controlled Room Temperature, 20 to 25°C (68 to 77°F) [see USP].

Rx only

Aventis Pharmaceuticals Inc.

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US Pat. Nos. 6,143,329 and 5,976,573.

Other patents pending.

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INFORMATION FOR THE PATIENT

Rev. XXXX

Using your

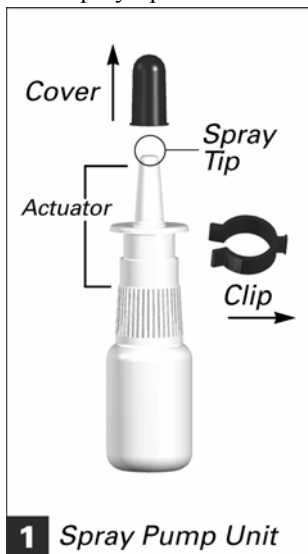
Nasacort[®]AQ

Nasal Spray

IMPORTANT: Please read these instructions carefully before using your **Nasacort[®] AQ** Nasal Spray

Prior To Use

1 Pull the cover and the clip off the spray pump unit. Do not attempt to enlarge the tiny hole in the spray tip. If the actuator has come off the pump stem, re-insert stem in actuator.



2 Shake the spray pump unit.

Preparing For Use

3 To prepare for use, the spray pump unit must be primed prior to the first use. To prime, put two fingers on the “shoulders” of the bottle. Push bottle with thumb **FIRMLY** and **QUICKLY** for a full-stroke actuation until a fine spray appears (5 pumps). Now your spray pump unit is primed and ready for use.



3

4 A fine mist can only be produced by a rapid and firm pumping action.

5 Repriming is only necessary when the spray pump unit has not been used for more than 14 days. To reprime, shake the bottle and spray one full-stroke actuation. Now the spray pump unit is reprimed.

To Use

6 Gently blow nose to clean nostrils, if needed.



6

7 Pull the cover and the clip off the spray pump unit, and shake pump unit.



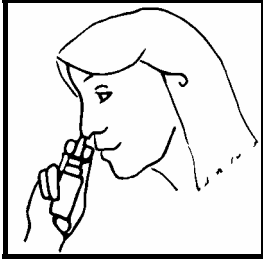
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8 Hold spray pump unit firmly as shown with the index and middle finger on either side of the spray tip and thumb on bottom of the bottle. Rest back of index finger against upper lip. **BE CAREFUL SO FINGERS WILL NOT SLIP OFF SPRAY PUMP UNIT AS YOU SPRAY.**



8

9 Put the spray tip into one nostril (tip should not reach far into the nose). **BEND HEAD FORWARD** so spray will aim toward the back of the nose.



9

10 Point tip straight back into nose. Close the other nostril with finger. Pump spray unit by pushing the bottle with thumb **FIRMLY** and **QUICKLY** for a full-stroke actuation and sniff gently at the same time. Repeat procedure for the other nostril.



10

11 Repeat steps 8, 9 and 10 if instructed to use more than one spray per nostril.

12 Avoid blowing nose for 15 minutes following dosing.

13 Keep the cover and the clip on the spray pump unit when not in use.

13



An Important Note

Repriming is only necessary when the spray pump unit has not been used for more than 14 days. To reprime, shake the bottle and only pump the spray pump unit one time. Do not reprime between more frequent usage.

Store your spray pump unit at room temperature. Avoid excessive heat.

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 120 “Full Sprays” of medication present. Please note that the bottle has been filled with extra suspension to accommodate the initial priming activity.

Nasacort® AQ 120 Spray Check-Off

- Retain with medication or affix to convenient location.
- Starting with spray #1, check off one circle for each spray used.

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	101	102	103	104
105	106	107	108	109	110	111	112
113	114	115	116	117	118	119	120

DISCARD MEDICATION AFTER 120 SPRAYS.

Your physician has determined that this product is likely to help your personal health. **USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR PHYSICIAN.** If you have any questions about alternatives, consult with your physician.

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