

PRODUCT MONOGRAPH

Pr **RHINOCORT[®] AQUA[™]**

budesonide

(Aqueous Nasal Spray)

64 µg per metered dose

Glucocorticosteroid Spray for the Treatment of
Seasonal and Perennial Rhinitis and Nasal Polyposis

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Control No. 124950

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PRODUCT MONOGRAPH

NAME OF DRUG

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budesonide

(Aqueous Nasal Spray)

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THERAPEUTIC CLASSIFICATION

Glucocorticosteroid Spray for the Treatment of
Seasonal and Perennial Rhinitis and Nasal Polyposis

ACTIONS AND CLINICAL PHARMACOLOGY

RHINOCORT AQUA (budesonide) contains budesonide which is a potent synthetic glucocorticosteroid with strong topical and weak systemic effects.

RHINOCORT AQUA has a high topical anti-inflammatory potency and it is rapidly biotransformed in the liver. This favourable separation between topical anti-inflammatory activity and systemic effect is due to strong glucocorticosteroid receptor affinity and an effective first pass metabolism with a short half-life. The mechanism of action of intranasally administered budesonide has not yet been completely defined.

The systemic availability of oral budesonide in man is low (about 10%). With reference to the metered dose, the systemic availability of budesonide from RHINOCORT AQUA is 33%. After application of budesonide in solution directly on the nasal mucosa, all the dose is systemically available, indicating that budesonide does not undergo local metabolism in the nose.

The maximal plasma concentration after administration of 256 µg budesonide from RHINOCORT AQUA is 0.64 nmol/L and is reached within 0.7 hours.

INDICATIONS AND CLINICAL USE

The treatment of seasonal allergic and allergic/non-allergic perennial and vasomotor rhinitis unresponsive to conventional therapy. Also indicated for the treatment of nasal polyps and in the prevention of nasal polyps after polypectomy.

CONTRAINDICATIONS

- Hypersensitivity to any of the nasal spray's components;
- Active or quiescent tuberculosis;
- Untreated fungal, bacterial, or viral infections;
- Children under 6 years of age.

WARNINGS

In patients previously on prolonged periods or high doses of systemic steroids, withdrawal of steroids may cause symptoms such as tiredness, aches and pains, and depression. In severe cases, adrenal insufficiency may occur necessitating a temporary resumption of systemic steroids.

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.

Use in Pregnancy

See PRECAUTIONS.

PRECAUTIONS

Glucocorticosteroids may mask some signs of infection and new infections may appear during their use.

In transferring patients from a systemic steroid to RHINOCORT AQUA (budesonide), the reduction of the systemic steroid must be very gradual and carefully supervised by the physician since systemic withdrawal symptoms (e.g., joint and/or muscular pain, lassitude, depression) may occur in spite of maintenance or improvement of respiratory functions (see DOSAGE AND ADMINISTRATION).

Patients should be informed that the full effect of RHINOCORT AQUA therapy is not achieved until 2 to 3 days of treatment have been completed. In rare cases the full effect of RHINOCORT AQUA therapy is not achieved until 2 weeks of treatment have been completed. Treatment of seasonal rhinitis should, if possible, start before the exposure to allergens.

Treatment with RHINOCORT AQUA should not be stopped abruptly but tapered off gradually.

Special care is needed in patients with fungal and viral nasal infections. Children who are on immunosuppressant drugs are more susceptible to infections than healthy children. Chicken pox and measles, for example, can have a more serious or fatal course in children on immunosuppressant 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 chicken pox develops, treatment with antiviral agents may be considered.

Concomitant treatment may sometimes be required to counteract eye symptoms caused by allergy.

The long term effects of budesonide in human subjects are still unknown, in particular, its local effects, and on developmental or immunologic processes. The nasal mucosa of those patients receiving long term, continuous therapy should be inspected at least twice a year. The possibility of atrophic rhinitis and/or pharyngeal candidiasis should be kept in mind.

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

When budesonide is administered intranasally, the following should be kept in mind:

Glucocorticosteroid effects may be enhanced in patients with hypothyroidism and in those with cirrhosis. Reduced liver function may affect the elimination of corticosteroids. The intravenous pharmacokinetics of budesonide however, are similar in cirrhotic patients and in healthy subjects. The pharmacokinetics after oral ingestion of budesonide were affected by compromised liver function as evidenced by increased systemic availability. This is however, of limited clinical importance for RHINOCORT AQUA, as the oral contribution to the systemic availability is relatively small.

In hypoprothrombinemia, salicylates should be used cautiously in conjunction with glucocorticosteroids.

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.

Use in Pregnancy

In experimental animal studies, budesonide was found to cross the placental barrier. Like other glucocorticosteroids, budesonide is teratogenic to rodent species. High doses of budesonide administered subcutaneously produced fetal malformations, primarily skeletal defects, in rabbits, rats, and in mice. Results from world-wide post marketing experience indicate inhaled budesonide during pregnancy has no adverse effects on the health of the fetus/new born child. Review of published literature of orally inhaled budesonide, including results from a large case control study performed with cases identified from 3 Swedish health registers showed that there was no association between exposure to inhaled budesonide and overall congenital malformations. Results from a similar study performed with intranasal budesonide, using the same 3 Swedish health registers showed that the use of intranasal budesonide was associated with a subgroup "less severe cardiovascular defects"; however

there was no statistically significant association between the use of intranasal budesonide during pregnancy and overall congenital malformations, or overall frequency of cardiovascular defects in the offspring. Budesonide should be used during pregnancy only if the potential benefits clearly outweigh the risk to the fetus. Infants born of mothers who have received substantial doses of corticosteroids, especially oral steroids, during pregnancy should be carefully observed for hypoadrenalism.

Lactation

Budesonide is excreted in breast milk. The administration of RHINOCORT AQUA to women who are breastfeeding should only be considered if the expected benefit to the mother is greater than any possible risk to the child.

Children Under 6 Years of Age

RHINOCORT AQUA is not presently recommended for children younger than 6 years of age due to limited clinical data in this age group.

Glucocorticosteroids may mask some signs of infections and new infections may appear. A decreased resistance to localized infection has been observed during glucocorticosteroid therapy. During long-term therapy, pituitary-adrenal function, hematological status and height (in children) should be periodically assessed.

Patients should be advised to inform subsequent physicians of the prior use of glucocorticosteroids.

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 RHINOCORT AQUA (see INFORMATION FOR THE PATIENT).

Dose-related suppression of plasma and urinary cortisol has been observed in healthy volunteers after short-term administration of RHINOCORT AQUA. Although no important changes in basal plasma cortisol levels were manifested in patients with rhinitis using RHINOCORT AQUA at recommended doses, caution is advised.

Drug Interactions

To date budesonide has not been observed to interact with other drugs used for the treatment of rhinitis.

Cimetidine

The kinetics of budesonide were investigated in a study in healthy subjects without and with cimetidine, 1000 mg daily. After a 4 mg oral dose the values for C_{max} (nmol/L) and systemic availability (%) of budesonide without and with cimetidine (3.3 vs 5.1 nmol/L and 10 vs 12%, respectively) indicated a slight inhibitory effect on hepatic metabolism of budesonide, caused by cimetidine. This should be of little clinical importance.

Ketoconazole

The metabolism of budesonide is primarily mediated by CYP3A4, a subfamily of cytochrome P450. CYP3A4 inhibitors like ritonavir and azole antifungals (e.g. ketoconazole and itraconazole) increase the systemic exposure to budesonide. Therefore, concomitant use of budesonide and ritonavir or azole antifungals should be avoided unless the potential benefit outweighs the risk of systemic corticosteroids side-effects.

Omeprazole

At recommended doses, omeprazole has no effect on the pharmacokinetics of oral budesonide.

ADVERSE REACTIONS

The adverse reactions reported with RHINOCORT AQUA (budesonide) are consistent with what one would expect when applying a topical treatment to an already inflamed membrane. All side effects were transient. The most commonly reported side effects include: nasal and throat irritation, nasal bleeding and crusting. Other adverse events reported are itching throat, sore throat, cough, fatigue, nausea/dizziness, and headache. When patients are transferred to RHINOCORT AQUA from a systemic steroid, allergic conditions such as asthma or eczema may be unmasked. Uncommon side effects such as immediate and delayed hypersensitivity reactions (urticaria, rash, dermatitis, angioedema, pruritus etc.) may occur in association with local corticosteroid therapy. Very rare cases of anaphylactic reaction have been reported following the use of RHINOCORT AQUA. Additionally, very rare cases of ulcerations of the mucous membranes and nasal septal perforation have been reported following the use of intranasal corticosteroids.

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. 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 recur, the dosage of RHINOCORT AQUA (budesonide) should be discontinued slowly consistent with accepted procedures for discontinuation of chronic steroid therapy (see DOSAGE AND ADMINISTRATION).

The restoration of the hypothalamic-pituitary-axis may be a slow process and during periods with pronounced physical stress such as severe infections, trauma, and surgical operations, 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 RHINOCORT AQUA (budesonide). Initially,

RHINOCORT AQUA 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.

Rhinitis

Adults and Children Over 6 Years

Initially: The recommended starting dose is 256 µg daily. The dose can be administered once daily in the morning or divided into two administrations morning and evening. For example: 128 µg (2 sprays) into each nostril in the morning or, 64 µg (1 spray) into each nostril morning and evening.

Maintenance

After the desired clinical effect is obtained, the maintenance dose should be reduced to the smallest amount necessary to control the symptoms.

Treatment or Prevention of Nasal Polyps

The recommended dose is 64 µg (1 spray) into each nostril morning and evening (total daily dose is 256 µg).

Children Under 6 Years

Not recommended for children in this age group.

Patients should be informed that the full effect of RHINOCORT AQUA therapy may not become evident until 2 to 3 days of treatment have been completed. Full therapeutic benefit requires regular usage. Explain the absence of an immediate effect to the patient in order to ensure cooperation and continuation of the treatment with a regular dosage regime. Treatment of seasonal rhinitis should, if possible, start before exposure to the allergens. Concomitant treatment may sometimes be necessary to counteract eye symptoms caused by the allergy. In continuous long-term treatment, the nasal mucosa should be inspected regularly, e.g., every 6 months.

If the nasal passages are severely blocked, the drug may fail to reach the site of action. In such cases, a course of oral steroids or decongestants may be required before initiating RHINOCORT AQUA therapy.

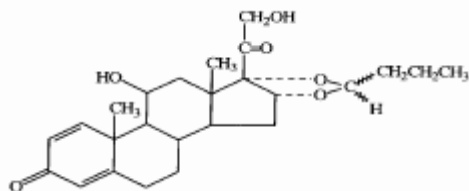
Although systemic effects are negligible at recommended doses, RHINOCORT AQUA treatment should not be continued beyond three weeks in the absence of significant

symptomatic improvement. RHINOCORT AQUA should not be used in the presence of untreated localized infections involving the nasal mucosa.

PHARMACEUTICAL INFORMATION

Drug Substance

Chemical Structure:



Generic Name: Budesonide

Chemical Name: Budesonide is a mixture of two isomers:
1. Pregna-1,4-diene-3,20-dione,16,17-butyridenebis(oxy)-11,21-dihydroxy-,[11 β ,16 α (R)] and
2. Pregna-1,4-diene-3,20-dione,16,17-butyridenebis(oxy)-11,21-dihydroxy-,[11 β ,16 α (S)]

Molecular Formula: C₂₅H₃₄O₆

Molecular Weight: 430.5

Description: Budesonide is a glucocorticosteroid and consists of a 1:1 mixture of two epimers, 22R and 22S. It is a white to off-white crystalline powder and is freely soluble in chloroform, sparingly soluble in ethanol, practically insoluble in water and in heptane. Budesonide melts at 224°C to 231.5°C, with decomposition.

Dosage Form

Composition

per metered dose

Active: budesonide 64 μ g

Non-medicinal: microcrystalline cellulose, carboxymethylcellulose sodium, glucose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, hydrochloric acid, purified water.

Stability and Storage Recommendations

RHINOCORT AQUA should be stored at room temperature (15-30°C).

AVAILABILITY OF DOSAGE FORMS

RHINOCORT AQUA 64 μ g/dose is a white to off-white, thixotropic suspension of budesonide in water supplied in amber glass bottles provided with a pump spray mechanism, nasal adapter and Patient Instruction leaflet in bottles of 120 doses.

INFORMATION FOR THE PATIENT
IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT

Pf RHINOCORT[®] AQUA[™]

budesonide (aqueous nasal spray)

BEFORE using RHINOCORT AQUA, read this leaflet carefully. It contains general points about RHINOCORT AQUA and should add to more specific advice from your doctor or pharmacist.

Please keep this leaflet to refer to until you have used up all medication in RHINOCORT AQUA.

WHAT IS RHINOCORT AQUA USED FOR AND HOW DOES IT WORK?

RHINOCORT is a brand name for a drug called budesonide. RHINOCORT is an intranasal spray of the drug budesonide. It belongs to a group of medicines called corticosteroids which are used to reduce inflammation. RHINOCORT AQUA reduces and prevents the inflammation.

You should use RHINOCORT AQUA when you experience symptoms such as congestion (blocked nose), runny nose, sneezing and nasal itching. These symptoms may be felt when you are exposed to pollen such as ragweed or grass (hay fever) or dust in your house.

RHINOCORT AQUA can also be used to treat nasal polyps. It can prevent new polyps from appearing as well as get rid of ones you already have.

WHAT IS IN RHINOCORT AQUA?

RHINOCORT AQUA contains budesonide as the active ingredient and comes in a concentration of 64 µg per spray.

Most medicines contain more ingredients than just the active drug. Check with your doctor if you think you might be allergic to any of these items (listed in alphabetical order): budesonide, carboxymethylcellulose sodium, disodium edetate, glucose anhydrous, hydrochloric acid, microcrystalline cellulose, polysorbate 80, potassium sorbate, and purified water.

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING RHINOCORT AQUA?

- Tell your doctor:
- About all health problems you have now or have had in the past, especially if you have had lung tuberculosis or any other recent infection;
- about other medicines you take, including ones you can buy without a prescription;
- if you take, or have taken steroid medicines within the past several months;

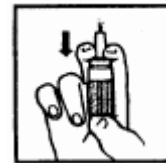
- if you have ever had a bad, unusual or allergic reaction to budesonide or any of the other ingredients;
- if you are pregnant, plan to become pregnant or are breastfeeding;
- if you take medications against fungal infections or ritonavir (medication used to treat HIV infection or AIDS). These medications may interact with RHINOCORT AQUA.

HOW DO I TAKE RHINOCORT AQUA PROPERLY?

It is important that you use RHINOCORT AQUA daily at the intervals recommended by your doctor. Do not stop or change dosage without asking your doctor.

If you follow the instructions below, you will receive the medication.

1. Before use, turn the bottle upside-down 3 to 4 times. Remove the protective cap from the nose piece.
2. When using the spray for the first time, you must load the pump by pressing downwards on the collar. Use your index and middle fingers while supporting the base of the bottle with your thumb (as illustrated). Press down 5 to 10 times until a fine mist spray appears. The spray is now ready for use. If not used daily the pump must be loaded again. This time it is sufficient to pump just once into the air.
3. Gently blow your nose. Hold the bottle as shown. Tilt your head forward slightly, close one nostril with a finger and gently insert the tip of the nose piece into the other nostril.
4. For each spray your doctor has instructed you to take, press firmly downwards once on the collar. Breathe gently inwards through the nostril, then breathe out through the mouth.
5. Repeat the procedure for the other nostril.
6. Replace the protective cap on the nose piece. Keep the bottle in an upright position. Store at 15-30°C.



Cleaning: Clean the nose piece and protective cap regularly. To clean the nose piece, remove the protective cap, press upwards on the collar and the nose piece will come off. Wash the nose piece and protective cap under lukewarm water. Air dry and replace the nose piece and the protective cap back on the bottle and reload as in Instruction #2. **Do not try to clean the nasal applicator by using a pin or sharp object.**

HOW MUCH RHINOCORT AQUA SHOULD I TAKE?

The dosage of RHINOCORT AQUA is individual. Follow your doctor's directions carefully. They may differ from the information in this leaflet.

CAUTION: RHINOCORT AQUA does not give immediate relief of your nasal symptoms. It may take a few days (and up to 2 weeks) before you notice any improvement. Contact your doctor if:

- no improvement occurs after 3 weeks,
- the inside of your nose becomes sore (nasal irritation),
- coloured (yellow or green) nasal secretions appear,
- repeated bleeding from the nose occurs.

Adults and Children Over 6 Years

Rhinitis

Suggested **starting doses** are: Total daily dose 4 sprays (256 µg). In children, do not exceed this dose. RHINOCORT AQUA can be taken once or twice daily.

Once Daily: 2 sprays (128 µg) into each nostril, once in the morning.

Twice Daily: 1 spray (64 µg) into each nostril, morning and evening.

Maintenance Dose: Use lowest effective dose.

Nasal Polyps

1 spray (64 µg) into each nostril, morning and evening (total daily dose 256 µg).

IMPORTANT: Use regularly as directed by your doctor. **DO NOT EXCEED THE DOSE PRESCRIBED BY YOUR DOCTOR.**

WHAT DO I DO IF I MISS A DOSE?

If you miss a dose of RHINOCORT AQUA, take it as soon as possible. Then go back to your regular schedule. If it is almost time to take your next dose, skip the missed dose and take the next dose on time.

Never take a double dose of RHINOCORT AQUA to make up for ones you missed. If you are still unsure, check with your doctor or pharmacist to see what you should do.

You may notice that your symptoms improve after the first dose of RHINOCORT AQUA. However, several weeks may pass before the full effect is achieved. Don't forget to take RHINOCORT AQUA even when you feel well.

Treatment with RHINOCORT AQUA should not be stopped abruptly, but tapered off gradually.

WHAT SHOULD I DO IN CASE OF OVERDOSE?

Telephone your doctor or go to your nearest hospital right away if you think that you or anyone else may have taken too much RHINOCORT AQUA.

ARE THERE ANY SIDE EFFECTS?

Like any medication, RHINOCORT AQUA may result in side effects in some people.

Common side effects are nasal and throat irritation, nasal bleeding and crusting. Other side effects include itching throat, sore throat, cough, fatigue, nausea/dizziness and headache.

Uncommon side effects include allergic conditions such as asthma or a skin rash. These may not be caused by RHINOCORT AQUA in your case, but only a doctor can tell this. Very few people who have used steroids in the nose, such as RHINOCORT AQUA, have experienced a severe allergic reaction, or have found small holes or ulcers in the skin inside the nose. The likelihood of these side effects occurring is very rare. If you notice anything unusual about the skin inside your nose, talk to your doctor.

Medicines affect different people in different ways. Just because side effects have occurred in other patients does not mean you will get them. If any side effects bother you, please contact your doctor.

Do not stop taking RHINOCORT AQUA on your own. Your doctor may want to slowly reduce your dose, especially if you have been using RHINOCORT AQUA for a long time. Although rare, symptoms of steroid withdrawal (i.e. fatigue, muscle or joint aches) may occur if RHINOCORT AQUA is stopped too quickly.

WHERE SHOULD I KEEP RHINOCORT AQUA?

Remember to **keep RHINOCORT AQUA out of the reach of children** when you are not using it.

Store the bottle at room temperature (15-30°C) in a dry place, away from moisture.

Do not keep or use RHINOCORT AQUA after the expiry date indicated on the label.

Important Note: **This leaflet alerts you to some of the times you should call your doctor. Other situations which cannot be predicted may arise. Nothing about this leaflet should stop you from calling your doctor or pharmacist with any questions or concerns you have about using RHINOCORT AQUA.**

NOTE: This INFORMATION FOR THE PATIENT leaflet provides you with the most current information at the time of printing.

For the most current information, the Consumer Information Leaflet plus the full Product Monograph, prepared for health professionals can be found at:

www.astrazeneca.ca

or by contacting the sponsor, AstraZeneca Canada Inc. at:

Customer Inquiries – 1 (800) 668-6000,

Renseignements – 1 (800) 461-3787.

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AstraZeneca Canada Inc.

Mississauga, Ontario

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PHARMACOLOGY

Studies with animals have shown that budesonide has a 2-10 times better ratio between topical anti-inflammatory and systemic glucocorticosteroid effects than that obtained with beclomethasone dipropionate or triamcinolone acetonide. In the blanching test for topical anti-inflammatory activity in humans, budesonide was about twice as potent as beclomethasone dipropionate. Beclomethasone dipropionate was, however, more active than budesonide with regard to systemic activity as measured by depression of morning plasma cortisol. The favourable topical anti-inflammatory activity to systemic effect ratio demonstrated by budesonide is due to its high glucocorticosteroid receptor affinity and high first pass metabolism with a short half-life.

Budesonide has been shown to counteract the mainly "IgE" mediated lung anaphylaxis in guinea pigs. No significant bronchorelaxing activity, either *in vitro* or *in vivo*, could be demonstrated. Budesonide did not potentiate beta-mediated bronchorelaxation, and did not affect theophylline-induced relaxation or respiratory airway smooth muscle in guinea pigs.

Budesonide exhibits typical glucocorticosteroid effects in that subcutaneous administration to adrenalectomised rats induced glycogen deposition in the liver, increased urinary volume and only slightly affected sodium excretion. Whole body autoradiography in mice has shown budesonide and its metabolites to have a similar distribution pattern to other glucocorticosteroids with a high distribution to endocrine organs.

Human Pharmacokinetics

The systemic bioavailability of oral budesonide in man is low (about 10%). With reference to the metered dose, the systemic availability of budesonide from RHINOCORT AQUA is 33%. After application of budesonide in solution directly on the nasal mucosa, all the dose is systemically available, indicating that budesonide does not undergo local metabolism in the nose. The maximal plasma concentration after administration of 400 µg budesonide from RHINOCORT AQUA is 1.0 nmol/L and is reached within 0.7 hours.

The distribution volume (Vd) of budesonide is 301.3±41.7 L, indicating the high tissue affinity of the drug. Plasma protein binding is estimated at 88.3±1.5%.

After nasal administration of tritiated budesonide in human volunteers, 56.1±2.6% of the discharged dose was recovered in the urine (0-96 hours) while during the same period, 33.4±2.0% of the dose could be recovered in the feces. In those subjects who took the compound intravenously, 56.7±1.2% was recovered in the urine, 34.0±3.0% in the feces.

In vitro studies with human liver have shown that budesonide is rapidly metabolised to more polar compounds than the parent drug. Two major metabolites have been isolated and identified as 6β-hydroxybudesonide and 16α-hydroxyprednisolone. The metabolism of budesonide in the liver is primarily mediated by cytochrome P450 3A. The glucocorticosteroid activity of these two metabolites was at least 100-fold lower than the parent compound as shown in the rat ear edema test. No qualitative differences between the *in*

vitro and *in vivo* metabolic patterns could be detected. Negligible biotransformation was observed in human lung and serum preparations.

TOXICOLOGY

Acute Toxicity

| Species | Sex | Route | LD ₅₀ (mg/kg) After 3 Weeks |
|---------|--------|-------|---|
| mouse | male | s.c. | 35± 18 |
| mouse | male | p.o. | > 800 |
| mouse | female | p.o. | > 800 |
| rat | male | s.c. | 15.1± 4.4 |
| rat | female | s.c. | 20.3± 7.1 |
| rat | male | p.o. | ≈400 |

Surviving animals exhibited a marked decrease in body weight gain.

Toxicity After Repeated Administration Of Budesonide To Rats, Rabbits And Dogs

| Animal | | Number and Sex Per Group | No. of Dose Groups | Daily Dose Levels | | Route of Administration | Duration | Toxic Effects |
|---------|-------------------|--------------------------|--------------------|----------------------------|----------------------|-------------------------|-----------|--|
| Species | Strain | | | mg/kg | mg/animal | | | |
| Rat | Sprague-Dawley | 6 males 6 females | 4 | 0.05 0.5 5.0 50.0 | | p.o. | 1 month | Atrophy of adrenal gland and lymphoid system. Gastric ulceration. |
| Rat | Wistar | 10 males 10 females | 3 | 0.02 0.10 0.2-0.5 | | inhalation | 3 months | Hair loss, dose related reduction in lymphocytes, leukocytes, increase in neutrophils. In high dose group, reduced adrenal, thymic, splenic and hepatic weights. No pulmonary impairment observed. |
| Rat | Wistar | 40 males 40 females | 3 | 0.005 0.01 0.05 | | inhalation | 12 months | As above. |
| Rabbit | New Zealand White | 3 males 3 females | 2 | | 0.025 0.1 | s.c. | 1 month | High dose caused slight liver mass increase, slight decrease in adrenal mass, thymal regression. |
| Dog | Beagle | 1 male 1 female | 3 | 0.01 0.1 1.0 | | p.o. | 1 month | High dose - typical steroid effects - adrenal, lymphoid system atrophy, increased fat in myocardium, glycogen in liver. |
| Dog | Beagle | 2 males 2 females | 3 | 0.02 0.06 0.2 | | inhalation | 6 weeks | High dose - induced thymal atrophy, adrenal atrophy. No changes in respiratory system observed. |
| Dog | Beagle | 5 males 5 females | 3 | | 0.20 0.60 2.00 | inhalation | 6 months | High dose - decreased plasma cortisol, cortical atrophy of the adrenal gland, thymal regression. Slight visceral obesity. |
| Dog | Beagle | 5 males 5 females | 3 | | 0.20 0.60 2.00 | inhalation | 12 months | High dose - obesity, alopecia, females showed no evidence of estrous cycle. Systemic steroid effects - lymphoid and adrenal atrophy. |

All effects observed were consistent with those expected during prolonged corticosteroid exposure.

Teratology and Reproduction Studies

Effects on Pregnancy

Rat

Daily doses of 20, 100, and 500 µg/kg body mass were administered subcutaneously to pregnant rats during days 6-15 of gestation. In the high dose group, all of the rats showed a deteriorated general condition including piloerection, drowsiness, decreased food consumption and decreased body mass gain. Fetal loss was increased and pup masses decreased in comparison to the control group. The frequency of fetal abnormalities was also increased. Doses in excess of 100 µg/kg must be considered teratogenic in the rat.

Daily doses of 0.01, 0.05 and 0.1-0.25 mg/kg were administered by inhalation to pregnant rats during days 6-15 of gestation. At the highest dose a slight significant reduction in fetal weight gain was observed, but there was no evidence of any effect on fetal development attributable to budesonide at any dose level.

Rabbit

Daily doses of 5, 25, and 125 µg/kg body mass were administered subcutaneously during days 6-18 of gestation. In the low and medium dose groups, food consumption and body mass gain were decreased during the fourth gestational week.

Some does also showed signs of diarrhea and vaginal bleeding. In the high dose group, all does aborted at the end of the gestation period. In the medium dose group, a marked increase in the frequency of abnormalities, mainly skeletal defects, was observed. Most commonly, defects were skull and vertebral abnormalities.

Effects on Fertility and General Reproductive Performance

Rat

To evaluate the effect of budesonide on fertility and general reproductive performance, daily doses of 0.01, 0.05, 0.19 µmol/kg were given subcutaneously to males for 9 weeks prior to and throughout mating. Females received the same doses for two weeks before, throughout gestation and up to 21 days postpartum. The offspring of the high dose group showed a decrease of peri- and post-natal viability. Dams showed a decrease in body mass gain.

Mutagenicity Studies

Budesonide showed no mutagenic activity in the Ames Salmonella/microsome plate test or in the mouse micronucleus test.

Carcinogenicity

The carcinogenic potential of budesonide was evaluated in long term mouse and rat studies.

Chronic Drinking Water Study in Mice

Budesonide was administered in the drinking water for 91 weeks to three groups of CD[®]-1 mice at dose levels of 10, 50 and 200 µg/kg/day.

A statistically significant dose-related decrease in survival was noted for the males only. All other evaluation criteria were comparable in all groups. Upon microscopic examination, a variety of spontaneous lesions was observed which were not related to treatment. No carcinogenic effect was present.

Chronic Drinking Water Study (104 Weeks) with Budesonide in Rats

Three rat carcinogenicity studies have been performed. In the first study, budesonide was administered for 104 weeks in doses of 10, 25 and 50 µg/kg/day.

A small but statistically significant increase in gliomas was noted in male animals from the high dose group. These results were considered equivocal since the S-D rat is very variable with regard to spontaneous glioma incidence.

To elucidate these results, two further 104 week carcinogenicity studies with budesonide 50 µg/kg/day were performed, one using male S-D rats, and one using male Fischer rats (which have a lower and less variable incidence of gliomas). Prednisolone and triamcinolone acetone were used as reference glucocorticosteroids in both studies.

The results from these new carcinogenicity studies in male rats did not demonstrate an increased glioma incidence in budesonide treated animals, as compared to concurrent controls or reference glucocorticosteroid treated groups.

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