

PRODUCT MONOGRAPH

 **RHINOCORT[®] TURBUHALER[®]**

budesonide

Powder for Nasal Inhalation
100 µg/metered dose

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

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PRODUCT MONOGRAPH

NAME OF DRUG

Pr **RHINOCORT[®] TURBUHALER[®]**

(budesonide)

Powder for Nasal Inhalation
100 µg/metered dose

THERAPEUTIC CLASSIFICATION

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

ACTIONS AND CLINICAL PHARMACOLOGY

RHINOCORT TURBUHALER contains pure budesonide which is a potent synthetic glucocorticosteroid with strong topical and weak systemic effects.

RHINOCORT TURBUHALER 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 TURBUHALER is 22%. 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 800 µg budesonide from RHINOCORT TURBUHALER is 1.1 nmol/L and is reached within 0.4 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 the prevention of nasal polyps after polypectomy.

CONTRAINDICATIONS

- Hypersensitivity to budesonide;
- 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

In transferring patients from a systemic steroid to RHINOCORT TURBUHALER, 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 TURBUHALER therapy is not achieved until 2 to 3 days of treatment have been completed. In rare cases the full effect of RHINOCORT TURBUHALER 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.

During long-term therapy, pituitary-adrenal function, hematological status and height (in children) should be periodically assessed.

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

Glucocorticosteroids may mask some signs of infection and new infections may appear during their use. A decreased resistance to localized infections has been observed during glucocorticosteroid therapy; this may require treatment with appropriate therapy or stopping the administration of RHINOCORT TURBUHALER.

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 RHINOCORT TURBUHALER are still unknown, in particular, its local effects; 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 TURBUHALER, as after inhalation, 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 blood-placenta 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 TURBUHALER to women who are breastfeeding should only be considered if the expect benefit to the mother is greater than any possible risk to the child.

Children Under 6 Years of Age

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

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

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

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 TURBUHALER (see INFORMATION FOR THE CONSUMER).

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 corticosteroid side-effects.

Omeprazole

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

ADVERSE REACTIONS

The adverse reactions reported with RHINOCORT TURBUHALER are consistent with what one would expect when applying a topical treatment to an already inflamed membrane. All side effects are 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 TURBUHALER 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 TURBUHALER. 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 TURBUHALER 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 TURBUHALER. Initially, RHINOCORT TURBUHALER 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

Initial Dose - Adults

Two applications into each nostril in the morning (total daily dose: 400 µg).

Children (6 Years and Older)

Two applications into each nostril in the morning (total daily dose: 400 µg). This dose should not be exceeded in children.

Maintenance Dose - Adults and Children (6 Years and Older)

Use the lowest effective dose necessary to control symptoms.

Children Under 6 Years

Not recommended for children in this age group.

Treatment or Prevention of Nasal Polyps

Dose: One application (100 µg) into each nostril, morning and evening (total daily dose 400 µg).

Patients should be informed that the full effect of RHINOCORT TURBUHALER 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 co-operation 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 six 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 TURBUHALER therapy.

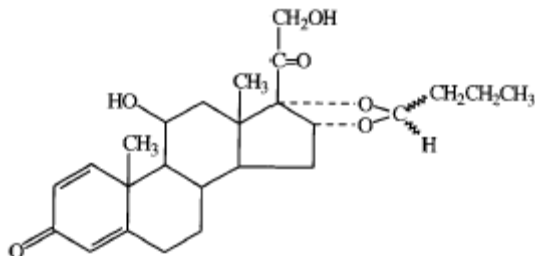
The patient may not taste or feel any medication when using RHINOCORT TURBUHALER due to the small amount of drug dispensed.

Although systemic effects are negligible at recommended doses, RHINOCORT TURBUHALER treatment should not be continued beyond three weeks in the absence of significant symptomatic improvement. RHINOCORT TURBUHALER 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 100 μ g

Non-medicinal: none

Stability and Storage Recommendations

RHINOCORT TURBUHALER should be stored with the cover tightened, at room temperature (15-30°C).

AVAILABILITY OF DOSAGE FORMS

RHINOCORT TURBUHALER is a dry powder inhaler containing 200 doses of 100 μ g of micronized budesonide. Each inhalation from TURBUHALER will provide 100 μ g of budesonide active substance; no additives or carrier substances are included. RHINOCORT TURBUHALER cannot be refilled and should be discarded when finished.

INFORMATION FOR THE CONSUMER
IMPORTANT INFORMATION YOU SHOULD KNOW ABOUT

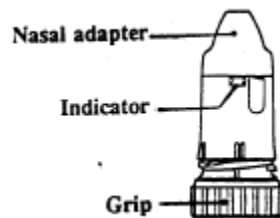
Pr **RHINOCORT® TURBUHALER®**

budesonide (powder for nasal inhalation)

BEFORE using RHINOCORT TURBUHALER, please read this leaflet carefully. It contains general points about RHINOCORT TURBUHALER 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 TURBUHALER.

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



RHINOCORT is a brand name for a drug called budesonide. RHINOCORT is a nasal inhalation form of the drug budesonide. It belongs to a group of medicines called corticosteroids which are used to reduce inflammation. Rhinitis is caused by inflammation of the nasal mucosa. RHINOCORT TURBUHALER reduces and prevents this inflammation. In some cases, 1-2 weeks of regular use may be needed before the full effect is seen. RHINOCORT TURBUHALER can also be used to treat nasal polyps and/or prevent new nasal polyps from appearing again after surgery (polypectomy).

TURBUHALER is the brand name for a multiple-dose, dry-powder inhaler. When you breathe in through the inhaler, your indrawn breath provides the necessary force to deliver the drug to your nasal passages.

WHAT IS IN RHINOCORT TURBUHALER?

RHINOCORT TURBUHALER contains budesonide as the active ingredient and comes in one strength: 100 µg per inhalation.

If you happen to shake the inhaler, the sound you hear is the drying agent built into the turning grip. This is not the medication and cannot be inhaled. RHINOCORT TURBUHALER contains no other ingredients.

WHAT SHOULD I TELL MY DOCTOR BEFORE TAKING RHINOCORT TURBUHALER?

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";
- 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 TURBUHALER.

HOW DO I TAKE RHINOCORT TURBUHALER PROPERLY?

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

NOTE: You may not taste or feel any medication when inhaling from RHINOCORT TURBUHALER. This is common.

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

Using the inhaler

To administer a dose, simply follow the instructions below.

Fig. 1



Fig. 2



Blow your nose. Unscrew and lift off the cover.

TURN

Hold the inhaler upright with the grip downwards (Fig. 1). To load the inhaler with a dose **turn the grey grip as far as it will go in one direction and then back to the original position.**

CLICK

The "click" you heard means the inhaler is ready to use. **Breathe out.** Do not breathe out through the nasal adapter.

INHALE

Place the nasal adapter so the nostril fits tightly around the adapter and block the opposite nostril with a finger. Sniff **quickly** and

forcefully (Fig. 2).

Remove RHINOCORT TURBUHALER from your nose, before breathing out.

Repeat the above steps for the other nostril. Replace the cover and screw it shut.

If you accidentally drop, shake or breathe out into RHINOCORT TURBUHALER after it is loaded, you will lose your dose. If this happens, you should load a new dose and inhale it.

Cleaning: Clean the outside of the nasal adapter once a week with a **dry** tissue. **Never** use water or any other fluid for cleaning the nasal adapter. If fluid enters RHINOCORT TURBUHALER it may not work properly.

HOW DO I KNOW WHEN RHINOCORT TURBUHALER IS EMPTY?



Approx. 20 doses left

DISCARD

RHINOCORT TURBUHALER has a dose indicator. When a red mark first appears in the little window underneath the nasal adapter, there are approximately 20 doses left. Now is the time to obtain your next inhaler.

When the red mark reaches the bottom of the window, you should discard your inhaler. The sound you hear when you shake the inhaler is produced by a drying agent, not the medication. RHINOCORT TURBUHALER cannot be re-filled with drug and should be discarded.

HOW MUCH RHINOCORT TURBUHALER SHOULD I TAKE?

The dosage of RHINOCORT TURBUHALER is individual.

Follow your doctor's directions carefully. They may differ from the information in this leaflet.

IMPORTANT: DO NOT EXCEED THE DOSE PRESCRIBED BY YOUR DOCTOR.

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

Rhinitis

Initial Dose: **Adults:** Two applications into each nostril in the morning (total daily dose: 400 µg). **Children** (6 years and older): Two applications into each nostril in the morning (total daily dose: 400 µg). This dose should not be exceeded in children.

Maintenance Dose: Adults and Children (6 years and older): Use the lowest effective dose necessary to control symptoms.

Nasal Polyps

One application (100 µg) into each nostril, morning and evening (total daily dose: 400 µg).

CAUTION: RHINOCORT TURBUHALER is not intended to give immediate relief of your nasal symptoms and 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,
- nasal irritation occurs,
- coloured (yellow or green) nasal secretions appear,
- repeated nasal bleeding occurs.

WHAT DO I DO IF I MISS A DOSE?

Rhinitis

If you miss a dose of RHINOCORT TURBUHALER and remember within 12 hours, you should take your usual dose as soon as possible. Then go back to your regular schedule. If it is more than 12 hours when you remember, do not take the missed dose. Just take the next dose on time.

Nasal Polyps

If you miss a dose of RHINOCORT TURBUHALER and remember within 6 hours, you should take your usual dose as soon as possible. Then go back to your regular schedule. If it is more than 6 hours when you remember, do not take the missed dose. Just take the next dose on time.

Never take a double dose of RHINOCORT TURBUHALER to make up for a missed dose. 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 TURBUHALER. However, several weeks may pass before the full effect is achieved. Don't forget to take it even when you feel well.

Treatment with RHINOCORT TURBUHALER should not be stopped abruptly, but tapered off gradually. Follow your doctor's directions.

If you have been prescribed RHINOCORT TURBUHALER and are still using "cortisone" tablets, your doctor may gradually (over a period of weeks or months) reduce your dose of tablets. You may even be able to eventually stop using the tablets.

NOTE: If your medication is changed from "cortisone" tablets to RHINOCORT TURBUHALER, you may temporarily regain symptoms which may have bothered you earlier, e.g. runny nose, rash, pain in muscle and joints. If any of these symptoms bothers you, or if you get symptoms such as headache, tiredness, nausea or vomiting, contact your doctor.

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 TURBUHALER.

ARE THERE ANY SIDE EFFECTS?

Like any medication, RHINOCORT TURBUHALER may cause side effects in some people.

Common side effects include: 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 like skin rash may occur in association with local corticosteroid therapy. Very few people who have used steroids in the nose, such as RHINOCORT TURBUHALER, 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, contact your doctor.

WHERE SHOULD I KEEP RHINOCORT TURBUHALER?

Remember to keep RHINOCORT TURBUHALER out of the reach of children.

Always replace the cover after using RHINOCORT TURBUHALER. Store the inhaler at room temperature (15-30°C) in a dry place, away from moisture.

Do not keep or use RHINOCORT TURBUHALER 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 TURBUHALER.

NOTE: This INFORMATION FOR THE CONSUMER 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

L4Y 1M4

Last Revised: December 23, 2008

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 availability of oral budesonide in man is low (about 10%). With reference to the metered dose, the systemic availability of budesonide from RHINOCORT TURBUHALER is 22%. The maximal plasma concentration after administration of 800 µg budesonide from RHINOCORT TURBUHALER is 1.1 nmol/L and is reached within 0.4 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 $88.3 \pm 1.5\%$.

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