

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 20-441/S-018

NDA 20-746/S-011

NDA 20-929/S-015

Trade Name: Pulmicort Turbohaler; Rhinocort Aqua Nasal Spray;
and Pulmicort Respules

Generic Name: budesonide inhalation powder; budesonide; and
budesonide inhalation suspension

Sponsor: AstraZeneca LP

Approval Date: September 26, 2003

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APPLICATION NUMBER:

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NDA 20-929/S0-15

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-441/S-018, 20-746/S-011 and 20-929/S-015

AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Christopher Blango
Director, Regulatory Affairs

Dear Mr. Blango:

Please refer to your supplemental new drug applications dated March 25, 2003, received March 26, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Turbuhaler (budesonide inhalation powder), Rhinocort Aqua (budesonide) Nasal Spray and Pulmicort Respules (budesonide inhalation suspension), respectively.

These "Changes Being Effected" supplemental new drug applications provide for revisions to the Drug Interactions subsection of the PRECAUTIONS section of the package insert.

We completed our review of these supplemental new drug applications. They are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on March 25, 2003.

We remind you that you must submit patent information on form FDA 3542, *Patent Information Submitted Upon and After Approval of an NDA or Supplement*, within 30 days of the date of this letter as required by 21 CFR 314.53(c)(2)(ii) and 314.53(d)(2) at the address provided by 21 CFR 314.53(d)(4). The form may be obtained at <http://www.fda.gov/opacom/morechoices/fdaforms/cder.html>. To expedite review of this patent declaration form, we request you submit an additional copy of the form to these applications and to the Center for Drug Evaluation and Research "Orange Book" staff at

Food and Drug Administration
Office of Generic Drugs, HFD-610
Orange Book Staff
7500 Standish Place
Metro Park North II
Rockville, MD 20855-2773

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Colette Jackson, Regulatory Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Division Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Badrul Chowdhury
9/26/03 04:57:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-441/S-018

NDA 20-746/S-011

NDA 20-929/S-015

APPROVED LABELING

808179-02

PULMICORT TURBUHALER 200 mcg

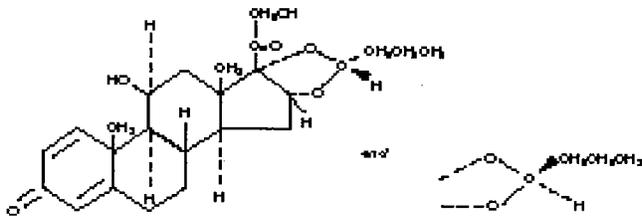
(budesonide inhalation powder)

For Oral Inhalation Only.

Rx only

DESCRIPTION

Budesonide, the active component of PULMICORT TURBUHALER 200 mcg, is a corticosteroid designated chemically as (RS)-11 β , 16 α , 17,21-Tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C₂₅H₃₄O₆ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3 .

PULMICORT TURBUHALER is an inhalation-driven multi-dose dry powder inhaler which contains only micronized budesonide. Each actuation of PULMICORT TURBUHALER provides 200 mcg budesonide per metered dose, which delivers approximately 160 mcg budesonide from the mouthpiece (based on *in vitro* testing at 60 L/min for 2 sec).

In vitro testing has shown that the dose delivery for PULMICORT TURBUHALER is substantially dependent on airflow through the device. Patient factors such as inspiratory flow rates will also affect the dose delivered to the lungs of patients in actual use (see *Patient's Instructions for Use*). In adult patients with asthma (mean FEV₁ 2.9 L [0.8 - 5.1 L]) mean peak inspiratory flow (PIF) through PULMICORT TURBUHALER was 78 (40-111) L/min. Similar results (mean PIF 82 [43-125] L/min) were obtained in asthmatic children (6 to 15 years, mean FEV₁ 2.1 L [0.9 - 5.4 L]). Patients should be carefully instructed on the use of this drug product to assure optimal dose delivery.

CLINICAL PHARMACOLOGY

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The precise mechanism of corticosteroid actions on inflammation in asthma is not known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic and non-allergic-mediated inflammation. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activity and systemic corticosteroid effects over a wide range of doses from PULMICORT TURBUHALER. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%), and the low potency of formed metabolites (see below).

Pharmacokinetics

The activity of PULMICORT TURBUHALER is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert. The 22R form was preferentially cleared by the liver with systemic clearance of 1.4 L/min vs. 1.0 L/min for the 22S form. The terminal half-life, 2 to 3 hours, was the same for both epimers and was independent of dose. In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both a single dose and repeated dosing from PULMICORT TURBUHALER.

Absorption: After oral administration of budesonide, peak plasma concentration was achieved in about 1 to 2 hours and the absolute systemic availability was 6-13%. In contrast, most of budesonide delivered to the lungs is systemically absorbed. In healthy subjects, 34% of the metered dose was deposited in the lungs (as assessed by plasma concentration method) with an absolute systemic availability of 39% of the metered dose. Pharmacokinetics of budesonide do not differ significantly in healthy volunteers and asthmatic patients. Peak plasma concentrations of budesonide occurred within 30 minutes of inhalation from PULMICORT TURBUHALER.

Distribution: The volume of distribution of budesonide was approximately 3 L/kg. It was 85-90% bound to plasma proteins. Protein binding was constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended doses of PULMICORT TURBUHALER. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism: *In vitro* studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16 α -hydroxyprednisolone and 6 β -hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative differences between the *in vitro* and *in vivo* metabolic patterns have been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion: Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabelled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special Populations: No pharmacokinetic differences have been identified due to race, gender or advanced age.

Pediatric: Following intravenous dosing in pediatric patients age 10-14 years, plasma half-life was shorter than in adults (1.5 hours vs. 2.0 hours in adults). In the same population following inhalation of budesonide via a pressurized metered-dose inhaler, absolute systemic availability was similar to that in adults.

Hepatic Insufficiency: Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy subjects.

Drug-drug Interactions: Ketoconazole, a potent inhibitor of cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide. At recommended doses, cimetidine had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

Pharmacodynamics

To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered-dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract.

Generally, PULMICORT TURBUHALER has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhalation of PULMICORT TURBUHALER can occur within 24 hours of beginning treatment although maximum benefit may not be achieved for 1 to 2 weeks, or longer.

PULMICORT TURBUHALER has been shown to decrease airway reactivity to various challenge models, including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate in hyperreactive patients. The clinical relevance of these models is not certain.

Pretreatment with PULMICORT TURBUHALER 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV₁ following inhaled allergen challenge.

The effects of PULMICORT TURBUHALER on the hypothalamic-pituitary-adrenal (HPA) axis were studied in 905 adults and 404 pediatric patients with asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by cosyntropin (ACTH) stimulation test, remained intact with PULMICORT TURBUHALER treatment at recommended doses. For adult patients treated with 100, 200, 400, or 800 mcg twice daily for 12 weeks, 4%, 2%, 6%, and 13% respectively, had an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography following short-cosyntropin test) as compared to 8% of patients treated with placebo. Similar results were obtained in pediatric patients. In another study in adults, doses of 400, 800 and 1600 mcg budesonide twice daily via PULMICORT TURBUHALER for 6 weeks were examined; 1600 mcg twice daily (twice the maximum recommended dose) resulted in a 27% reduction in stimulated cortisol (6-hour ACTH infusion) while 10 mg prednisone resulted in a 35% reduction. In this study, no patient on PULMICORT TURBUHALER at doses of 400 and 800 mcg twice daily met the criterion for an abnormal stimulated cortisol response (peak cortisol <14.5 mcg/dL assessed by liquid chromatography) following ACTH infusion. An open-label, long-term follow-up of 1133 patients for up to 52 weeks confirmed the minimal effect on the HPA axis (both basal and stimulated plasma cortisol) of PULMICORT TURBUHALER when administered at recommended doses. In patients who had previously been oral steroid-dependent, use of PULMICORT TURBUHALER in recommended doses was associated with higher stimulated cortisol response compared to baseline following 1 year of therapy.

The administration of budesonide via PULMICORT TURBUHALER in doses up to 800 mcg/day (mean daily dose 445 mcg/day) or via a pressurized metered-dose inhaler in doses up to 1200 mcg/day (mean daily dose 620 mcg/day) to 216 pediatric patients (age 3 to 11 years) for 2 to 6 years had no significant effect on statural growth compared with non-corticosteroid therapy in 62 matched control patients. However, the long-term effect of PULMICORT TURBUHALER on growth is not fully known.

CLINICAL TRIALS

The therapeutic efficacy of PULMICORT TURBUHALER has been evaluated in controlled clinical trials involving more than 1300 patients (6 years and older) with asthma of varying disease duration (<1 year to >20 years) and severity.

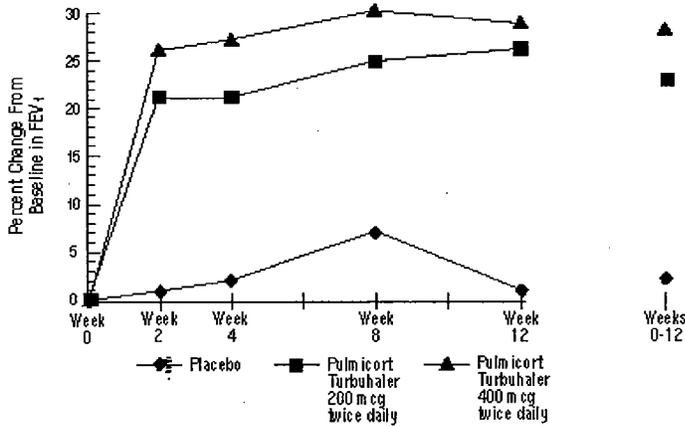
Double-blind, parallel, placebo-controlled clinical trials of 12 weeks duration and longer have shown that, compared with placebo, PULMICORT TURBUHALER significantly improved lung function (measured by PEF and FEV₁), significantly decreased morning and evening symptoms of asthma, and significantly reduced the need for as-needed inhaled β_2 -agonist use at doses of 400 mcg to 1600 mcg per day (200 mcg to 800 mcg twice daily) in adults and 400 mcg to 800 mcg per day (200 mcg to 400 mcg twice daily) in pediatric patients 6 years of age and older.

Improved lung function (morning PEF) was observed within 24 hours of initiating treatment in both adult and pediatric patients 6 years of age and older, although maximum benefit was not achieved for 1 to 2 weeks, or longer, after starting treatment. Improved lung function was maintained throughout the 12 weeks of the double-blind portion of the trials.

Patients Not Receiving Corticosteroid Therapy

In a 12-week clinical trial in 273 patients with mild to moderate asthma (mean baseline FEV₁ 2.27 L) who were not well controlled by bronchodilators alone, PULMICORT TURBUHALER was evaluated at doses of 200 mcg twice daily and 400 mcg twice daily versus placebo. The FEV₁ results from this trial are shown in the figure below. Pulmonary function improved significantly on both doses of PULMICORT TURBUHALER compared with placebo.

A 12-Week Trial in Patients Not on Corticosteroid Therapy Prior to Study Entry

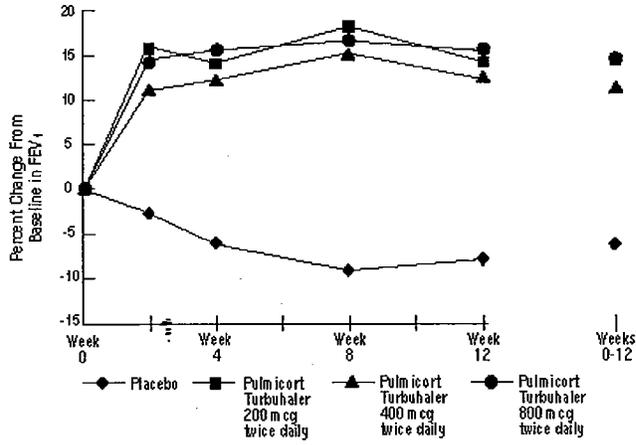


In a 12-month controlled trial in 75 patients not previously receiving corticosteroids, PULMICORT TURBUHALER at 200 mcg twice daily resulted in improved lung function (measured by PEF) and reduced bronchial hyperreactivity compared to placebo.

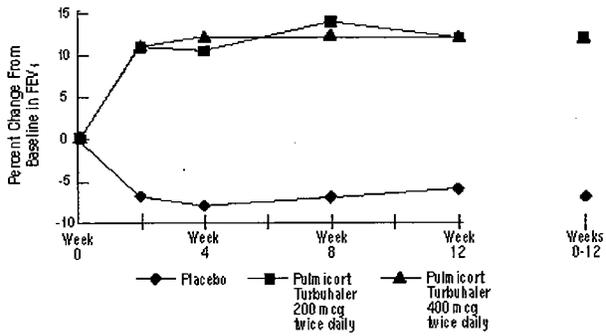
Patients Previously Maintained on Inhaled Corticosteroids

The safety and efficacy of PULMICORT TURBUHALER was also evaluated in adult and pediatric patients (age 6 to 18 years) previously maintained on inhaled corticosteroids (adults: N=473, mean baseline FEV₁ 2.04 L, baseline doses of beclomethasone dipropionate 126-1008 mcg/day; pediatrics: N=404, mean baseline FEV₁ 2.09 L, baseline doses of beclomethasone dipropionate 126-672 mcg/day or triamcinolone acetonide 300-1800 mcg/day). The FEV₁ results of these two trials, both 12 weeks in duration, are presented in the following figures. Pulmonary function improved significantly with all doses of PULMICORT TURBUHALER compared to placebo in both trials.

Adult Patients Previously Maintained on Inhaled Corticosteroids



Pediatric Patients Age 6 to 18 Years Previously Maintained on Inhaled Corticosteroids



Patients Receiving PULMICORT TURBUHALER Once Daily

The efficacy and safety of once-daily administration of PULMICORT TURBUHALER 200 mcg and 400 mcg and placebo were also evaluated in 309 adult asthmatic patients (mean baseline FEV₁ 2.7 L) in an 18-week study. Compared with placebo, patients receiving Pulmicort 200 or 400 mcg once daily showed significantly better asthma stability as assessed by PEF and FEV₁ over an initial 6-week treatment period, which was maintained with a 200 mcg daily dose over the subsequent 12 weeks. Although the study population included both patients previously treated with inhaled corticosteroids, as well as patients not previously receiving corticosteroid therapy, the results showed that once-daily dosing was most clearly effective for those patients previously maintained on orally inhaled corticosteroids (see DOSAGE AND ADMINISTRATION).

Patients Previously Maintained on Oral Corticosteroids

In a clinical trial in 159 severe asthmatic patients requiring chronic oral prednisone therapy (mean baseline prednisone dose 19.3 mg/day) PULMICORT TURBUHALER at doses of 400 mcg twice daily and 800 mcg twice daily was compared to placebo over a 20-week period. Approximately two-thirds (68% on 400 mcg twice daily and 64% on 800 mcg twice daily) of PULMICORT TURBUHALER-treated patients were able to achieve sustained (at least 2 weeks) oral corticosteroid cessation (compared with 8% of placebo-treated patients) and improved asthma control. The average oral corticosteroid dose was reduced by 83% on 400 mcg twice daily and 79% on 800 mcg twice daily for PULMICORT TURBUHALER-treated patients vs. 27% for placebo. Additionally, 58 out of 64 patients (91%) who completely eliminated oral corticosteroids during the double-blind phase of the trial remained off oral corticosteroids for an additional 12 months while receiving PULMICORT TURBUHALER.

INDICATIONS AND USAGE

PULMICORT TURBUHALER is indicated for the maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients six years of age or older. It is also indicated for patients requiring oral corticosteroid therapy for asthma. Many of those patients may be able to reduce or eliminate their requirement for oral corticosteroids over time.

PULMICORT TURBUHALER is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

PULMICORT TURBUHALER is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to budesonide contraindicates the use of PULMICORT TURBUHALER.

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to PULMICORT TURBUHALER because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although PULMICORT TURBUHALER may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of glucocorticoid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instruction. These patients should also be instructed to carry a medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic corticosteroid therapy to PULMICORT TURBUHALER may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, and eczema (see DOSAGE AND ADMINISTRATION).

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

PULMICORT TURBUHALER is not a bronchodilator and is not indicated for rapid relief of bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If bronchospasm occurs following dosing with PULMICORT TURBUHALER, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with PULMICORT TURBUHALER should be discontinued and alternate therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with PULMICORT TURBUHALER. During such episodes, patients may require therapy with oral corticosteroids.

PRECAUTIONS

General: During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

PULMICORT TURBUHALER will often permit control of asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active at higher doses, the full beneficial effects of PULMICORT TURBUHALER in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing PULMICORT TURBUHALER.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients postoperatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, PULMICORT TURBUHALER should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

A reduction of growth velocity in children or teenagers may occur as a result of inadequate control of chronic diseases such as asthma or from use of corticosteroids for treatment. Physicians should closely follow the growth of all pediatric patients taking corticosteroids by any route and weigh the benefits of corticosteroid therapy and asthma control against the possibility of growth suppression (see PRECAUTIONS, Pediatric Use).

Although patients in clinical trials have received PULMICORT TURBUHALER on a continuous basis for periods of 1 to 2 years, the long-term local and systemic effects of PULMICORT TURBUHALER in human subjects are not completely known. In particular, the effects resulting from chronic use of PULMICORT TURBUHALER on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown.

In clinical trials with PULMICORT TURBUHALER, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while still continuing with PULMICORT TURBUHALER therapy, but at times therapy with PULMICORT TURBUHALER may need to be temporarily interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral or parasitic infections, or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

Information for Patients: For proper use of PULMICORT TURBUHALER and to attain maximum improvement, the patient should read and follow the accompanying *Patient's Instructions for Use* carefully. In addition, patients being treated with PULMICORT TURBUHALER should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects.

- Patients should use PULMICORT TURBUHALER at regular intervals as directed since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.
- PULMICORT TURBUHALER is not a bronchodilator and is not intended to treat acute or life-threatening episodes of asthma.

- PULMICORT TURBUHALER must be in the upright position (mouthpiece on top) during loading in order to provide the correct dose. PULMICORT TURBUHALER must be primed when the unit is used for the very first time. To prime the unit, hold the unit in an upright position and turn the brown grip fully to the right, then fully to the left until it clicks. Repeat. The unit is now primed and ready to load the first dose by turning the grip fully to the right and fully to the left until it clicks.

On subsequent uses, it is not necessary to prime the unit. However, it must be loaded in the upright position immediately prior to use. Turn the brown grip fully to the right, then fully to the left until it clicks. During inhalation, PULMICORT TURBUHALER must be held in the upright (mouthpiece up) or horizontal position. Do not shake the inhaler. Place the mouthpiece between lips and inhale forcefully and deeply. The powder is then delivered to the lungs.

- Patients should not exhale through PULMICORT TURBUHALER.
- Due to the small volume of powder, the patient may not taste or sense the presence of any medication entering the lungs when inhaling from the TURBUHALER inhaler. This lack of "sensation" does not indicate that the patient is not receiving benefit from PULMICORT TURBUHALER.
- Rinsing the mouth with water without swallowing after each dosing may decrease the risk of the development of oral candidiasis.
- When there are 20 doses remaining in PULMICORT TURBUHALER, a red mark will appear in the indicator window.
- PULMICORT TURBUHALER should not be used with a spacer.
- The mouthpiece should not be bitten or chewed.
- The cover should be replaced securely after each opening.
- Keep PULMICORT TURBUHALER clean and dry at all times.
- Improvement in asthma control following inhalation of PULMICORT TURBUHALER can occur within 24 hours of beginning treatment although maximum benefit may not be achieved for 1 to 2 weeks, or longer. If symptoms do not improve in that time frame, or if the condition worsens, the patient should be instructed to contact the physician.
- Patients should be warned to avoid exposure to chicken pox or measles and if they are exposed, to consult their physicians without delay.

- For proper use of PULMICORT TURBUHALER and to attain maximum improvement, the patient should read and follow the accompanying *Patient's Instructions for Use*.

Drug Interactions: In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of other known inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known CYP3A4 inhibitors.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies were conducted in mice and rats using oral administration to evaluate the carcinogenic potential of budesonide.

There was no evidence of a carcinogenic effect when budesonide was administered orally for 91 weeks to mice at doses up to 200 mcg/kg/day (approximately $\frac{1}{2}$ the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis).

In a 104-week oral study in Sprague-Dawley rats, a statistically significant increase in the incidence of gliomas was observed in male rats receiving an oral dose of 50 mcg/kg/day (approximately $\frac{1}{4}$ the maximum recommended daily inhalation dose on a mcg/m² basis); no such changes were seen in male rats receiving oral doses of 10 and 25 mcg/kg/day (approximately $\frac{1}{20}$ and $\frac{1}{40}$ the maximum recommended daily inhalation dose on a mcg/m² basis) or in female rats at oral doses up to 50 mcg/kg/day (approximately $\frac{1}{4}$ the maximum recommended human daily inhalation dose on a mcg/m² basis).

Two additional 104-week carcinogenicity studies have been performed with oral budesonide at doses of 50 mcg/kg/day (approximately ? the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis) in male Sprague-Dawley and Fischer rats. These studies did not demonstrate an increased glioma incidence in budesonide-treated animals as compared with concurrent controls or reference corticosteroid-treated groups (prednisolone and triamcinolone acetonide). Compared with concurrent controls, a statistically significant increase in the incidence of hepatocellular tumors was observed in all three steroid groups (budesonide, prednisolone, triamcinolone acetonide) in these studies.

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

The effect of subcutaneous budesonide on fertility and general reproductive performance was studied in rats. At 20 mcg/kg/day (approximately ? the maximum recommended daily inhalation dose in adults on a mcg/m² basis), decreases in maternal body weight gain, prenatal viability, and viability of the young at birth and during lactation were observed. No such effects were noted at 5 mcg/kg (approximately 1/32 the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

Pregnancy: Teratogenic Effects: Pregnancy Category B: As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (approximately ? the maximum recommended daily inhalation dose in adults on a mcg/m² basis) and 500 mcg/kg/day in rats (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

No teratogenic or embryocidal effects were observed in rats when budesonide was administered by inhalation at doses up to 250 mcg/kg/day (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

Experience with oral corticosteroids since their introduction in pharmacologic as opposed to physiologic doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Studies of pregnant women, however, have not shown that PULMICORT TURBUHALER increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (i.e., Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2,014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8 % vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).

These same data were utilized in a second study bringing the total to 2,534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, PULMICORT TURBUHALER should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: Corticosteroids are secreted in human milk. Because of the potential for adverse reactions in nursing infants from any corticosteroid, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Actual data for budesonide are lacking.

Pediatric Use: Safety and effectiveness of PULMICORT TURBUHALER in pediatric patients below 6 years of age have not been established.

In pediatric asthma patients the frequency of adverse events observed with PULMICORT TURBUHALER was similar between the 6- to 12-year age group (N=172) compared with the 13- to 17-year age group (N=124).

Oral corticosteroids have been shown to cause growth suppression in pediatric and adolescent patients, particularly with higher doses over extended periods. If a pediatric or adolescent patient on any corticosteroid appears to have growth suppression, the possibility that they are particularly sensitive to this effect of corticosteroids should be considered (see PRECAUTIONS).

Geriatric Use: One hundred patients 65 years or older were included in the US and non-US controlled clinical trials of PULMICORT TURBUHALER. There were no differences in the safety and efficacy of the drug compared to those seen in younger patients.

ADVERSE REACTIONS

The following adverse reactions were reported in patients treated with PULMICORT TURBUHALER.

The incidence of common adverse events is based upon double-blind, placebo-controlled US clinical trials in which 1116 adult and pediatric patients age 6-70 years (472 females and 644 males) were treated with PULMICORT TURBUHALER (200 to 800 mcg twice daily for 12 to 20 weeks) or placebo.

The following table shows the incidence of adverse events in patients previously receiving bronchodilators and/or inhaled corticosteroids in US controlled clinical trials. This population included 232 male and 62 female pediatric patients (age 6 to 17 years) and 332 male and 331 female adult patients (age 18 years and greater).

Adverse Events with $\geq 3\%$ Incidence reported by Patients on PULMICORT TURBUHALER				
Adverse Event	Placebo N=284 %	PULMICORT TURBUHALER		
		200 mcg twice daily N=286 %	400 mcg twice daily N=289 %	800 mcg twice daily N=98 %
Respiratory System				
Respiratory infection	17	20	24	19
Pharyngitis	9	10	9	5
Sinusitis	7	11	7	2
Voice alteration	0	1	2	6
Body As A Whole				
Headache	7	14	13	14
Flu syndrome	6	6	6	14
Pain	2	5	5	5
Back pain	1	2	3	6
Fever	2	2	4	0
Digestive System				
Oral candidiasis	2	2	4	4
Dyspepsia	2	1	2	4
Gastroenteritis	1	1	2	3
Nausea	2	2	1	3
Average Duration of Exposure (days)	59	79	80	80

The table above includes all events (whether considered drug-related or non-drug-related by the investigators) that occurred at a rate of $\geq 3\%$ in any one PULMICORT TURBUHALER group and were more common than in the placebo group. In considering these data, the increased average duration of exposure for PULMICORT TURBUHALER patients should be taken into account.

The following other adverse events occurred in these clinical trials using PULMICORT TURBUHALER with an incidence of 1 to 3% and were more common on PULMICORT TURBUHALER than on placebo.

Body As A Whole: neck pain
Cardiovascular: syncope
Digestive: abdominal pain, dry mouth, vomiting
Metabolic and Nutritional: weight gain
Musculoskeletal: fracture, myalgia
Nervous: hypertonia, migraine
Platelet, Bleeding and Clotting: ecchymosis
Psychiatric: insomnia
Resistance Mechanisms: infection
Special Senses: taste perversion

In a 20-week trial in adult asthmatics who previously required oral corticosteroids, the effects of PULMICORT TURBUHALER 400 mcg twice daily (N=53) and 800 mcg twice daily (N=53) were compared with placebo (N=53) on the frequency of reported adverse events. Adverse events, whether considered drug-related or non-drug-related by the investigators, reported in more than five patients in the PULMICORT TURBUHALER group and which occurred more frequently with PULMICORT TURBUHALER than placebo are shown below (% PULMICORT TURBUHALER and % placebo). In considering these data, the increased average duration of exposure for PULMICORT TURBUHALER patients (78 days for PULMICORT TURBUHALER vs. 41 days for placebo) should be taken into account.

Body As A Whole:	asthenia (9% and 2%) headache (12% and 2%) pain (10% and 2%)
Digestive:	dyspepsia (8% and 0%) nausea (6% and 0%) oral candidiasis (10% and 0%)
Musculoskeletal:	arthralgia (6% and 0%)
Respiratory:	cough increased (6% and 2%) respiratory infection (32% and 13%) rhinitis (6% and 2%) sinusitis (16% and 11%)

Patients Receiving PULMICORT TURBUHALER Once Daily

The adverse event profile of once-daily administration of PULMICORT TURBUHALER 200 mcg and 400 mcg, and placebo, was evaluated in 309 adult asthmatic patients in an 18-week study. The study population included both patients previously treated with inhaled corticosteroids, and patients not previously receiving corticosteroid therapy. There was no clinically relevant difference in the pattern of adverse events following once-daily administration of PULMICORT TURBUHALER when compared to twice-daily dosing.

Pediatric Studies: In a 12-week placebo-controlled trial in 404 pediatric patients 6 to 18 years of age previously maintained on inhaled corticosteroids, the frequency of adverse events for each age category (6 to 12 years, 13 to 18 years) was comparable for PULMICORT TURBUHALER (at 100, 200 and 400 mcg twice daily) and placebo. There were no clinically relevant differences in the pattern or severity of adverse events in children compared with those reported in adults.

Adverse Event Reports From Other Sources: Rare adverse events reported in the published literature or from marketing experience include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm; symptoms of hypocorticism and hypercorticism; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety and psychosis.

OVERDOSAGE

The potential for acute toxic effects following overdose of PULMICORT TURBUHALER is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur (see PRECAUTIONS). PULMICORT TURBUHALER at twice the highest recommended dose (3200 mcg daily) administered for 6 weeks caused a significant reduction (27%) in the plasma cortisol response to a 6-hour infusion of ACTH compared with placebo (+1%). The corresponding effect of 10 mg prednisone daily was a 35% reduction in the plasma cortisol response to ACTH.

The minimal inhalation lethal dose in mice was 100 mg/kg (approximately 320 times the maximum recommended daily inhalation dose in adults and approximately 380 times the maximum recommended daily inhalation dose in children on a mcg/m² basis). There were no deaths following the administration of an inhalation dose of 68 mg/kg in rats (approximately 430 times the maximum recommended daily inhalation dose in adults and approximately 510 times the maximum recommended daily inhalation dose in children on a mcg/m² basis). The minimal oral lethal dose was 200 mg/kg in mice (approximately 630 times the maximum recommended daily inhalation dose in adults and approximately 750 times the maximum recommended daily inhalation dose in children on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 630 times the maximum recommended daily inhalation dose in adults and approximately 750 times the maximum recommended daily inhalation dose in children based on a mcg/m² basis).

DOSAGE AND ADMINISTRATION

PULMICORT TURBUHALER should be administered by the orally inhaled route in asthmatic patients age 6 years and older. Individual patients will experience a variable onset and degree of symptom relief. Generally, PULMICORT TURBUHALER has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhaled administration of PULMICORT TURBUHALER can occur within 24 hours of initiation of treatment, although maximum benefit may not be achieved for 1 to 2 weeks, or longer. The safety and efficacy of PULMICORT TURBUHALER when administered in excess of recommended doses have not been established.

The recommended starting dose and the highest recommended dose of PULMICORT TURBUHALER, based on prior asthma therapy, are listed in the following table.

	Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults:	Bronchodilators alone	200 to 400 mcg twice daily	400 mcg twice daily
	Inhaled Corticosteroids*	200 to 400 mcg twice daily	800 mcg twice daily
	Oral Corticosteroids	400 to 800 mcg twice daily	800 mcg twice daily
Children:	Bronchodilators alone	200 mcg twice daily	400 mcg twice daily
	Inhaled Corticosteroids*	200 mcg twice daily	400 mcg twice daily
	Oral Corticosteroids	The highest recommended dose in children is 400 mcg twice daily	

*In patients with mild to moderate asthma who are well controlled on inhaled corticosteroids, dosing with PULMICORT TURBUHALER 200 mcg or 400 mcg once daily may be considered. PULMICORT TURBUHALER can be administered once daily either in the morning or in the evening.

If the once-daily treatment with PULMICORT TURBUHALER does not provide adequate control of asthma symptoms, the total daily dose should be increased and/or administered as a divided dose.

Patients Maintained on Chronic Oral Corticosteroids

Initially, PULMICORT TURBUHALER should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid is started by reducing the daily or alternate daily dose. The next reduction is made after an interval of one or two weeks, depending on the response of the patient. Generally, these decrements should not exceed 2.5 mg of prednisone or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for asthma instability, including objective measures of airway function, and for adrenal insufficiency (see WARNINGS). During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with PULMICORT TURBUHALER but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

NOTE: In all patients it is desirable to titrate to the lowest effective dose once asthma stability is achieved.

Patients should be instructed to prime PULMICORT TURBUHALER prior to its initial use, and instructed to inhale deeply and forcefully each time the unit is used. Rinsing the mouth after inhalation is also recommended.

Directions for Use: Illustrated *Patient's Instructions for Use* accompany each package of PULMICORT TURBUHALER.

HOW SUPPLIED

PULMICORT TURBUHALER consists of a number of assembled plastic details, the main parts being the dosing mechanism, the storage unit for drug substance and the mouthpiece. The inhaler is protected by a white outer tubular cover screwed onto the inhaler. The body of the inhaler is white and the turning grip is brown. The following wording is printed on the grip in raised lettering, "Pulmicort™ 200 mcg". The TURBUHALER inhaler cannot be refilled and should be discarded when empty.

PULMICORT TURBUHALER is available as 200 mcg/dose, 200 doses (NDC 0186-0915-42) and has a target fill weight of 104 mg.

When there are 20 doses remaining in PULMICORT TURBUHALER, a red mark will appear in the indicator window. If the unit is used beyond the point at which the red mark appears at the bottom of the window, the correct amount of medication may not be obtained. The unit should be discarded.

Store with the cover tightened in a dry place at controlled room temperature 20-25°C (68-77°F) [see USP]. Keep out of the reach of children.

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Manufactured for: AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca AB, Södertälje, Sweden

808179-02 Rev. 03/03

808201-05

RHINOCORT AQUA[®] (budesonide)

Nasal Spray 32 mcg

For Intranasal Use Only.

Rx only

DESCRIPTION

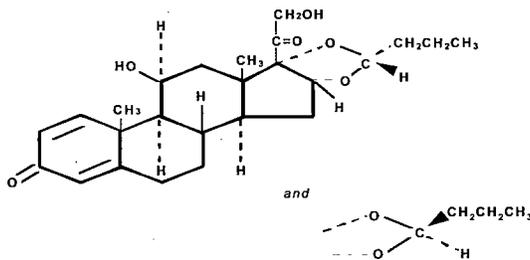
Budesonide, the active ingredient of RHINOCORT AQUA[®] Nasal Spray, is an anti-inflammatory synthetic corticosteroid.

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

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

The empirical formula of budesonide is C₂₅H₃₄O₆ and its molecular weight is 430.5.

Its structural formula is:



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

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

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

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

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

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

CLINICAL PHARMACOLOGY

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

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

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

Pharmacokinetics

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

Absorption

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

Distribution

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

Metabolism

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

Elimination

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

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

Special Populations

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

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

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

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

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

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

Pharmacodynamics

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

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

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

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

Clinical Trials

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

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

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

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

WARNINGS

The replacement of a systemic corticosteroid with a topical corticosteroid can be accompanied by signs of adrenal insufficiency, and in addition some patients may experience symptoms of corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression. Patients previously treated for prolonged periods with systemic corticosteroids and transferred to topical corticosteroids should be carefully monitored for acute adrenal insufficiency in response to stress. In those patients who have asthma or other clinical conditions requiring long-term systemic corticosteroid treatment, too rapid a decrease in systemic corticosteroids may cause a severe exacerbation of their symptoms.

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

PRECAUTIONS

General

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

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

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

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

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

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

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

Information for Patients

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

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

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

The patient should take the medication as directed and should not exceed the prescribed dosage. The patient should contact the physician if symptoms do not improve after two weeks, or if the condition worsens. Patients who experience recurrent episodes of epistaxis (nosebleeds) or nasal septum discomfort while taking this medication should contact their physician. For proper use of this unit and to attain maximum improvement, the patient should read and follow the accompanying patient instructions carefully.

It is important to shake the bottle well before each use. The RHINOCORT AQUA Nasal Spray 32 mcg bottle has been filled with an excess to accommodate the priming activity. The bottle should be discarded after 120 sprays following initial priming, since the amount of budesonide delivered per spray thereafter may be substantially less than the labeled dose. Do not transfer any remaining suspension to another bottle.

Drug Interactions

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

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in the male rats receiving an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (approximately equal to and two times the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis, respectively). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis). However, in male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (approximately twice the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately 3 times the maximum recommended daily intranasal dose in adults and children on a mcg/m² basis).

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

In rats, budesonide caused a decrease in prenatal viability and viability of the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended daily intranasal dose in adults on a mcg/m² basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily intranasal dose in adults on a mcg/m² basis).

Pregnancy

Teratogenic Effects: Pregnancy Category C: Budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits and 500 mcg/kg in rats (approximately 2 and 16 times the maximum recommended daily intranasal dose in adults on a mcg/m² basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 8 times the maximum recommended daily intranasal dose in adults on a mcg/m² basis).

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

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers

It is not known whether budesonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when RHINOCORT AQUA Nasal Spray is administered to nursing women.

Pediatric Use

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

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

Geriatric Use

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

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

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

Individualization of Dosage

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

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

Directions for Use

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

HOW SUPPLIED

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

NDC 0186-1070-08

RHINOCORT AQUA Nasal Spray

32 mcg, 120 metered sprays; net fill weight 8.6 g

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

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Distributed by:
AstraZeneca LP, Wilmington, DE 19850

Rev. 03/03 808201-05

721851-03

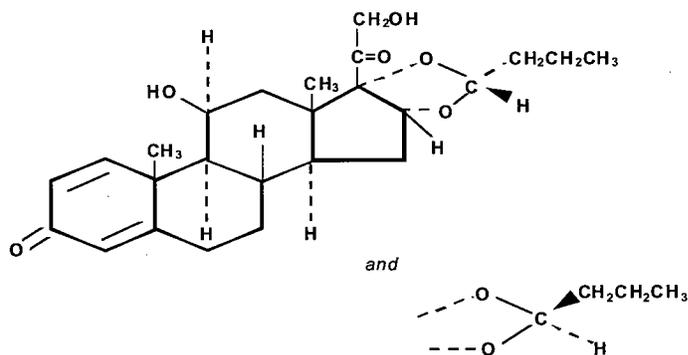
Pulmicort Respules
(budesonide inhalation suspension)
0.25 mg and 0.5 mg

Rx only

For inhalation use via compressed air driven jet nebulizers only (not for use with ultrasonic devices). Not for injection. Read patient instructions before using.

DESCRIPTION

Budesonide, the active component of PULMICORT RESPULES[®], is a corticosteroid designated chemically as (RS)-11 β , 16 α , 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C₂₅H₃₄O₆ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3 .

PULMICORT RESPULES is a sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide (micronized), and the inactive ingredients disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80, and Water for Injection. Two dose strengths are available in single-dose ampules (Respules™ ampules): 0.25 mg and 0.5 mg per 2 mL RESPULE ampule. For PULMICORT RESPULES, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari-LC-Jet Plus Nebulizer/Pari Master compressor system, under *in vitro* conditions, the mean delivered dose at the mouthpiece (% nominal dose) was approximately 17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less. PULMICORT RESPULES should be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Mechanism of Action

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The precise mechanism of corticosteroid actions on inflammation in asthma is not well known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic- and non-allergic-mediated inflammation. The anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activities and systemic corticosteroid effects over a wide dose range of inhaled budesonide in a variety of formulations and delivery systems including Pulmicort Turbuhaler® (an inhalation-driven, multi-dose dry powder inhaler) and the inhalation suspension for nebulization. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%) and the low potency of metabolites (see below).

Pharmacokinetics

The activity of PULMICORT RESPULES is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

Budesonide is primarily cleared by the liver. In asthmatic children 4-6 years of age, the terminal half-life of budesonide after nebulization is 2.3 hours, and the systemic clearance is 0.5 L/min, which is approximately 50% greater than in healthy adults after adjustment for differences in weight.

After a single dose of 1 mg budesonide, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20 minutes after nebulization in asthmatic children 4-6 years of age. The exposure (AUC) of budesonide following administration of a single 1 mg dose of budesonide by nebulization to asthmatic children 4-6 years of age is comparable to healthy adults given a single 2 mg dose by nebulization.

Absorption: In asthmatic children 4-6 years of age, the total absolute bioavailability (ie, lung + oral) following administration of PULMICORT RESPULES via jet nebulizer was approximately 6% of the labeled dose.

The peak plasma concentration of budesonide occurred 10-30 minutes after start of nebulization.

Distribution: In asthmatic children 4-6 years of age, the volume of distribution at steady-state of budesonide was 3 L/kg, approximately the same as in healthy adults. Budesonide is 85-90% bound to plasma proteins, the degree of binding being constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended doses. Budesonide showed little or no binding to corticosteroid-binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism: *In vitro* studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16 α -hydroxyprednisolone and 6 β -hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns has been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion: Budesonide is excreted in urine and feces in the form of metabolites. In adults, approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special Populations: No differences in pharmacokinetics due to race, gender, or age have been identified.

Hepatic Insufficiency: Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy adults.

Pharmacodynamics

The therapeutic effects of conventional doses of orally inhaled budesonide are largely explained by its direct local action on the respiratory tract. To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in adult patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels.

Improvement in the control of asthma symptoms following inhalation of PULMICORT RESPULES can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks.

Budesonide administered via Turbuhaler[®] has been shown in various challenge models (including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate) to decrease bronchial hyperresponsiveness in asthmatic patients. The clinical relevance of these models is not certain.

Pre-treatment with budesonide administered via TURBUHALER 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV₁ following inhaled allergen challenge.

The effects of PULMICORT RESPULES on the hypothalamic-pituitary-adrenal (HPA) axis were studied in three, 12-week, double-blind, placebo-controlled studies in 293 pediatric patients, 6 months to 8 years of age, with persistent asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by the short cosyntropin (ACTH) stimulation test, remained intact with PULMICORT RESPULES treatment at recommended doses. In the subgroup of children age 6 months to 2 years (n=21) receiving a total daily dose of PULMICORT RESPULES equivalent to 0.25 mg (n=5), 0.5 mg (n=5), 1 mg (n=8), or placebo (n=3), the mean change from baseline in ACTH-stimulated cortisol levels showed a decline in peak stimulated cortisol at 12 weeks compared to an increase in the placebo group. These mean differences were not statistically significant compared to placebo. Another 12-week study in 141 pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing was conducted. All patients were randomized to receive either 0.5 mg or 1 mg of PULMICORT RESPULES or placebo once daily. A total of 28, 17, and 31 patients in the PULMICORT RESPULES 0.5 mg, 1 mg, and placebo arms respectively, had an evaluation of serum cortisol levels post-ACTH stimulation both at baseline and at the end of the study. The mean change from baseline to Week 12 ACTH-stimulated minus basal plasma cortisol levels did not indicate adrenal suppression in patients treated with PULMICORT RESPULES versus placebo. However, 7 patients in this study (4 of whom received PULMICORT RESPULES 0.5 mg, 2 of whom received PULMICORT RESPULES 1 mg and 1 of whom received placebo) showed a shift from normal baseline stimulated cortisol level (≥ 500 nmol/L) to a subnormal level (< 500 nmol/L) at Week 12. In 4 of these patients receiving PULMICORT RESPULES, the cortisol values were near the cutoff value of 500 nmol/L.

The effects of PULMICORT RESPULES at doses of 0.5 mg twice daily, and 1 mg and 2 mg twice daily (2 times and 4 times the highest recommended total daily dose, respectively) on 24-hour urinary cortisol excretion were studied in 18 patients between 6 to 15 years of age with persistent asthma in a cross-over study design (4 weeks of treatment per dose level). There was a dose-related decrease in urinary cortisol excretion at 2 and 4 times the recommended daily dose. The two higher doses of PULMICORT RESPULES (1 and 2 mg twice daily) showed statistically significantly reduced (43-52%) urinary cortisol excretion compared to the run-in period. The highest recommended dose of PULMICORT RESPULES, 1 mg total daily dose, did not show statistically significantly reduced urinary cortisol excretion compared to the run-in period.

PULMICORT RESPULES, like other inhaled corticosteroid products, may impact the HPA axis, especially in susceptible individuals, in younger children, and in patients given high doses for prolonged periods.

CLINICAL TRIALS

Three double-blind, placebo-controlled, parallel group, randomized U.S. clinical trials of 12-weeks duration each were conducted in 1018 pediatric patients, 6 months to 8 years of age, with persistent asthma of varying disease duration (2 to 107 months) and severity. Doses of 0.25 mg, 0.5 mg, and 1 mg administered either once or twice daily were compared to placebo to provide information about appropriate dosing to cover a range of asthma severity. A Pari-LC-Jet Plus Nebulizer (with a face mask or mouthpiece) connected to a Pari Master compressor was used to deliver PULMICORT RESPULES to patients in the 3 U.S. controlled clinical trials. The co-primary endpoints were nighttime and daytime asthma symptom scores (0-3 scale). Each of the five doses discussed below were studied in one or two, but not all three of the U.S. studies.

Results of the 3 controlled clinical trials for recommended dosages of budesonide inhalation suspension (0.25 mg to 0.5 mg once or twice daily, or 1 mg once daily, up to a total daily dose of 1 mg) in 946 patients, 12 months to 8 years of age, are presented below. Compared to placebo, PULMICORT RESPULES significantly decreased both nighttime and daytime symptom scores of asthma at doses of 0.25 mg once daily (one study), 0.25 mg twice daily, and 0.5 mg twice daily. PULMICORT RESPULES significantly decreased either nighttime or daytime symptom scores, but not both, at doses of 1 mg once daily, and 0.5 mg once daily (one study). Symptom reduction in response to PULMICORT RESPULES occurred across gender and age. PULMICORT RESPULES significantly reduced the need for bronchodilator therapy at all the doses studied.

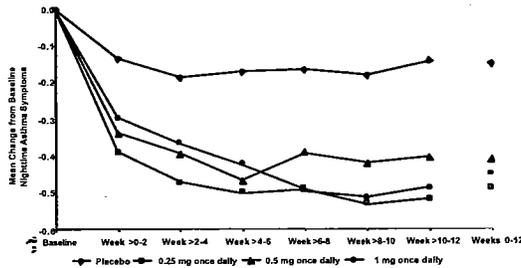
Improvements in lung function were associated with PULMICORT RESPULES in the subgroup of patients capable of performing lung function testing. Significant improvements were seen in FEV₁ [PULMICORT RESPULES 0.5 mg once daily and 1 mg once daily (one study); 0.5 mg twice daily] and morning PEF [PULMICORT RESPULES 1 mg once daily (one study); 0.25 mg twice daily; 0.5 mg twice daily] compared to placebo.

A numerical reduction in nighttime and daytime symptom scores (0-3 scale) of asthma was observed within 2-8 days, although maximum benefit was not achieved for 4-6 weeks after starting treatment. The reduction in nighttime and daytime asthma symptom scores was maintained throughout the 12 weeks of the double-blind trials.

Patients Not Receiving Inhaled Corticosteroid Therapy

The efficacy of PULMICORT RESPULES at doses of 0.25 mg, 0.5 mg, and 1 mg once daily was evaluated in 344 pediatric patients, 12 months to 8 years of age, with mild to moderate persistent asthma (mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.07 to 1.34) who were not well controlled by bronchodilators alone. The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 1. Nighttime asthma symptom scores improved significantly in the patients treated with PULMICORT RESPULES compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

Figure 1: A 12-Week Trial in Pediatric Patients Not on Inhaled Corticosteroid Therapy Prior to Study Entry.

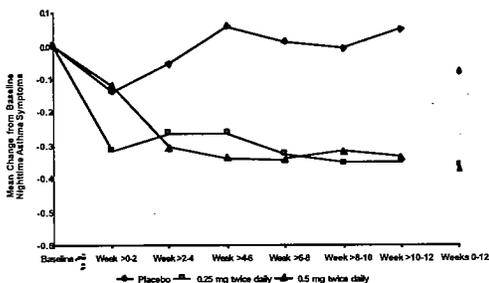


Patients Previously Maintained on Inhaled Corticosteroids

The efficacy of PULMICORT RESPULES at doses of 0.25 mg and 0.5 mg twice daily was evaluated in 133 pediatric asthma patients, 4 to 8 years of age, previously maintained on inhaled corticosteroids (mean FEV₁ 79.5% predicted; mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.04 to 1.18; mean baseline dose of beclomethasone dipropionate of 265 mcg/day, ranging between 42 to 1008 mcg/day; mean baseline dose of triamcinolone acetonide of 572 mcg/day, ranging between 200 to 1200 mcg/day). The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 2. Nighttime asthma symptom scores were significantly improved in patients treated with PULMICORT RESPULES compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

PULMICORT RESPULES at a dose of 0.5 mg twice daily significantly improved FEV₁, and both doses (0.25 mg and 0.5 mg twice daily) significantly increased morning PEF, compared to placebo.

Figure 2: A 12-Week Trial in Pediatric Patients Previously Maintained on Inhaled Corticosteroid Therapy Prior to Study Entry.



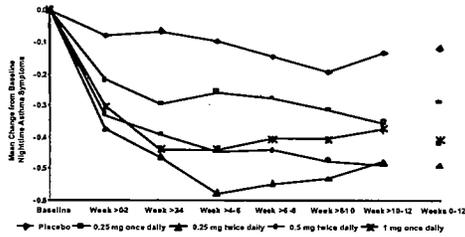
Patients Receiving Once-Daily or Twice-Daily Dosing

The efficacy of PULMICORT RESPULES at doses of 0.25 mg once daily, 0.25 mg twice daily, 0.5 mg twice daily, and 1 mg once daily, was evaluated in 469 pediatric patients 12 months to 8 years of age (mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.13 to 1.31). Approximately 70% were not previously receiving inhaled corticosteroids. The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 3. PULMICORT RESPULES at doses of 0.25 mg and 0.5 mg twice daily, and 1 mg once daily, significantly improved nighttime asthma symptom scores compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

PULMICORT RESPULES at a dose of 0.5 mg twice daily significantly improved FEV₁, and at doses of 0.25 mg and 0.5 mg twice daily and 1 mg once daily significantly improved morning PEF, compared to placebo.

The evidence supports the efficacy of the same nominal dose of PULMICORT RESPULES administered on either a once-daily or twice-daily schedule. However, when all measures are considered together, the evidence is stronger for twice-daily dosing (see DOSAGE AND ADMINISTRATION).

Figure 3: A 12-Week Trial in Pediatric Patients Either Maintained on Bronchodilators Alone or Inhaled Corticosteroid Therapy Prior to Study Entry.



INDICATIONS

PULMICORT RESPULES is indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age.

PULMICORT RESPULES is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

PULMICORT RESPULES is contraindicated as the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to budesonide or any of the ingredients of this preparation contraindicates the use of PULMICORT RESPULES.

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of HPA-axis function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn.

During this period of HPA-axis suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although PULMICORT RESPULES may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instructions. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic corticosteroid therapy to PULMICORT RESPULES may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, and eczema (see DOSAGE AND ADMINISTRATION).

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

PULMICORT RESPULES is not a bronchodilator and is not indicated for the rapid relief of acute bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If acute bronchospasm occurs following dosing with PULMICORT RESPULES, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with PULMICORT RESPULES should be discontinued and alternate therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with PULMICORT RESPULES.

PRECAUTIONS

General

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

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function.

Because budesonide is absorbed into the circulation and may be systemically active, particularly at higher doses, suppression of HPA function may be associated when PULMICORT RESPULES is administered at doses exceeding those recommended (see DOSAGE AND ADMINISTRATION), or when the dose is not titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing PULMICORT RESPULES.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with these drugs should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, PULMICORT RESPULES should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic corticosteroids.

Although patients in clinical trials have received PULMICORT RESPULES on a continuous basis for periods of up to 1 year, the long-term local and systemic effects of PULMICORT RESPULES in human subjects are not completely known. In particular, the effects resulting from chronic use of PULMICORT RESPULES on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown.

In clinical trials with PULMICORT RESPULES, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. The incidences of localized infections of *Candida albicans* were similar between the placebo and PULMICORT RESPULES treatment groups. If symptomatic oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while still continuing with PULMICORT RESPULES therapy, but at times therapy with PULMICORT RESPULES may need to be interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

Information for Patients

For instructions on the proper use of PULMICORT RESPULES and to attain the maximum improvement in asthma symptoms, the patient or the parent/guardian of the patient should receive, read, and follow the accompanying patient information and instructions carefully. In addition, patients being treated with PULMICORT RESPULES should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects.

- Patients should take PULMICORT RESPULES at regular intervals once or twice a day as directed, since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.
- The effects of mixing PULMICORT RESPULES with other nebulizable medications have not been adequately assessed. PULMICORT RESPULES should be administered separately in the nebulizer.
- PULMICORT RESPULES is not a bronchodilator, and its use is not intended to treat acute life-threatening episodes of asthma.

- PULMICORT RESPULES should be administered with a jet nebulizer connected to a compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. The face mask should be properly adjusted to optimize delivery and to avoid exposing the eyes to the nebulized medication (see DOSAGE AND ADMINISTRATION).
- Ultrasonic nebulizers are not suitable for the adequate administration of PULMICORT RESPULES and, therefore, are not recommended (see DOSAGE AND ADMINISTRATION).
- Rinsing the mouth with water after each treatment may decrease the risk of development of local candidiasis. Corticosteroid effects on the skin can be avoided if the face is washed after the use of a face mask.
- Improvement in asthma control following treatment with PULMICORT RESPULES can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks after starting treatment. If the asthma symptoms do not improve in that time frame, or if the condition worsens, the patient or the patient's parent/guardian should be instructed to contact the physician.
- Care should be taken to avoid exposure to chicken pox and measles. If exposure occurs, and the child has not had chicken pox or been properly vaccinated, a physician should be consulted without delay.
- PULMICORT RESPULES should be stored upright at controlled room temperature 20-25°C (68-77°F) and protected from light. PULMICORT RESPULES should not be refrigerated or frozen.
- When an aluminum foil envelope has been opened, the shelf life of the unused RESPULES ampules is two weeks when protected from light. The date the envelope was opened should be recorded on the back of the envelope in the space provided.

- After opening the aluminum foil envelope, the unused RESPULES ampules should be returned to the envelope to protect them from light. Any individually opened RESPULES ampules must be used promptly.
- For proper usage of PULMICORT RESPULES and to attain maximum improvement, the accompanying Patient's Instructions for Use should be read and followed.

Drug Interactions

In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of other known inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known CYP3A4 inhibitors. Omeprazole did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of CYP1A2, caused a slight decrease in budesonide clearance and a corresponding increase in its oral bioavailability.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis).

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

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

Pregnancy

Teratogenic Effects: Pregnancy Category B — As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis) and 500 mcg/kg in rats (approximately 4 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

Studies of pregnant women, however, have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8 % vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, PULMICORT RESPULES should be used during pregnancy only if clearly needed.

Non-teratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers

It is not known whether budesonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised if budesonide is administered to nursing women.

Pediatric Use

Safety in children six months to 12 months of age has been evaluated. Safety and effectiveness in children 12 months to 8 years of age have been established (see CLINICAL PHARMACOLOGY, Pharmacodynamics, CLINICAL TRIALS and ADVERSE REACTIONS).

A 12-week study in 141 pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing was conducted. All patients were randomized to receive either 0.5 mg or 1 mg of PULMICORT RESPULES or placebo once daily. Adrenal axis function was assessed with an ACTH stimulation test at the beginning and end of the study, and mean changes from baseline in this variable did not indicate adrenal suppression in patients who received PULMICORT RESPULES versus placebo. However, on an individual basis, 7 patients in this study (6 in the PULMICORT RESPULES treatment arms and 1 in the placebo arm) experienced a shift from having a normal baseline stimulated cortisol level to having a subnormal level at Week 12 (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Pneumonia was observed more frequently in patients treated with PULMICORT RESPULES than in patients treated with placebo, (N = 2, 1, and 0) in the PULMICORT RESPULES 0.5 mg, 1 mg, and placebo groups, respectively.

A dose dependent effect on growth was also noted in this 12-week trial. Infants in the placebo arm experienced an average growth of 3.7 cm over 12 weeks compared with 3.5 cm and 3.1 cm in the PULMICORT RESPULES 0.5 mg and 1 mg arms respectively. This corresponds to estimated mean (95% CI) reductions in 12-week growth velocity between placebo and PULMICORT RESPULES 0.5 mg of 0.2 cm (-0.6 to 1.0) and between placebo and PULMICORT RESPULES 1 mg of 0.6 cm (-0.2 to 1.4). These findings support that the use of PULMICORT RESPULES in infants 6 to 12 months of age may result in systemic effects and are consistent with findings of growth suppression in other studies with inhaled corticosteroids.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving inhaled corticosteroids, including PULMICORT RESPULES, should be monitored routinely (eg, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of inhaled corticosteroids, including PULMICORT RESPULES, each patient should be titrated to his/her lowest effective dose.

Geriatric Use

Of the 215 patients in 3 clinical trials of PULMICORT RESPULES in adult patients, 65 (30%) were 65 years of age or older, while 22 (10%) were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients, and other reported clinical or medical surveillance experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS

The following adverse reactions were reported in pediatric patients treated with PULMICORT RESPULES.

The incidence of common adverse reactions is based on three double-blind, placebo-controlled, U.S. clinical trials in which 945 patients, 12 months to 8 years of age, (98 patients ≥ 12 months and < 2 years of age; 225 patients ≥ 2 and < 4 years of age; and 622 patients ≥ 4 and ≤ 8 years of age) were treated with PULMICORT RESPULES (0.25 to 1 mg total daily dose for 12 weeks) or vehicle placebo. The incidence and nature of adverse events reported for PULMICORT RESPULES was comparable to that reported for placebo. The following table shows the incidence of adverse events in U.S. controlled clinical trials, regardless of relationship to treatment, in patients previously receiving bronchodilators and/or inhaled corticosteroids. This population included a total of 605 male and 340 female patients.

Adverse Events with $\geq 3\%$ Incidence Reported by Patients on PULMICORT RESPULES

Adverse Events	Vehicle Placebo (n=227) %	PULMICORT RESPULES Total Daily Dose		
		0.25 mg (n=178) %	0.5 mg (n=223) %	1 mg (n=317) %
Respiratory System Disorder				
Respiratory Infection	36	34	35	38
Rhinitis	9	7	11	12
Coughing	5	5	9	8
Resistance Mechanism Disorders				
Otitis Media	11	12	11	9
Viral Infection	3	4	5	3
Moniliasis	2	4	3	4
Gastrointestinal System Disorders				
Gastroenteritis	4	5	5	5
Vomiting	3	2	4	4
Diarrhea	2	4	4	2
Abdominal Pain	2	3	2	3
Hearing and Vestibular Disorders				
Ear Infection	4	2	4	5
Platelet, Bleeding, and Clotting Disorders				
Epistaxis	1	2	4	3
Vision Disorders				
Conjunctivitis	2	<1	4	2
Skin and Appendages Disorders				
Rash	3	<1	4	2

The table above shows all adverse events with an incidence of 3% or more in at least one active treatment group where the incidence was higher with PULMICORT RESPULES than with placebo.

The following adverse events occurred with an incidence of 3% or more in at least one PULMICORT RESPULES group where the incidence was equal to or less than that of the placebo group: fever, sinusitis, pain, pharyngitis, bronchospasm, bronchitis, and headache.

Incidence 1% to ≤3% (by body system)

The information below includes all adverse events with an incidence of 1 to ≤3%, in at least one PULMICORT RESPULES treatment group where the incidence was higher with PULMICORT RESPULES than with placebo, regardless of relationship to treatment.

Body as a whole: allergic reaction, chest pain, fatigue, flu-like disorder
Respiratory system: stridor
Resistance mechanisms: herpes simplex, external ear infection, infection
Central & peripheral nervous system: dysphonia, hyperkinesia
Skin & appendages: eczema, pustular rash, pruritus
Hearing & vestibular: earache
Vision: eye infection
Psychiatric: anorexia, emotional lability
Musculoskeletal system: fracture, myalgia
Application site: contact dermatitis
Platelet, bleeding & clotting: purpura
White cell and resistance: cervical lymphadenopathy

The incidence of reported adverse events was similar between the 447 PULMICORT RESPULES-treated (mean total daily dose 0.5 to 1 mg) and 223 conventional therapy-treated pediatric asthma patients followed for one year in three open-label studies.

Cases of growth suppression have been reported for inhaled corticosteroids including post-marketing reports for PULMICORT RESPULES (see PRECAUTIONS, Pediatric Use).

Less frequent adverse events (<1%) reported in the published literature, long-term, open-label clinical trials, or from marketing experience for inhaled budesonide include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, angioedema, and bronchospasm; symptoms of hypocorticism and hypercorticism; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety, and psychosis; and bone disorders including avascular necrosis of the femoral head and osteoporosis.

OVERDOSAGE

The potential for acute toxic effects following overdose of PULMICORT RESPULES is low. If inhaled corticosteroids are used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism or growth suppression may occur (see PRECAUTIONS).

In mice the minimal lethal inhalation dose was 100 mg/kg (approximately 410 or 120 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m^2 basis). In rats there were no deaths at an inhalation dose of 68 mg/kg (approximately 550 or 160 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m^2 basis). In mice the minimal oral lethal dose was 200 mg/kg (approximately 810 or 240 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m^2 basis). In rats, the minimal oral lethal dose was less than 100 mg/kg (approximately 810 or 240 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION

PULMICORT RESPULES is indicated for use in asthmatic patients 12 months to 8 years of age. PULMICORT RESPULES should be administered by the inhaled route via jet nebulizer connected to an air compressor. Individual patients will experience a variable onset and degree of symptom relief. Improvement in asthma control following inhaled administration of PULMICORT RESPULES can occur within 2-8 days of initiation of treatment, although maximum benefit may not be achieved for 4-6 weeks. The safety and efficacy of PULMICORT RESPULES when administered in excess of recommended doses have not been established. In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved. The recommended starting dose and highest recommended dose of PULMICORT RESPULES, based on prior asthma therapy, are listed in the following table.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	0.5 mg total daily dose administered either once daily or twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered either once daily or twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily	1 mg total daily dose

In symptomatic children not responding to non-steroidal therapy, a starting dose of 0.25 mg once daily of PULMICORT RESPULES may also be considered.

If once-daily treatment with PULMICORT RESPULES does not provide adequate control of asthma symptoms, the total daily dose should be increased and/or administered as a divided dose.

Patients Not Receiving Systemic (Oral) Corticosteroids

Patients who require maintenance therapy of their asthma may benefit from treatment with PULMICORT RESPULES at the doses recommended above. Once the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose. For the patients who do not respond adequately to the starting dose, consideration should be given to administering the total daily dose as a divided dose, if a once-daily dosing schedule was followed. If necessary, higher doses, up to the maximum recommended doses, may provide additional asthma control.

Patients Maintained on Chronic Oral Corticosteroids

Initially, PULMICORT RESPULES should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid may be initiated by reducing the daily or alternate daily dose. Further incremental reductions may be made after an interval of one or two weeks, depending on the response of the patient. Generally, these decrements should not exceed 25% of the prednisone dose or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for asthma instability, including objective measures of airway function, and for adrenal insufficiency (see WARNINGS). During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with PULMICORT RESPULES but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

A Pari-LC-Jet Plus Nebulizer (with face mask or mouthpiece) connected to a Pari Master compressor was used to deliver PULMICORT RESPULES to each patient in 3 U.S. controlled clinical studies. The safety and efficacy of PULMICORT RESPULES delivered by other nebulizers and compressors have not been established.

PULMICORT RESPULES should be administered via jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. Ultrasonic nebulizers are not suitable for the adequate administration of PULMICORT RESPULES and, therefore, are NOT recommended.

The effects of mixing PULMICORT RESPULES with other nebulizable medications have not been adequately assessed. PULMICORT RESPULES should be administered separately in the nebulizer (see PRECAUTIONS, Information for Patients).

Directions for Use

Illustrated *Patient's Instructions for Use* accompany each package of PULMICORT RESPULES.

HOW SUPPLIED

PULMICORT RESPULES is supplied in sealed aluminum foil envelopes containing one plastic strip of five single-dose RESPULES ampules together with patient instructions for use. There are 30 RESPULES ampules in a carton. Each single-dose RESPULE ampule contains 2 mL of sterile liquid suspension.

PULMICORT_F RESPULES is available in two strengths, each containing 2 mL:

NDC 0186-1988-04	0.25 mg/2 mL
NDC 0186-1989-04	0.5 mg/2 mL

Storage

PULMICORT RESPULES should be stored upright at controlled room temperature 20-25°C (68-77°F) [see USP], and protected from light. When an envelope has been opened, the shelf life of the unused RESPULES ampules is 2 weeks when protected. After opening the aluminum foil envelope, the unused RESPULES ampules should be returned to the aluminum foil envelope to protect them from light. Any opened RESPULE ampule must be used promptly. Gently shake the RESPULE ampule using a circular motion before use. Keep out of reach of children. Do not freeze.

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721851-03
Rev. 03/03

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-441/S-018

NDA 20-746/S-011

NDA 20-929/S-015

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE

Project Manager Labeling Review

NDA 20-441/S-017 and S-018

DRUG: Pulmicort Turbuhaler (budesonide inhalation powder)

SPONSOR: AstraZeneca

SUBMISSION DATED: February 28, 2002 (S-017) and March 25, 2003 (S-018)

RECEIVED: March 01, 2002 (S-017) and March 26, 2003 (S-018)

S-017 is was submitted as a prior approval supplement and provides for the removal of the black box surrounding the warning about the risk of hypothalamic-pituitary-adrenal (HPA) axis suppression when patients are switched from systemic corticosteroids to inhaled corticosteroids. This revision was the subject of a citizen's petition from GlaxoSmithKline that was granted on January 11, 2002.

S-018 was submitted as changes being effected supplemental application and provides for revisions to the Drug interaction subsection of the PRECAUTIONS section of the package insert as well as minor editorial revisions throughout the package insert. These revisions were made in order to harmonize the wording for all of the U.S. approved budesonide drug products. The harmonized wording was the approved wording for NDA 20-746 with the addition of a sentence advising care should be exercised when budesonide is coadministered with long-term ketoconazole and other CYP3A4 inhibitors. The cautionary statement is a revised wording of the cautionary statement approved in NDAs 20-441 and 20-929.

Astra provide documentation showing that this wording was appropriate for all budesonide products.

I compared the labeling dated March 27, 2002, and March 25, 2003, to the last approved labeling (Approved December 31, 2001) and there are no changes other than those requested by these supplements, therefore these supplements should be approved. These supplements will be approved in separates letter because S-017 was submitted as a prior approval supplement and S-018 was submitted as a Changes Being Effected Supplement.

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products

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/s/

Sandra Barnes
9/26/03 04:23:15 PM
CSO

Badrul Chowdhury
9/26/03 04:54:22 PM
MEDICAL OFFICER

Project Manager Labeling Review

NDA 20-746/S-011 and 20-929/S-015

DRUG: Rhinocort Aqua (budesonide) Nasal Spray
Pulmicort Respules (budesonide inhalation suspension)

SPONSOR: AstraZeneca

SUBMISSIONS DATED: March 25, 2003 RECEIVED: March 26, 2003

These changes being effected supplemental applications provide for revisions to the 1st paragraph of the Drug Interaction subsection of the PRECAUTIONS section of the package insert as well as minor editorial revisions throughout the package insert. These revisions were made in order to harmonize the wording for all of the U.S. approved budesonide drug products. The harmonized wording was the approved wording for NDA 20-746 with the addition of a sentence advising care should be exercised when budesonide is coadministered with long-term ketoconazole and other CYP3A4 inhibitors. The cautionary statement is a revised wording of the cautionary statement approved in NDAs 20-441 and 20-929.

Astra provide documentation showing that this wording was appropriate for all budesonide products

I compared the labeling dated March 25, 2003, to the last approved labeling (Approved October 26, 2001) and there are no changes other than those requested by these supplements therefore these supplements should be approved.

Sandy Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products

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/s/

Sandra Barnes
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CSO

Badrul Chowdhury
9/26/03 04:56:33 PM
MEDICAL OFFICER