808201-XX

RHINOCORT AQUA
(budesonide)
Nasal Spray 32 mcg

For Intranasal Use Only.

Rx only

DESCRIPTION

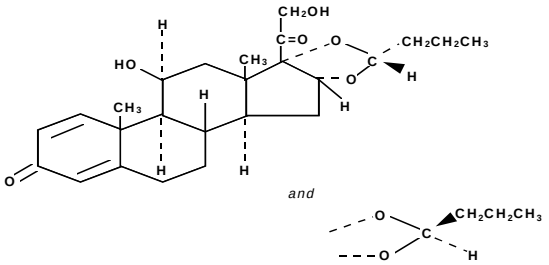
Budesonide, the active ingredient of RHINOCORT AQUA® Nasal Spray, is an anti-inflammatory synthetic corticosteroid.

It is designated chemically as (RS)-11-beta, 16-alpha, 17, 21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16, 17-acetal with butyraldehyde.

Budesonide is provided as the mixture of two epimers (22R and 22S).

The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.5.

Its structural formula is:



Budesonide is a white to off-white, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform.

Its partition coefficient between octanol and water at pH 5 is 1.6×10^3.

RHINOCORT AQUA is an unscented, metered-dose, manual-pump spray formulation containing a micronized suspension of budesonide in an aqueous medium. Microcrystalline cellulose and carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, and purified water are contained in this medium; hydrochloric acid is added to adjust the pH to a target of 4.5.

RHINOCORT AQUA Nasal Spray delivers 32 mcg of budesonide per spray.

Each bottle of RHINOCORT AQUA Nasal Spray 32 mcg contains 120 metered sprays after initial priming.

Prior to initial use, the container must be shaken gently and the pump must be primed by actuating eight times. If used daily, the pump does not need to be reprimed. If not used for two consecutive days, reprime with one spray or until a fine spray appears. If not used for more than 14 days, rinse the applicator and reprime with two sprays or until a fine spray appears.

CLINICAL PHARMACOLOGY

Budesonide is a synthetic corticosteroid having potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay. In glucocorticoid receptor affinity studies, the 22R form was twice as active as the 22S epimer.

The precise mechanism of corticosteroid actions in seasonal and perennial allergic rhinitis is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic mediated inflammation.

Corticosteroids affect the delayed (6 hour) response to an allergen challenge more than the histamine-associated immediate response (20 minute). The clinical significance of these findings is unknown.

Pharmacokinetics

The pharmacokinetics of budesonide have been studied following nasal, oral, and intravenous administration. Budesonide is relatively well absorbed after both inhalation and oral administration, and is rapidly metabolized into metabolites with low corticosteroid potency. The clinical activity of RHINOCORT AQUA Nasal Spray is therefore believed to be due to the parent drug, budesonide. *In vitro* studies indicate that the two epimeric forms of budesonide do not interconvert.

Absorption:

Following intranasal administration of RHINOCORT AQUA, the mean peak plasma concentration occurs at approximately 0.7 hours. Compared to an intravenous dose, approximately 34% of the delivered intranasal dose reaches the systemic circulation, most of which is absorbed through the nasal mucosa. While budesonide is well absorbed from the GI tract, the oral bioavailability of budesonide is low (~10%) primarily due to extensive first pass metabolism in the liver.

Distribution:

Budesonide has a volume of distribution of approximately 2-3 L/kg. The volume of distribution for the 22R epimer is almost twice that of the 22S epimer. Protein binding of budesonide *in vitro* is constant (85-90%) over a concentration range (1-100 nmol/L) which exceeded that achieved after administration of recommended doses. Budesonide shows little to no binding to glucocorticosteroid binding globulin. It rapidly equilibrates with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism:

Budesonide is rapidly and extensively metabolized in humans by the liver. Two major metabolites (16α-hydroxyprednisolone and 6β-hydroxybudesonide) are formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4)-catalyzed biotransformation. Known metabolic inhibitors of CYP3A4 (eg, ketoconazole), or significant hepatic impairment, may increase the systemic exposure of unmetabolized budesonide (see WARNINGS and PRECAUTIONS). *In vitro* studies on the binding of the two primary metabolites to the glucocorticoid receptor indicate that they have less than 1% of the affinity for the receptor as the parent compound budesonide. *In vitro* studies have evaluated sites of metabolism and showed negligible metabolism in skin, lung, and serum. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns could be detected.

Elimination:

Budesonide is excreted in the urine and feces in the form of metabolites. After intranasal administration of a radiolabeled dose, 2/3 of the radioactivity was found in the urine and the remainder in the feces. The main metabolites of budesonide in the 0-24 hour urine sample following IV administration are 16α-hydroxyprednisolone (24%) and 6β-hydroxybudesonide (5%). An additional 34% of the radioactivity recovered in the urine was identified as conjugates.

The 22R form was preferentially cleared with clearance value of 1.4 L/min vs. 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was similar for both epimers and it appeared to be independent of dose.

Special Populations:

Geriatric:

No specific pharmacokinetic study has been undertaken in subjects >65 years of age.

Pediatric Info

Pediatric:

After administration of RHINOCORT AQUA Nasal Spray, the time to reach peak drug concentrations and plasma half-life were similar in children and in adults. Children had plasma concentrations approximately twice those observed in adults due primarily to differences in weight between children and adults.

Gender:
No specific pharmacokinetic study has been conducted to evaluate the effect of gender on budesonide pharmacokinetics. However, following administration of 400 mcg of RHINOCORT AQUA Nasal Spray to 7 male and 8 female volunteers in a pharmacokinetic study, no major gender differences in the pharmacokinetic parameters were found.

Race:
No specific study has been undertaken to evaluate the effect of race on budesonide pharmacokinetics.

Renal Insufficiency:
The pharmacokinetics of budesonide have not been investigated in patients with renal insufficiency.

Hepatic Insufficiency:
Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of orally administered budesonide were affected by compromised liver function as evidenced by a doubled systemic availability. The relevance of this finding to intranasally administered budesonide has not been established.

Pharmacodynamics
A 3-week clinical study in seasonal rhinitis, comparing RHINOCORT Nasal Inhaler, orally ingested budesonide, and placebo in 98 patients with allergic rhinitis due to birch pollen, demonstrated that the therapeutic effect of RHINOCORT Nasal Inhaler can be attributed to the topical effects of budesonide.

The effects of RHINOCORT AQUA Nasal Spray on adrenal function have been evaluated in several clinical trials. In a four-week clinical trial, 61 adult patients who received 256 mcg daily of RHINOCORT AQUA Nasal Spray demonstrated no significant differences from patients receiving placebo in plasma cortisol levels measured before and 60 minutes after 0.25 mg intramuscular cosyntropin. There were no consistent differences in 24-hour urinary cortisol measurements in patients receiving up to 400 mcg daily. Similar results were seen in a study of 150 children and adolescents aged 6 to 17 with perennial rhinitis who were treated with 256 mcg daily for up to 12 months.

After treatment with the recommended maximal daily dose of RHINOCORT AQUA (256 mcg) for seven days, there was a small, but statistically significant decrease in the area under the plasma cortisol-time curve over 24 hours ($AUC_{0\text{-}24h}$) in healthy adult volunteers.

A dose-related suppression of 24-hour urinary cortisol excretion was observed after administration of RHINOCORT AQUA doses ranging from 100-800 mcg daily for up to four days in 78 healthy adult volunteers. The clinical relevance of these results is unknown.

Clinical Trials

The therapeutic efficacy of RHINOCORT AQUA Nasal Spray has been evaluated in placebo-controlled clinical trials of seasonal and perennial allergic rhinitis of 3-6 weeks duration.

The number of patients treated with budesonide in these studies was 90 males and 51 females aged 6-12 years and 691 males and 694 females 12 years and above. The patients were predominantly Caucasian.

Overall, the results of these clinical trials showed that RHINOCORT AQUA Nasal Spray administered once daily provides statistically significant reduction in the severity of nasal symptoms of seasonal and perennial allergic rhinitis including runny nose, sneezing, and nasal congestion.

An improvement in nasal symptoms may be noted in patients within 10 hours of first using RHINOCORT AQUA Nasal Spray. This time to onset is supported by an environmental exposure unit study in seasonal allergic rhinitis patients which demonstrated that RHINOCORT AQUA Nasal Spray led to a statistically significant improvement in nasal symptoms compared to placebo by 10 hours. Further support comes from a clinical study of patients with perennial allergic rhinitis which demonstrated a statistically significant improvement in nasal symptoms for both RHINOCORT AQUA Nasal Spray and for the active comparator (mometasone furoate) compared to placebo by 8 hours. Onset was also assessed in this study with peak nasal inspiratory flow rate and this endpoint failed to show efficacy for either active treatment. Although statistically significant improvements in nasal symptoms compared to placebo were noted within 8-10 hours in these studies, about one half to two thirds of the ultimate clinical improvement with RHINOCORT AQUA Nasal Spray occurs over the first 1-2 days, and maximum benefit may not be achieved until approximately 2 weeks after initiation of treatment.

INDICATIONS AND USAGE

RHINOCORT AQUA Nasal Spray is indicated for the management of nasal symptoms of seasonal or perennial allergic rhinitis in adults and children six years of age and older.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients in this preparation contraindicates the use of RHINOCORT AQUA Nasal Spray.

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 corticosteroid withdrawal, eg, 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.

Patients who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on immunosuppressant doses of corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General:

Pediatric Info

Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use).

Rarely, immediate and/or delayed hypersensitivity reactions may occur after the intranasal administration of budesonide. Rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal application of corticosteroids, including budesonide.

Although systemic effects have been minimal with recommended doses of RHINOCORT AQUA Nasal Spray, any such effect is dose dependent. Therefore, larger than recommended doses of RHINOCORT AQUA Nasal Spray should be avoided and the minimal effective dose for the patient should be used (see DOSAGE AND ADMINISTRATION). When used at larger doses, systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear. If such changes occur, the dosage of RHINOCORT AQUA Nasal Spray should be discontinued slowly, consistent with accepted procedures for discontinuing oral corticosteroid therapy.

In clinical studies with budesonide administered intranasally, the development of localized infections of the nose and pharynx with *Candida albicans* has occurred only rarely. When such an infection develops, it may require treatment with appropriate local or systemic therapy and discontinuation of treatment with RHINOCORT AQUA Nasal Spray. Patients using RHINOCORT AQUA Nasal Spray over several months or longer should be examined periodically for evidence of *Candida* infection or other signs of adverse effects on the nasal mucosa.

RHINOCORT AQUA Nasal Spray should be used with caution, if at all, in patients with active or quiescent tuberculous infection, untreated fungal, bacterial, or systemic viral infections, or ocular herpes simplex.

Because of the inhibitory effect of corticosteroids on wound healing, patients who have experienced recent nasal septal ulcers, nasal surgery, or nasal trauma should not use a nasal corticosteroid until healing has occurred.

Hepatic dysfunction influences the pharmacokinetics of budesonide, similar to the effect on other corticosteroids, with a reduced elimination rate and increased systemic availability (see CLINICAL PHARMACOLOGY, Special Populations).

Information for Patients:

Patients being treated with RHINOCORT AQUA Nasal Spray should receive the following information and instructions. Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to obtain medical advice.

Patients should use RHINOCORT AQUA Nasal Spray at regular intervals since its effectiveness depends on its regular use (see DOSAGE AND ADMINISTRATION).

An improvement in nasal symptoms may be noted in patients within 10 hours of first using RHINOCORT AQUA Nasal Spray. This time to onset is supported by an environmental exposure unit study in seasonal allergic rhinitis patients which demonstrated that RHINOCORT AQUA Nasal Spray led to a statistically significant improvement in nasal symptoms compared to placebo by 10 hours. Further support comes from a clinical study of patients with perennial allergic rhinitis which demonstrated a statistically significant improvement in nasal symptoms for both RHINOCORT AQUA Nasal Spray and for the active comparator (mometasone furoate) compared to placebo by 8 hours. Onset was also assessed in this study with peak nasal inspiratory flow rate and this endpoint failed to show efficacy for either active treatment. Although statistically significant improvements in nasal symptoms compared to placebo were noted within 8-10 hours in these studies, about one half to two thirds of the ultimate clinical improvement with RHINOCORT AQUA Nasal Spray occurs over the first 1-2 days, and maximum benefit may not be achieved until approximately 2 weeks after initiation of treatment. 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 two weeks, or if the condition worsens. Patients who experience recurrent episodes of epistaxis (nosebleeds) or nasal septum discomfort while taking this medication should contact their physician. For 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. The RHINOCORT AQUA Nasal Spray 32 mcg bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after 120 sprays following initial priming, since the amount of budesonide delivered per spray thereafter may be substantially less than the labeled dose. Do not transfer any remaining suspension to another bottle.

Drug Interactions:

The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased by more than seven-fold. Concomitant administration of other known inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide (see WARNINGS and PRECAUTIONS, General). Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known CYP3A4 inhibitors.

Omeprazole, an inhibitor of CYP2C19, did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of CYP1A2, caused a slight decrease in budesonide clearance and corresponding increase in its oral bioavailability.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in the male rats receiving an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (approximately equal to and two times the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis, respectively). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis). However, in male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 3 times the maximum recommended daily intranasal dose in adults and children on a mcg/m^2 basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hematocyte culture.

In rats, budesonide caused a decrease in prenatal viability and viability of the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis).

Pregnancy:

Teratogenic Effects: Pregnancy Category C:

Budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits and 500 mcg/kg in rats (approximately 2 and 16 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 8 times the maximum recommended daily intranasal dose in adults on a mcg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women. RHINOCORT AQUA Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Experience with oral corticosteroids since their introduction 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 corticosteroid 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 budesonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when RHINOCORT AQUA Nasal Spray is administered to nursing women.

Pediatric Info

Pediatric Use:

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

Controlled clinical studies have shown that intranasal corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with intranasal corticosteroids, including the impact on final adult height, are unknown. The potential for "catch-up" growth following discontinuation of treatment with intranasal corticosteroids has not been adequately studied. The growth of pediatric patients receiving intranasal corticosteroids, including RHINOCORT AQUA Nasal Spray, should be monitored routinely (eg, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of safe and effective noncorticosteroid treatment alternatives. To minimize the systemic effects of intranasal corticosteroids, including RHINOCORT AQUA Nasal Spray, each patient should be titrated to the lowest dose that effectively controls his/her symptoms.

A one-year placebo-controlled clinical growth study was conducted in 229 pediatric patients (ages 4 through 8 years of age) to assess the effect of RHINOCORT AQUA (single-daily dose of 64 mcg, the recommended starting dose for children ages 6 years and above) on growth velocity. From a population of 141 patients receiving RHINOCORT AQUA Nasal Spray and 67 receiving placebo, the point estimate for growth velocity with RHINOCORT AQUA Nasal Spray was 0.25 cm/year lower than that noted with placebo (95% confidence interval ranging from 0.59 cm/year lower than placebo to 0.08 cm/year higher than placebo).

The potential for RHINOCORT AQUA to cause growth suppression in susceptible patients or when given at doses above 64 mcg daily cannot be ruled out. The recommended dosage range in patients 6 to 11 years of age is 64 to 128 mcg per day (see DOSAGE AND ADMINISTRATION).

Geriatric Use:

Of the 2,461 patients in clinical studies of RHINOCORT AQUA Nasal Spray, 5% were 60 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, except for an adverse event reporting frequency of epistaxis which increased with age. Further, other reported clinical experience has not identified any other differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The incidence of common adverse reactions is based upon two U.S. and five non-U.S. controlled clinical trials in 1,526 patients [110 females and 239 males less than 18 years of age, and 635 females and 542 males 18 years of age and older] treated with RHINOCORT AQUA Nasal Spray at doses up to 400 mcg once daily for 3-6 weeks. The table below describes adverse events occurring at an incidence of 2% or greater and more common among RHINOCORT AQUA Nasal Spray-treated patients than in placebo-treated patients in controlled clinical trials. The overall incidence of adverse events was similar between RHINOCORT AQUA and placebo.

Adverse Event	RHINOCORT AQUA	Placebo Vehicle
Epistaxis	8%	5%
Pharyngitis	4%	3%
Bronchospasm	2%	1%
Coughing	2%	<1%
Nasal Irritation	2%	<1%

Pediatric Info

A similar adverse event profile was observed in the subgroup of pediatric patients 6 to 12 years of age.

Two to three percent (2-3%) of patients in clinical trials discontinued because of adverse events. Systemic corticosteroid side effects were not reported during controlled clinical studies with RHINOCORT AQUA Nasal Spray.

If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's Syndrome, could occur.

Rare adverse events reported from post-marketing experience include: nasal septum perforation, pharynx disorders (throat irritation, throat pain, swollen throat, burning throat, and itchy throat), angioedema, anosmia, and palpitations.

Cases of growth suppression have been reported for intranasal corticosteroids including RHINOCORT AQUA Nasal Spray (see PRECAUTIONS, Pediatric Use).

OVERDOSAGE

Acute overdosage with this dosage form is unlikely since one 120 spray bottle of RHINOCORT AQUA Nasal Spray 32 mcg only contains approximately 5.4 mg of budesonide. Chronic overdosage may result in signs/symptoms of hypercorticism (see WARNINGS and PRECAUTIONS).

DOSAGE AND ADMINISTRATION

Pediatric Info

The recommended starting dose for adults and children 6 years of age and older is 64 mcg per day administered as one spray per nostril of RHINOCORT AQUA Nasal Spray 32 mcg once daily. The maximum recommended dose for adults (12 years of age and older) is 256 mcg per day administered as four sprays per nostril once daily of RHINOCORT AQUA Nasal Spray 32 mcg and the maximum recommended dose for pediatric patients (<12 years of age) is 128 mcg per day administered as two sprays per nostril once daily of RHINOCORT AQUA Nasal Spray 32 mcg (see HOW SUPPLIED).

Prior to initial use, the container must be shaken gently and the pump must be primed by actuating eight times. If used daily, the pump does not need to be reprimed. If not used for two consecutive days, reprime with one spray or until a fine spray appears. If not used for more than 14 days, rinse the applicator and reprime with two sprays or until a fine spray appears.

Individualization of Dosage

Pediatric Info

It is always desirable to titrate an individual patient to the minimum effective dose to reduce the possibility of side effects. In adults and children 6 years of age and older, the recommended starting dose is 64 mcg daily administered as one spray per nostril of RHINOCORT AQUA Nasal Spray 32 mcg, once daily. Some patients who do not achieve symptom control at the recommended starting dose may benefit from an increased dose. The maximum daily dose is 256 mcg for adults and 128 mcg for pediatric patients (<12 years of age). When the maximum benefit has been achieved and symptoms have been controlled, reducing the dose may be effective in maintaining control of the allergic rhinitis symptoms in patients who were initially controlled on higher doses.

An improvement in nasal symptoms may be noted in patients within 10 hours of first using RHINOCORT AQUA Nasal Spray. This time to onset is supported by an environmental exposure unit study in seasonal allergic rhinitis patients which demonstrated that RHINOCORT AQUA Nasal Spray led to a statistically significant improvement in nasal symptoms compared to placebo by 10 hours. Further support comes from a clinical study of patients with perennial allergic rhinitis which demonstrated a statistically significant improvement in nasal symptoms for both RHINOCORT AQUA Nasal Spray and for the active comparator (mometasone furoate) compared to placebo by 8 hours. Onset was also assessed in this study with peak nasal inspiratory flow rate and this endpoint failed to show efficacy for either active treatment. Although statistically significant improvements in nasal symptoms compared to placebo were noted within 8-10 hours in these studies, about one half to two thirds of the ultimate clinical improvement with RHINOCORT AQUA Nasal Spray occurs over the first 1-2 days, and maximum benefit may not be achieved until approximately 2 weeks after initiation of treatment. Initial assessment for response should be made during this time frame and periodically until the patient's symptoms are stabilized.

Directions for Use

Illustrated *Patient's Instructions for Use* accompany each package of RHINOCORT AQUA Nasal Spray 32 mcg.

HOW SUPPLIED

RHINOCORT AQUA Nasal Spray 32 mcg is available in a green coated glass bottle with a metered-dose pump spray and a green protection cap. RHINOCORT AQUA Nasal Spray 32 mcg provides 120 metered sprays after initial priming; net fill weight 8.6 g. The RHINOCORT AQUA Nasal Spray 32 mcg bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after 120 sprays following initial priming, since the amount of budesonide delivered per spray thereafter may be substantially less than the labeled dose. Each spray delivers 32 mcg of budesonide to the patient.

NDC 0186-1070-08
RHINOCORT AQUA Nasal Spray
32 mcg, 120 metered sprays; net fill weight 8.6 g

RHINOCORT AQUA Nasal Spray should be stored at controlled room temperature, 20 to 25°C (68 to 77°F) with the valve up. Do not freeze. Protect from light. **Shake gently before use.** Do not spray in eyes.

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