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

Its partition coefficient between octanol and water at pH 5 is $1.6 \times 10^{-3}$.

4-diene-3,20-dione cyclic 16, 17-acetal with butyraldehyde.

It is designated chemically as (RS)-11-beta, 16-alpha, 17, 21-tetrahydroxypregn-4-ene-3,20-dione. Budesonide is an inflammatory synthetic corticosteroid.

Pharmacodynamics:

Primarily to differences in weight between children and adults.

Pediatric:

Special Populations

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.

Elimination

Budesonide is rapidly and extensively metabolized in the liver. Two major metabolites (22S and 22R epimers) of budesonide are formed and rapidly eliminated in the urine. The 22S epimer is a more potent glucocorticoid receptor agonist as the parent compound budesonide.

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 is generally <10% with red blood cells in a concentration independent manner with a blood/plasma ratio of approximately 0.8.

Pharmacokinetics:

The pharmacokinetics of budesonide have been studied following nasal, oral, and intra-dermal administration. Budesonide is well absorbed from the nasal mucosa. While budesonide is well absorbed, only approximately 34% of the delivered intranasal dose reaches the systemic circulation.

Absorption

Following intranasal administration of RHINOCORT AQUA, the mean peak plasma levels were achieved approximately 30 minutes after initial priming.

Abnormalities

Budesonide Metabolism

Budesonide is metabolized mainly in the liver. The major pathways of metabolism include dehydroxylation at the 21 position to yield 21-hydroxybudesonide and glucuronidation of the 21-hydroxy metabolite. These reactions occur mainly in the liver. Glucuronidation of the 21-hydroxy metabolite is followed by further metabolic reactions resulting in the formation of a 21-carboxylic acid metabolite.

Adverse Reactions

Adverse effects have been reported with the administration of budesonide-containing products. These adverse effects include: nasopharyngitis, rhinitis, headache, and nasal congestion.

Contraindications

The use of RHINOCORT AQUA Nasal Spray is not recommended in patients with a history of hypersensitivity to any component of the formulation.

Warnings

Although systemic effects have been minimal with recommended doses of RHINOCORT AQUA Nasal Spray, patients should be monitored for evidence of corticosteroid side effects, particularly in those patients who are predisposed to these effects.

Drug Interactions

Budesonide has been shown to have a wide range of inhibitory activity against multiple cell types and enzymes. 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 approximately 0.8.

Non-clinical toxicology

Metabolism

Budesonide is rapidly and extensively metabolized in humans by the liver. Two major metabolites (6α-hydroxybudesonide and 6β-hydroxybudesonide) are formed via cytochrome P450 3A4 (CYP3A4)-catalyzed biotransformation. Known metabolites include 6β-hydroxybudesonide (clotrinol), which is a significant biologically active metabolite of budesonide, and 21-deoxy-21-hydroxybudesonide, which is a major metabolite generated in the liver.

Pharmacodynamics

Intranasal corticosteroids may cause a reduction in growth velocity when administered for prolonged periods of time. In animal studies, budesonide has been shown to have minimal effects on growth velocity in rats and rabbits.

Absorption

The bioavailability of budesonide is low (<10%) primarily due to extensive first pass metabolism in the liver.

Special Populations

Clinical Trials

The clinical trials for this preparation demonstrated no evidence of adverse effects in children, infants, and elderly patients.

Indications and Uses

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

Contraindications

Budesonide-containing products should not be used in patients with known hypersensitivity to any component of the formulation.

Precautions

Gender

Blood pressure and heart rate were monitored throughout the study, and no gender differences in the hemodynamic parameters were found.

Budesonide does not cause local or systemic side effects that are different from other corticosteroids.

Rhinocerous

The pharmacokinetics of budesonide have not been investigated in patients with normal rhinostenosis.

Hypertrophic Respiratory Tract

The effects of budesonide on the adrenal function may affect the therapeutic action of corticosteroids. The pharmacokinetics of orally administered budesonide were affected by concomitant therapy with other corticosteroids, and the clinical significance of this finding is uncertain.

Viral Infections

The effects of intranasal budesonide on the viral infections have been evaluated in animal studies. The results of these studies demonstrated that budesonide has no effect on the viral infections such as rhinovirus, influenza, and adenovirus.

Immunosuppressive Effects

The effects of intranasal budesonide on the immune system have been studied in animal and human models. Budesonide has been shown to have a broad spectrum of immunosuppressive effects, including suppression of the delayed-type hypersensitivity response, and suppression of the inflammatory response to various stimuli.

Ocular Symptoms

The effects of intranasal budesonide on the ocular symptoms have been evaluated in human studies. The results of these studies demonstrated that budesonide has no effect on the ocular symptoms such as conjunctivitis, keratoconjunctivitis, and blepharitis.

Hypertension

The effects of intranasal budesonide on the blood pressure and heart rate have been evaluated in human studies. The results of these studies demonstrated that budesonide has no effect on the blood pressure and heart rate.

Disease-Related Parameters

The effects of intranasal budesonide on the disease-related parameters have been evaluated in clinical trials. The results of these studies demonstrated that budesonide has no effect on the disease-related parameters.

Clinical Trials

In the clinical trials, the therapeutic efficacy of RHINOCORT AQUA Nasal Spray has been evaluated in placebo-controlled clinical trials of seasonal and perennial allergic rhinitis. The results of these studies demonstrated that RHINOCORT AQUA Nasal Spray delivered 32 mcg of budesonide per spray is effective in the treatment of seasonal and perennial allergic rhinitis.

Pediatric:

Pediatric studies of RHINOCORT AQUA Nasal Spray have not been conducted. Therefore, it is unknown whether the drug will exhibit different pharmacokinetics or pharmacodynamics in children compared to adults.

The safety and efficacy of RHINOCORT AQUA Nasal Spray have been demonstrated in placebo-controlled clinical trials of seasonal and perennial allergic rhinitis.

The results of these studies demonstrated that budesonide has no effect on the ocular symptoms such as conjunctivitis, keratoconjunctivitis, and blepharitis.

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The effects of intranasal budesonide on the ocular symptoms have been evaluated in human studies. The results of these studies demonstrated that budesonide has no effect on the ocular symptoms such as conjunctivitis, keratoconjunctivitis, and blepharitis.

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Disease-Related Parameters

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Information for Patients

Patients being treated with RHINOCORT AQUA Nasal Spray should receive the following instructions:

- If exposure to chicken pox or measles is imminent, and if it is not possible to avoid exposure to chicken pox or measles, patients should contact their physician.
- Treatment of recurrent respiratory symptoms, including use of intranasal corticosteroids, should be continued to avoid exacerbation of upper respiratory signs and symptoms.
- The maximum recommended daily dose of RHINOCORT AQUA Nasal Spray should not be exceeded.
- The table below describes adverse events occurring at an incidence of 2% or greater.

Geriatric Use

The incidence of common adverse reactions is based upon two U.S. and five non-U.S. controlled clinical trials in 1,180 patients (370 females and 205 males less than 18 years of age, and 436 and 542 males ages 18 and older). (see PRECAUTIONS, Pediatric Use). Further, no reports of clinical adverse experience have identified any other differences in response in comparison with younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Drug Interactions

The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 CYP3A4 (CYP3A4). Oral administration of salmeterol (a selective, potent inhaled bronchodilator) 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.

Absorption and Metabolism

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 human dose). No tumorigenicity was seen in male and female rats at oral doses up to 30 mg/kg (approximately twice the maximum recommended daily human dose in adults and children on a mg/m2 basis). No tumors were observed in oral doses of 1 mg/kg (approximately 50 times the maximum recommended daily human dose in adults and children on a mg/m2 basis) in the long-term carcinogenesis studies. The carcinogenic potential of intranasal corticosteroids, including RHINOCORT AQUA Nasal Spray, has not been specifically evaluated.

Dosage and Administration

The recommended starting dose for adults and children 6 years of age and older is RHINOCORT AQUA Nasal Spray 32 mcg, once daily. The maximum recommended dose for adults (12 years of age and older) is RHINOCORT AQUA Nasal Spray 32 mcg and the maximum recommended dose for pediatric patients 6 to 11 years of age is RHINOCORT AQUA Nasal Spray 32 mcg. The maximum recommended dose for children (12 years of age and older) is 256 mcg per day administered as four sprays per nostril once daily or one spray per nostril twice daily. The maximum recommended daily dose of RHINOCORT AQUA Nasal Spray for children under 12 years of age is 256 mcg per day administered as four sprays per nostril once daily or one spray per nostril twice daily. Increasing the dose beyond the maximum recommended dose for patients 12 years of age and older has not been associated with improved efficacy.

Adverse Events

A similar adverse event profile was observed in the subgroup of pediatric patients 6 to 11 years of age.

Two to three percent (2-3%) of patients in clinical trials discontinued due to adverse events.

Adverse reactions were reported more frequently in patients treated with intranasal corticosteroids, including RHINOCORT AQUA Nasal Spray (see PRECAUTIONS, Pediatric Use).

Adverse events reported with an incidence of 2% or greater

The incidence of common adverse reactions is based upon two U.S. and five non-U.S. controlled clinical trials in 1,180 patients (370 females and 205 males less than 18 years of age, and 436 and 542 males ages 18 and older). (see PRECAUTIONS, Pediatric Use). Further, no reports of clinical adverse experience have identified any other differences in response in comparison with younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Table of the 2-6 patients in clinical studies of RHINOCORT AQUA Nasal Spray, 4% were noted in U.S. controlled clinical trials and 4% were noted in non-U.S. controlled clinical trials. Safety and effectiveness were both observed in these subjects and younger subjects, except for an adverse event of viral upper respiratory infection. Further, no reports of clinical adverse experience have identified any other differences in response in comparison with younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Table of adverse reactions

The incidence of common adverse reactions is based upon two U.S. and five non-U.S. controlled clinical trials in 1,180 patients (370 females and 205 males less than 18 years of age, and 436 and 542 males ages 18 and older). (see PRECAUTIONS, Pediatric Use). Further, no reports of clinical adverse experience have identified any other differences in response in comparison with younger patients, but greater sensitivity of some older individuals cannot be ruled out.