

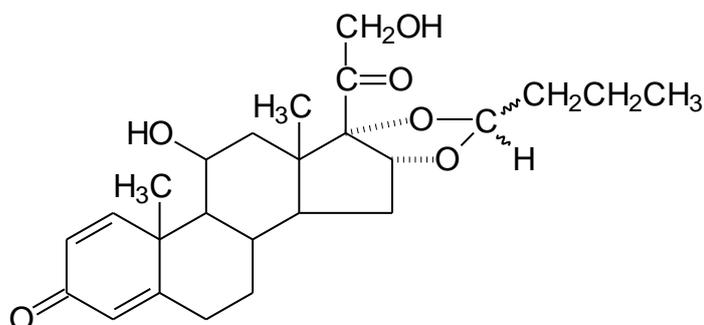
RHINOCORT®

(budesonide for nasal inhalation)

PRODUCT INFORMATION

NAME OF THE MEDICINE

The active ingredient, budesonide, is a non-halogenated glucocorticoid structurally related to 16 α hydroxyprednisolone. The chemical name is 16 α , 17 α -22 R, S-propylmethylenedioxypregna-1, 4-diene-11 β , 21-diol-3, 20-dione; MW 430.5.



CAS number: 51333-22-3

DESCRIPTION

Budesonide is a white to off-white powder, freely soluble in chloroform, sparingly soluble in ethanol and practically insoluble in water and heptane. Budesonide melts between 224°C and 231.5°C with decomposition.

RHINOCORT is registered as a 32 μ g per dose (not available as a Prescription only medicine) and 64 μ g per dose aqueous nasal suspension containing budesonide as the active ingredient with disodium edetate, potassium sorbate, glucose anhydrous, dispersible cellulose, polysorbate 80 and purified water. The pH of the solution may have been adjusted by hydrochloric acid, if required.

PHARMACOLOGY

Studies in animals and humans have shown an advantageous ratio between topical anti-inflammatory activity and systemic glucocorticoid effect over a wide dose range.

Budesonide is approximately twice as potent as beclomethasone dipropionate as shown in the skin blanching test for anti-inflammatory activity of topical steroids in humans. Budesonide has, however, less systemic effect than beclomethasone dipropionate, as measured by depression of morning plasma cortisol and effect on differential WBC count. The improved ratio of topical anti-inflammatory activity to systemic effect of budesonide is due to high glucocorticoid receptor affinity combined with a high first pass metabolism and a short half-life.

Pre-treatment for one week with intranasal budesonide 400 µg daily in asymptomatic patients with seasonal rhinitis, significantly inhibited the immediate reaction to allergen challenge.

The mechanism of action of intranasally administered budesonide has not yet been completely defined, however budesonide has been shown to counteract the mainly "IgE", mediated lung anaphylaxis in guinea pigs.

Pharmacokinetics

The systemic availability of budesonide from RHINOCORT, with reference to the metered dose, is 33%. Negligible biotransformation occurs in human nasal mucosa.

After nasal application of 256 µg budesonide peak plasma concentrations of approximately 0.63 nmol/L in adults and 1.53 nmol/L in children were observed within 45 minutes. The area under the curve (AUC) after administration of 256 µg budesonide from RHINOCORT is 2.7 nmol.h/L in adults and 5.5 nmol.h/L in children.

Budesonide has a volume of distribution of approximately 3 L/kg. Plasma protein binding averages 85-90%.

Budesonide is metabolised in the liver by cytochrome p450 3A to more polar metabolites with low glucocorticoid activity (ie 100 fold lower than the parent compound). The metabolites are inactive and excreted mainly via the kidneys. No intact budesonide has been detected in the urine. Budesonide has a high systemic clearance (approximately 1.2 L/min) and the plasma half-life after i.v. dosing averages 2-3 hours.

CLINICAL TRIALS

Seasonal and perennial allergic rhinitis

The therapeutic efficacy of RHINOCORT 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 (aged 6 years and above) treated with RHINOCORT nasal spray in these 8 studies was 1653.

Overall, the results of these clinical trials showed that RHINOCORT 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. In some studies, improvement versus placebo has been shown to occur within 24 hours of initiating treatment with RHINOCORT nasal spray. Maximum benefit can take up to 2 weeks after initiation of treatment.

Nasal polyps

A randomised, double blind placebo controlled study evaluated the efficacy of RHINOCORT nasal spray 128 µg bd over a 6 week treatment period in patients (n=46) with moderate to severe nasal polyps. After 6 weeks polyp size was significantly reduced and nasal symptoms improved compared to placebo (n=47).

INDICATIONS

Rhinitis

- Prophylaxis and treatment of seasonal allergic rhinitis
- Prophylaxis and treatment of perennial allergic rhinitis

Nasal polyps

Treatment of nasal polyps.

CONTRAINDICATIONS

Hypersensitivity to any ingredient.

Severe nasal infections, especially candidiasis.

Persons with haemorrhagic diatheses or with a history of recurrent nasal bleeding.

PRECAUTIONS

Clinical response

The full effect of RHINOCORT in allergic rhinitis is not achieved until after 2 to 3 days of treatment (in rare cases not until after 2 weeks).

Concomitant treatment

Concomitant treatment may sometimes be necessary to counteract potential eye symptoms caused by the allergy.

Concomitant corticosteroid therapy

If RHINOCORT is prescribed for patients already using corticosteroids, care should be taken to ensure that the daily dosage of RHINOCORT is included when determining total daily corticosteroid dose.

Continuous, long term use

In continuous long-term treatment, care should be exercised to avoid the development of nasal mucosal atrophy. The nasal mucosa should be inspected at least twice per year.

Severe nasal obstruction/congestion

In some patients with severe nasal obstruction and congestion, concomitant treatment with local decongestants should be considered for 2-3 days only. The decongestant should be administered a few minutes before budesonide. Nasal polypectomy may be indicated initially for patients with nasal obstruction due to nasal polyposis.

Tuberculosis

Whenever corticosteroid administration is required in patients with quiescent or active tuberculosis, the therapeutic advantages should be weighed against possible undesirable effects.

Infection

If infection of the respiratory tract, nasal passages or paranasal sinuses is present or occurs during administration of RHINOCORT, adequate antibacterial therapy should be promptly instituted (see also *Contraindications*).

Wound healing

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

Reduced liver function

Reduced liver function may affect the elimination of glucocorticosteroids. The pharmacokinetics after oral ingestion of 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.

Adrenocortical function

Topical corticosteroids may be absorbed in amounts that can have systemic effects. Use of higher than recommended doses may suppress HPA function. However, at recommended doses, RHINOCORT does not cause any clinically important changes in basal cortisol levels. Similar effects have been noted with inhaled budesonide, whilst still retaining the physiological circadian rhythms of plasma cortisol. This indicates that the HPA axis suppression represents a physiological adaptation in response to budesonide, not necessarily adrenal insufficiency. This is further supported by inhaled and intranasal budesonide studies, which found that, at recommended doses, there was no clinically relevant effect on the response to stimulation with ACTH (predictor for clinically manifest adrenal insufficiency).

Clinically important disturbances of the HPA axis and/or adrenal insufficiency induced by stress may be related to budesonide in specific patient populations, particularly patients administering concomitant medication metabolised by CYP3A4 (see *Interactions with other medicines*). Monitoring for signs of adrenal dysfunction is advisable in this patient group.

Use in children

Controlled clinical trials have shown that intranasal corticosteroids may cause a reduction in growth velocity in children. Whilst no long-term studies are available for intranasal budesonide, long-term studies in a clinical practice environment suggest that children treated with orally inhaled budesonide on average achieve their adult target height. However, in a long-term double-blind study, in which the budesonide dose was generally not titrated to the lowest effective dose, children treated with inhaled budesonide became on average 1.2 cm shorter as adults than those randomised to placebo.

Rare individuals may be exceptionally sensitive to intranasal corticosteroids. Height measurements (eg via stadiometry) should be performed to identify patients with increased sensitivity. The potential growth effects of prolonged treatment should be weighed against the clinical benefits and the availability of safe and effective non-corticosteroid alternatives. To minimise the systemic effects of intranasal corticosteroids, each patient should be titrated to his/her lowest effective dose (see *Dosage and Administration* section).

The continuous long term use of budesonide nasal spray in children is not recommended due to the possibility of reduced growth velocity. Studies of children with seasonal allergic rhinitis did not extend beyond four weeks of treatment.

Safety and effectiveness of RHINOCORT in children below 6 years of age has not been established.

Carcinogenicity and mutagenicity

The carcinogenic potential of budesonide has been evaluated in mouse and rat at oral doses up to 200 and 50 µg/kg/day, respectively. No oncogenic effect was noted in the mouse. One study indicated an increased incidence of brain gliomas in male Sprague-Dawley rats given budesonide, however the results were considered equivocal. Further studies performed in male Sprague-Dawley and Fischer rats showed that the incidence of gliomas in the budesonide-treated rats was low and did not differ from that in the reference glucocorticoid groups or the controls. It was concluded that treatment with budesonide does not increase the incidence of brain tumours in the rat.

In male rats dosed with 10, 25 and 50 µg/kg/day, those receiving 25 and 50 µg/kg/day showed an increased incidence of primary hepatocellular tumours. This was observed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in a repeat study in male Sprague-Dawley rats thus indicating a class effect of corticosteroids.

The mutagenic potential of budesonide was evaluated in 6 different test systems. No mutagenic or clastogenic effects of budesonide were found.

Use in pregnancy (Category A)

Results from a large prospective epidemiological study and from world-wide post marketing experience indicate that inhaled budesonide during pregnancy has no adverse effects on the health of the foetus or new born child. As with other medicines the administration of budesonide during pregnancy requires that the benefits for the mother be weighed against the risks for the foetus.

Intranasal glucocorticosteroids such as budesonide, should be considered because of the lower systemic effects, compared to oral glucocorticosteroids.

Use in lactation

Budesonide is excreted in breast milk. However, due to the relatively low doses used via the intranasal route the amount of medicine present in the breast milk, if any, is likely to be low. Breastfeeding can be considered if the potential benefit outweighs any potential risks.

INTERACTIONS WITH OTHER MEDICINES

The metabolism of budesonide is primarily mediated by CYP3A, a subfamily of cytochrome P450. After oral administration of ketoconazole, a potent inhibitor of cytochrome P450 3A, the mean plasma concentration of budesonide increased by more than seven fold. Concomitant administration of other known inhibitors of this enzyme, (eg itraconazole, clarithromycin, erythromycin) may inhibit the metabolism of, and increase the systemic exposure to, budesonide.

Cimetidine, primarily an inhibitor of cytochrome P450 1A2, caused a slight decrease in budesonide clearance and corresponding increase in its oral bioavailability.

ADVERSE REACTIONS

Adverse local reactions following RHINOCORT use are mild and usually transient. Systemic corticosteroid side-effects have not been reported during clinical studies of RHINOCORT in adults (refer *Precautions – Use in children* section for details relating to children). Growth suppression has been reported in association with administration of intranasal corticosteroids. Whilst no long-term studies are available for intranasal budesonide, long-term studies in a clinical practice environment suggest that children treated with orally inhaled budesonide on average achieve their adult target height. However, in a long-term double-blind study, in which the budesonide dose was generally not titrated to the lowest effective dose, children treated with inhaled budesonide became on average 1.2 cm shorter as adults than those randomised to placebo. See *Precautions - Use in children*.

Adverse events reported during studies with RHINOCORT

Common (more than 1%)	Nose and throat	Nasal irritation, itching of throat and larynx, sore throat, dry mucous membranes, dry mouth, sneezing after spraying, increased sputum, haemorrhagic secretion, epistaxis (nose bleeding), nasal crust, sinusitis
	Respiratory	Cough, dyspnoea
	Central Nervous System	Headache, dizziness, tiredness
Uncommon (less than 1%)	Nose and throat	Strong smell of spray, bad taste, earache
	Gastrointestinal	Loss of appetite, stomach disorder, nausea
	Skin and appendages	Skin itching
	Central Nervous System	Tremor, sedation
	Immune system	Immediate and delayed hypersensitivity reactions including urticaria, rash, dermatitis, angioedema and pruritus.
Rare (less than or equal to 0.2%)		Ear itching, joint aches, sexual dysfunction.
Very rare cases of ulcerations of the mucous membrane, nasal septal perforations and anaphylactic reactions have been reported following the use of intranasal corticosteroids.		

Laboratory variables

All changes in haematology, biochemistry and urinalysis were within the normal range and were not considered clinically significant.

DOSAGE AND ADMINISTRATION

There is no evidence that efficacy improves when the recommended dose is exceeded.

Seasonal allergic rhinitis (adults and children 6 years and over) and perennial allergic rhinitis (adults)

Initially

Total daily dose, 256 µg given as either a single daily application of 128 µg into each nostril in the morning, or divided into two applications of 64 µg into each nostril, morning and evening.

Maintenance – individualisation of dosage

When a satisfactory therapeutic response has been achieved, the maintenance dose should be titrated to the minimum effective dose. This may be a total daily dose of 128 µg given as 64 µg into each nostril in the morning, however clinical trials suggest that a maintenance dose of 32 µg in each nostril in the morning may be sufficient in some patients.

Continuous long-term use in children is not recommended due to the possibility of growth suppression. Whilst no long-term studies are available for intranasal budesonide, long-term studies in a clinical practice environment suggest that children treated with orally inhaled budesonide on average achieve their adult target height. However, in a long-term double-blind study, in which the budesonide dose was generally not titrated to the lowest effective dose, children treated with inhaled budesonide became on average 1.2 cm shorter as adults than those randomised to placebo. See *Precautions – Use in children*.

Patients should be informed that full response may not occur until after 2-3 days of treatment (in rare cases not until after 2 weeks). Ideally, in seasonal allergic rhinitis treatment should start before exposure to the allergen.

Treatment of nasal polyps – Adults (18 years and older)

Total daily dose, 256 µg given as a divided daily application of 64 µg into each nostril, morning and evening.

Patient instructions

Patients should be instructed in the correct use of RHINOCORT. An instruction leaflet is included in each pack of RHINOCORT. Patients should also be advised to clear secretions from nasal passages prior to use and not to exceed the recommended dose.

OVERDOSAGE

Acute overdosage with RHINOCORT, even in excessive doses, is not expected to be a clinical problem.

In the unlikely event of prolonged excessive use of RHINOCORT which could possibly lead to adrenal suppression, treatment should be discontinued. Overdosage may give rise to signs of Cushing's syndrome, such as increased bodyweight, lethargy, hypertension, hirsutism, cutaneous striae, personality change, ecchymosis, oedema, polyuria and polydipsia. In severe cases, the dosage of the corticosteroid should be gradually withdrawn to prevent the possibility of adrenal failure.

PRESENTATION

RHINOCORT nasal spray comes in a brown glass bottle with pump spray equipment and nasal adaptor.

The following strengths and pack sizes are registered:

- 32 µg per dose: 120 doses
- 64 µg per dose: 50 doses (sample pack), 120 doses (1x120 dose bottle) and 240 doses (2x120 dose bottles)

Not all pack sizes may be available in Australia.

Storage conditions

Store below 30°C. Do not freeze.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

24 August 2000

DATE OF MOST RECENT AMENDMENT

13 September 2017