CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-441/s-012

Trade Name: Pulmicort Turbuhaler

Generic Name: Budeesonide Inhalation Powder

Sponsor: AstraZeneca PL

Approval Date: December 31, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-441/s-012

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-441/ S-012

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-441/S-012

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

Dear Mr. Blango:

Please refer to your supplemental new drug application dated February 16, 2001, received February 20, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Turbuhaler® (budesonide inhalation powder).

We acknowledge receipt of your submissions dated October 22, November 1 and 15, and December 28, 2001. Your submission of October 22, 2001 constituted a complete response to our August 21, 2001, action letter.

This supplemental new drug application provides for changes to the Pregnancy subsection of the Precautions section related to a change in the pregnancy category from "C" to "B".

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted December 28, 2001).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-441/S-012." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
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 Anthony M. Zeccola, Regulatory Management Officer, at 301-827-1058.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Robert Meyer
12/31/01 08:33:26 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-441/ S-012

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-441/012

AstraZeneca
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Eric Couture, Ph.D.
Director, Regulatory Affairs

Dear Dr. Couture:

Please refer to your supplemental new drug application dated February 16, 2001, received February 20, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Turbuhaler (budesonide inhalation suspension).

This supplement proposes revisions to the PRECAUTIONS: Pregnancy subsection of the package insert.

We have completed the review of this application, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following comments.

1. Provide the following information, as discussed during a teleconference on August 8, 2001.

    a. A discussion of whether the epidemiological study and other human exposure data provided in this submission would support a change for Pulmicort Turbuhaler from Pregnancy Category "C" to Pregnancy Category "B."

    b. Comparative human gestational exposure data between budesonide and other inhaled corticosteroid products, particularly for beclomethasone dipropionate.

2. Consolidate the report of the Swedish epidemiological study and its update, rather than reporting them separately.

We remind you that the Pregnancy subsection of the current package insert for Pulmicort Respules (NDA 20-929) should also be updated, consistent with the above comments.

In addition, all previous revisions as reflected in the most recently approved labeling must be included.

To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, call Gretchen Trout, Project Manager, at (301) 827-1058.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

/s/

Robert Meyer
8/21/01 08:42:51 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-441 / S-012

APPROVED LABELING

808179-01

PULMICORT TURBUHALER 200 mcg

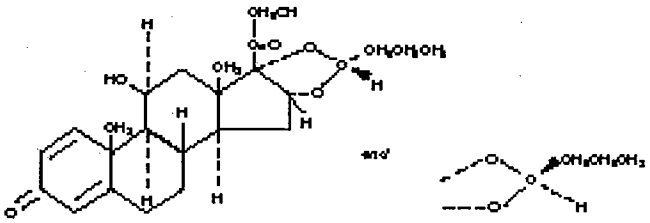
(budesonide inhalation powder)

For Oral Inhalation Only.

Rx only

DESCRIPTION

Budesonide, the active component of PULMICORT TURBUHALER 200 mcg, is a corticosteroid designated chemically as (RS)-11β, 16α, 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 $C_{25}H_{34}O_6$ 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 FEV_1 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 FEV_1 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 3A catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-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 3A, 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 FEV_1 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.

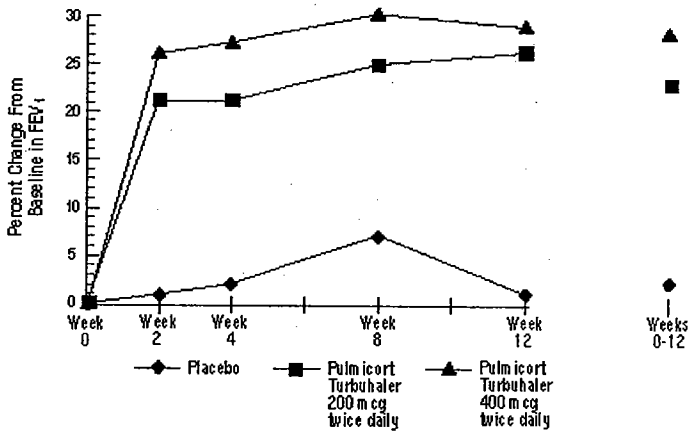
Double-blind, parallel, placebo-controlled clinical trials of 12 weeks duration and longer have shown that, compared with placebo, PULMICORT TURBUHALER significantly improved lung function (measured by PEF and FEV_1), significantly decreased morning and evening symptoms of asthma, and significantly reduced 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 FEV_1 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 FEV_1 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

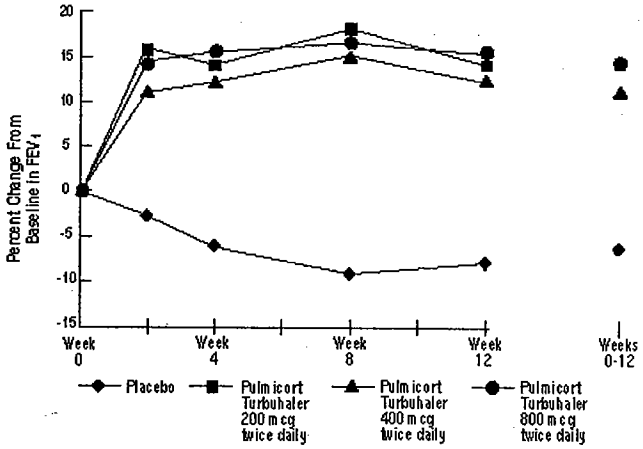


In a 12-month controlled trial in 75 patients not previously receiving corticosteroids, PULMICORT TURBUHALER at 200 mcg twice daily resulted in improved lung function (measured by PEF) and reduced bronchial hyperreactivity compared to placebo.

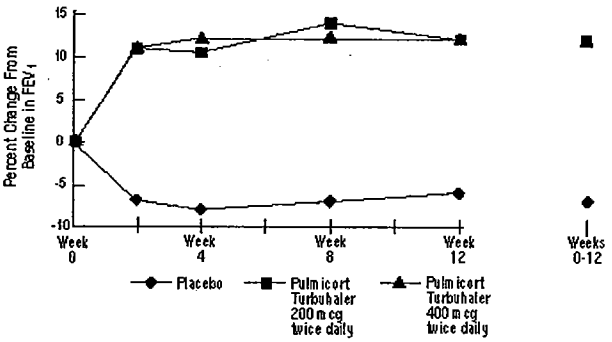
Patients Previously Maintained on Inhaled Corticosteroids

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 FEV_1 2.04 L, baseline doses of beclomethasone dipropionate 126-1008 mcg/day; pediatrics: N=404, mean baseline FEV_1 2.09 L, baseline doses of beclomethasone dipropionate 126-672 mcg/day or triamcinolone acetonide 300-1800 mcg/day). The FEV_1 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 FEV_1 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 FEV_1 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. Ketoconazole, a potent inhibitor of cytochrome P450 3A, may increase plasma levels of budesonide during concomitant dosing. The clinical significance of concomitant administration of ketoconazole with PULMICORT TURBUHALER is not known, but caution may be warranted.

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 1/2 the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 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 1/4 the maximum recommended daily inhalation dose on a mcg/m^2 basis); no such changes were seen in male rats receiving oral doses of 10 and 25 mcg/kg/day (approximately 1/20 and 1/8 the maximum recommended daily inhalation dose on a mcg/m^2 basis) or in female rats at oral doses up to 50 mcg/kg/day (approximately 1/4 the maximum recommended human daily inhalation dose on a mcg/m^2 basis).

Two additional 104-week carcinogenicity studies have been performed with oral budesonide at doses of 50 mcg/kg/day (approximately 1/3 the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 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 1/8 the maximum recommended daily inhalation dose in adults on a mcg/m^2 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/m^2 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 1/3 the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) and 500 mcg/kg/day in rats (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 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/m^2 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 ≥ 3% Incidence reported by Patients on PULMICORT TURBUHALER

		PULMICORT TURBUHALER		
Adverse Event	Placebo N=284 %	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 ≥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/m^2 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/m^2 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/m^2 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/m^2 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.

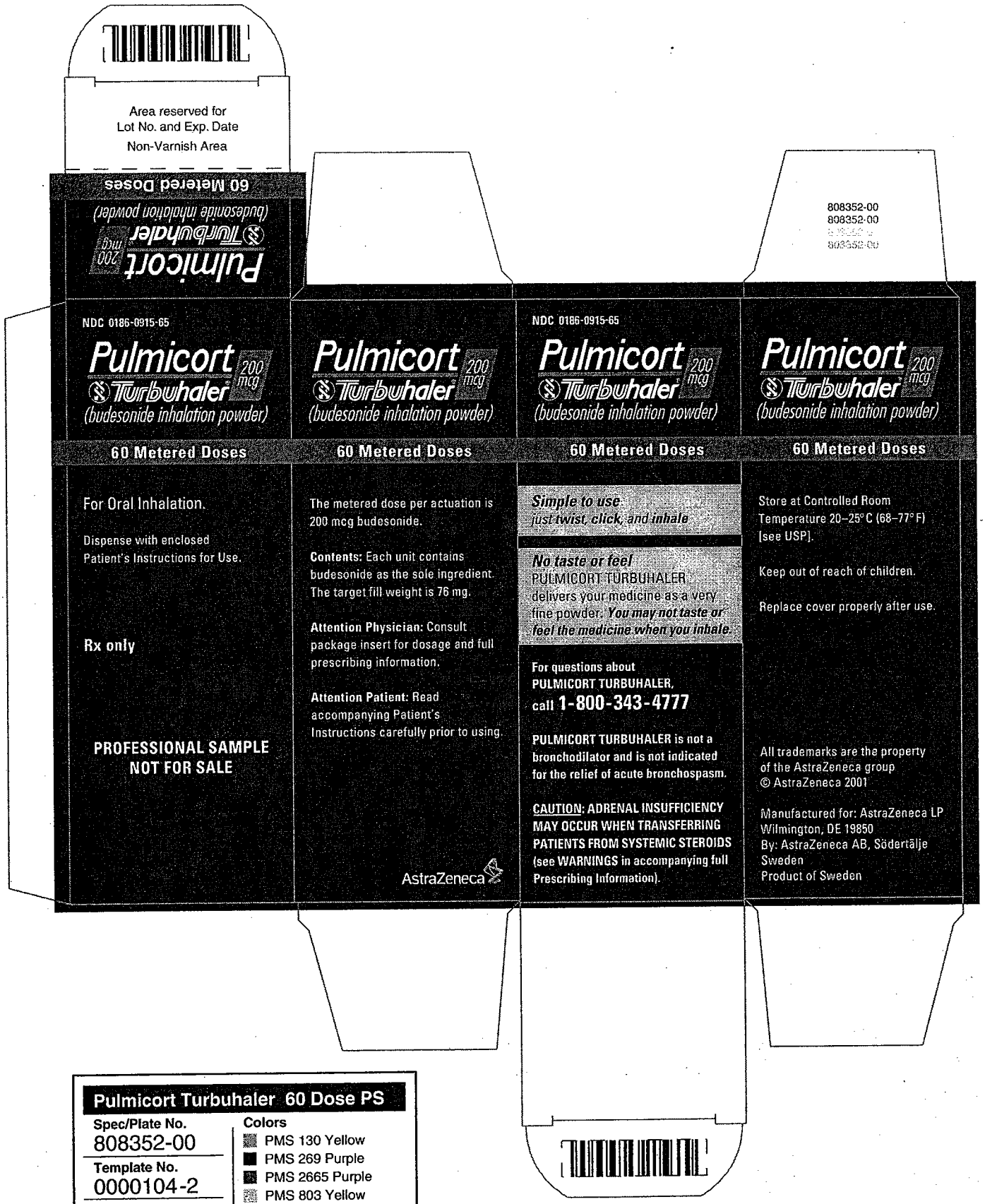
PULMICORT TURBUHALER is available as 200 mcg/dose, 200 doses (NDC 0186-0915-42) and has a target fill weight of 104 mg.

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.

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

808179-01 Rev. 12/01



Pulmicort Turbuhaler 60 Dose PS

Spec/Plate No.	Colors
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Template No.	PMS 269 Purple
0000104-2	PMS 2665 Purple
CMF No. 7637	PMS 803 Yellow
	Pattern Varnish

Plate Date
01/08/02 9:00 am JB

AstraZeneca

808350-00 p2-17.qxd 1/10/02 4:43 PM Page 1

Pulmicort Turbuhaler 200 mcg 60 Dose

Spec/Plate No.
808350-00

Template No.
0000288-0

CMF No. 7637

Colors
- PMS 269 Purple
- PMS 130 Yellow

Plate Date
01/10/02 4:40 pm JB

AstraZeneca

Pulmicort
Turbuhaler
(budesonide inhalation powder)

200 mcg

60 Metered Doses

PROFESSIONAL SAMPLE – NOT FOR SALE
For Oral Inhalation. **Rx only**
Store at 20–25°C (68–77°F) [see USP].
HOW TO USE PULMICORT TURBUHALER: Refer inside to Patient's Instructions for Use for additional information (including priming information).
Do not remove the leaflet until you have finished the medication.
Manufactured for: AstraZeneca LP, Wilmington, DE 19850.
By: AstraZeneca AB, Södertälje, Sweden
Product of Sweden

Area reserved for supplier logo

AstraZeneca

8 0 8 3 5 0 0 0

To Open: Peel back top corner of label.

Pulmicort Turbuhaler

(budesonide inhalation powder)

200 mcg

60 Metered Doses
For Oral Inhalation. **Rx only**

page 1

PROFESSIONAL SAMPLE – NOT FOR SALE 808350-00

Store at 20–25°C (68–77°F) [see USP].

HOW TO USE PULMICORT TURBUHALER: Refer to Patient's Instructions for Use for additional information (including priming information).

Loading a Dose: Twist cover and lift off. Hold inhaler upright (mouthpiece up). Turn brown grip fully to right. Twist it back again fully to left. You will hear a click.

Inhaling the Dose: Place mouthpiece between lips. Inhale deeply and forcefully. For more than one dose, repeat process. Place cover back on inhaler and twist shut. Rinse mouth with water. Keep inhaler clean and dry.

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

AstraZeneca

REMEMBER: This medicine has been prescribed for you by your doctor. DO NOT give this medicine to anyone else.

USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.

If you have further questions about the use of PULMICORT TURBUHALER, call: 1-800-237-8898

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WHAT YOU SHOULD KNOW ABOUT PULMICORT TURBUHALER®

Your doctor has prescribed PULMICORT TURBUHALER 200 mcg. It contains a medication called budesonide, which is a synthetic corticosteroid. Corticosteroids are natural substances found in the body that help fight inflammation. They are used to treat asthma because they reduce the swelling and irritation in the walls of the small air passages in the lungs and ease breathing problems. When inhaled regularly, corticosteroids also help to prevent attacks of asthma.

PULMICORT TURBUHALER treats the inflammation—the "quiet part" of asthma that you cannot hear, see, or feel. When inflammation is left untreated, your asthma symptoms and attacks can increase. PULMICORT TURBUHALER works to prevent and reduce your asthma symptoms and attacks.

- **When the red mark reaches the bottom of the window, your inhaler should be discarded as it may no longer deliver the correct amount of medication.** (You may still hear a sound if you shake it—this sound is not the medicine. This sound is produced by the drying agent inside the Turbuhaler.)
- **Do not immerse it in water to find out if it is empty. Simply check your dose indicator window.**

FURTHER INFORMATION ABOUT PULMICORT TURBUHALER

- PULMICORT TURBUHALER delivers your medicine as a very fine powder **that you may not taste, smell, or feel.** By following the instructions for use in this leaflet, you can be confident that you have received the correct dose.

5. This medicine is **NOT** intended to provide rapid relief of your breathing difficulties during an asthma attack. It must be taken at regular intervals as recommended by your doctor, and not as an emergency measure.
6. Your doctor may prescribe additional medication (such as bronchodilators) for emergency relief if an acute asthma attack occurs. Please contact your doctor if:
   - an asthma attack does not respond to the additional medication,
   - you require more of the additional medication than usual.
7. If you also use another medicine by inhalation, you should consult your doctor for instructions on when to use it in relation to using your PULMICORT TURBUHALER.

STORING YOUR PULMICORT TURBUHALER

- After each use, place the white cover back on and twist it firmly into place.
- Keep PULMICORT TURBUHALER in a dry place at controlled room temperature, 68–77°F (20–25°C).
- Keep your PULMICORT TURBUHALER out of the **reach of young children.**
- **DO NOT** use after the date shown on the body of your Turbuhaler.

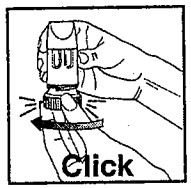
USING YOUR PULMICORT TURBUHALER

- Follow the instructions shown in the section "HOW TO USE YOUR PULMICORT TURBUHALER". If you have any problems, tell your doctor or pharmacist.
- It is important that you inhale each dose as directed by your doctor. The pharmacy label will usually tell you what dose to take and how often. If it doesn't, or you are not sure, ask your doctor or pharmacist.

- You will hear a click.

❷ INHALING THE DOSE

- When you are inhaling, PULMICORT TURBUHALER must be held in the upright (mouthpiece up) or horizontal position.
- Turn your head away from the inhaler and breathe out. **Do not shake the inhaler after loading it.**
- Place the mouthpiece between your lips and inhale deeply and forcefully. You may not taste or feel the medication.



- It may take 1 to 2 weeks or longer before you feel maximum improvement, so **IT IS VERY IMPORTANT THAT YOU USE PULMICORT TURBUHALER REGULARLY. DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU ARE FEELING BETTER,** unless told to do so by your doctor.
- If you miss a dose, just take your regularly scheduled next dose when it is due. **DO NOT DOUBLE** the dose.

HOW TO USE YOUR PULMICORT TURBUHALER

Read the complete instructions carefully and use only as directed.

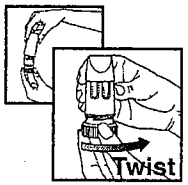
PRIMING INSTRUCTIONS:

Before you use a new PULMICORT TURBUHALER for the first time, you should prime it. To do this, turn the cover and lift off. Hold PULMICORT TURBUHALER upright (with mouthpiece up), then twist the brown grip fully to the right and back again to the left. Repeat. Now you are ready to take your first dose (see instructions for "TAKING A DOSE"). **You do not have to prime it any other time after this, even if you put it aside for a prolonged period of time.**

TAKING A DOSE:

❶ LOADING A DOSE

- Twist the cover and lift off.
- In order to provide the correct dose, **PULMICORT TURBUHALER must be held in the upright position (mouthpiece up) whenever a dose of medication is being loaded.**
- Twist the brown grip fully to the right as far as it will go. Twist it back again fully to the left.



DOSAGE

- Use as directed by your doctor.
- It is **VERY IMPORTANT** that you follow your doctor's instructions as to how many inhalations to take and how often to use your PULMICORT TURBUHALER.
- **DO NOT** inhale more doses or use your PULMICORT TURBUHALER more often than your doctor advises.

- Do not chew or bite on the mouthpiece.
- Remove the inhaler from your mouth and exhale. Do not blow or exhale into the mouthpiece.
- If more than one dose is required, just repeat the steps above.
- **When you are finished, place the cover back on** the inhaler and twist shut. **Rinse your mouth with water. Do not swallow.**
- **Keep your PULMICORT TURBUHALER clean and dry at all times.**
- Do not use PULMICORT TURBUHALER if it has been damaged or if the mouthpiece has become detached.

BEFORE USING YOUR PULMICORT TURBUHALER

TELL YOUR DOCTOR BEFORE STARTING TO TAKE THIS MEDICINE:

- if you are pregnant (or intending to become pregnant),
- if you are breast-feeding a baby,
- if you are allergic to budesonide or any other orally inhaled corticosteroid.

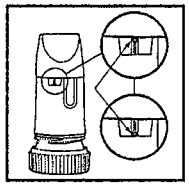
In some circumstances, this medicine may not be suitable and your doctor may wish to give you a different medicine. Make sure that your doctor knows what other medicines you are taking.

HOW TO KNOW WHEN YOUR PULMICORT TURBUHALER IS EMPTY

The label on the box or cover will tell you how many doses are in your PULMICORT TURBUHALER.

Your PULMICORT TURBUHALER has a convenient dose indicator window just below the mouthpiece.

- **When a red mark appears at the top of the window, there are 20 doses of medicine remaining.** Now is the time to get your next PULMICORT TURBUHALER.



IMPORTANT POINTS TO REMEMBER ABOUT PULMICORT TURBUHALER

1. MAKE SURE that this medicine is suitable for you (see "BEFORE USING YOUR PULMICORT TURBUHALER").
2. It is important that you inhale each dose as your doctor has advised.
3. Use your Turbuhaler as directed by your doctor. **DO NOT STOP TREATMENT OR REDUCE YOUR DOSE EVEN IF YOU FEEL BETTER,** unless told to do so by your doctor.
4. **DO NOT** inhale more doses or use your Turbuhaler more often than instructed by your doctor.

- PULMICORT TURBUHALER should not be used with a spacer.
- PULMICORT TURBUHALER contains only budesonide and does not contain any inactive ingredients.
- PULMICORT TURBUHALER is specially designed to deliver only one dose at a time, no matter how often you click the brown grip. If you accidentally blow into your inhaler after loading a dose, simply follow the instructions for loading a new dose.

This leaflet does not contain the complete information about your medicine. If you have any questions, or are not sure about something, then you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished your medicine.

Patient's Instructions for Use

Pulmicort 200 mcg
Turbuhaler®
(budesonide inhalation powder)

Please read this leaflet carefully before you start to take your medicine. It provides a summary of information on your medicine.

FOR FURTHER INFORMATION ASK YOUR DOCTOR OR PHARMACIST.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-441/s-012

MEDICAL REVIEW(s)

ABBREVIATIONS

ACAAI	American College of Asthma, Allergy, and Immunology
ACOG	American College of Obstetrics and Gynecology
ICS	Inhaled Corticosteroid
LMP	Last Menstrual Period
NAEPP	National Asthma Education and Prevention Program
PI	Package Insert/Label
RR	Relative Risk

EXECUTIVE SUMMARY

This submission is comprised of revised labeling for the **Pregnancy** subsection of the **PRECAUTIONS** Section for the approved PI for Pulmicort Turbuhaler. In support of these revisions, the sponsor has provided information from an epidemiological study of Swedish birth and congenital malformation registries mined for pregnancy outcome data. Also included are a position paper issued jointly by ACOG and ACAAI on the use of asthma and allergy medications during pregnancy, several original publications on the inter-relationship of asthma, asthma medication and pregnancy outcome, and the NAEPP-pregnancy working group guidelines.

The epidemiological study provides the primary basis for the new Pregnancy information labeling. The referenced study and its follow-up identified 2,543 births in which maternal exposure to inhaled budesonide occurred early during gestation (<12 weeks from LMP). Rates of congenital malformations among the exposed group (3.6%) were similar to background rates (3.5%). Among the exposed children with congenital abnormalities, four (4) had orofacial cleft compared to 3.3 expected. While reassuring that budesonide is not a major teratogen, the study is limited in that a more subtle effect of budesonide cannot be excluded (see "Review" below).

The sponsor has proposed including a description of this epidemiological study, in addition to retaining the present pre-clinical information, which describe the teratogenic and embryocidal effects of systemic budesonide on fetuses of pregnant rabbits. The sponsor has not requested a change in pregnancy category, which is presently "C" (see section below).

This submission and the data supporting the proposed labeling change were discussed internally, within the Division and at the Center level (with the Pregnancy Labeling Working Group). It was felt that the epidemiological study provided substantial human exposure data, and that the

sponsor should more fully explore how this information ought to be communicated in the label. Specifically, given existing regulations regarding the Pregnancy Section of the label and the current letter categories A, B, C, D, and X, the potential merits of changing the pregnancy category of Pulmicort Turbuhaler from "C" to "B" ought to be addressed by the sponsor. This information was shared with the sponsor via teleconference on 8 August 2001, at which time the general content of such a submission to address these issues was discussed. The sponsor agreed to reassess the data, provide comparative pregnancy risk information with other approved ICS's, and to provide a similar Pregnancy labeling supplement to NDA 20-929 for Pulmicort Respules. It is recommended that an "approvable" action be taken on this supplement pending submission and review of the requested data.

APPROVED LABELING WITH SPONSOR'S PROPOSED MODIFICATIONS

- Reviewer's comments appear in red.
- General Comment: For clarity, the sponsor should consider consolidating the results of the Swedish epidemiological study and its update into a single report rather than describing them separately.

Pregnancy

Teratogenic Effects: Pregnancy Category C: 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 1/3 the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) and 500 mcg/kg/day in rats (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 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/m^2 basis).

~~There are no adequate and well controlled studies in pregnant women. Budesonide 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.

results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from [redacted] 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 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 | | bringing the total to 2,534 infants whose mothers were exposed to inhaled budesonide. In this | | 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%).

[redacted] should be used during pregnancy only if [redacted]

1. REVIEW

1.1. Swedish Registry Data

In support of these revisions, the sponsor has included review of a recent epidemiological study[1] performed using data from the Swedish Medical Birth Registry (started in 1973) and two other linked medical registries, the Child Cardiology Registry and the Registry of Congenital Malformations. The latter are surveillance registers that track congenital cardiac defects and serious congenital malformations, respectively, diagnosed before the age of one year, and serve to complement the data available from the first registry. Together, these registries are believed to contain data for >99% of all live births or stillbirths occurring in Sweden (approx. 100,000/year), and were mined for information on all births between the years 1995 and 1997. These data were used to generate the "expected rate" of congenital malformations in the Swedish population and hence were used to define the "control group" in this cohort study.

Beginning July 1, 1994, linked data on medication usage by pregnant women at the time of their first prenatal visit became available. A total of 2014 infants born to the subset of women who

reported use of budesonide during early pregnancy served as the "study group." It is unclear from the original publication[1] whether subjects were included starting at the inception of this registry (1994), or whether the same 2-year time frame as the control group was mined (1995 – 7). This is irrelevant to the conclusion because rates are expressed using total births as the denominator, yielding a value that is independent of time. It is relevant to the proposed labeling, however, because the sponsor includes a time frame that is inaccurate (see above). Since drug use information was collected prospectively relative to the identification of a congenital anomaly, it is not likely to be biased by the result. The study can therefore be described as a large, population-based, prospective cohort study designed to investigate the impact of inhaled budesonide on the outcome of pregnancy, when taken early in pregnancy.

Of the 2014 infants whose mothers stated the use of inhaled budesonide in early pregnancy, 75 infants (3.8%, 95% CI 2.9, 4.6) had congenital malformations recorded in the Medical Birth Registry. Among all infants born in 1995 – 1997, the corresponding rate was 3.5%. Among the budesonide treated cohort, there were four infants with orofacial cleft, the most common malformation reported in association with CS administration in animal studies[3]. The expected number based on the control group would have been 3.3. Although the estimated risk ratio is 1.2, the CI around this point estimate is wide (0.3 – 3.1) and indicates that no increased risk was detected.

Subsequent to the publication of the original epidemiological study, updated information was added[2], bringing the total number of infants exposed to 2534 and percent with congenital malformations to 3.6% (95% CI 2.9 – 3.6).

While reassuring that budesonide is not a significant teratogen, the authors of the original reference[1] point out that the inability to demonstrate a teratogenic effect may not mean the absence of such effects. Assuming a two-sided α=0.05, in order to have an 80% chance of demonstrating a 20% increased risk for orofacial cleft, or a true risk ratio of 1.2, more than 100,000 exposures would have to be studied. To detect a doubling of the incidence of this malformation, an occurrence more likely to be recognized clinically, would require only 5000 exposures. With the total number of exposed infants reported as 2534 (1998 data), the achievement of the latter number of exposures is not an unrealistic expectation. How much

additional reassurance such exposures would add is questionable, however.

1.2 Additional Supporting Material

Inhaled budesonide for treatment of asthma has been available for 19 years (1982) when it was first approved in Europe as a pMDI. It has since become available worldwide, and was approved as a dry powder formulation (Pulmicort Turbuhaler) in Europe in 1988, and in the US in 1997. The aqueous suspension for nebulization (Pulmicort Respules) is also widely available, although it has only been approved for use in the US for about one year (August, 2000). According to the sponsor, a search of the AZ adverse event database from 1982 – June 2000 revealed only two (2) reports of fetal disorders associated with inhaled budesonide products.[4] Internal data derived from a search of the AERS database for all budesonide-containig products (inhaled and intranasal) disclosed a total of eight (8) possible drug-related gestational events: spontaneous abortion – 4, spina bifida – 2, and one event of each of the following: intrauterine growth retardation, stillbirth, tooth discoloration, trisomy 18, and agenesis of the left foot. There were no reports of orofacial cleft in the AERS database.

An association between poorly controlled and severe asthma and adverse perinatal outcome has been described in many different articles published in the medical literature over the past 25 years, several of which have been included by the sponsor. Most address the association between asthma and outcomes such as pre-eclampsia, premature labor, and low birth weight. The specific issue of congenital malformations associated with anti-asthma medication tends to be confounded by the severity of disease itself. One prospective cohort study of 824 pregnant asthmatic patients belong to a California-based HMO and 678 matched non-asthmatic controls found no association between first trimester use of short-acting β-agonists, theophylline, cromolyn and ICS, but an increased risk of pre-eclampsia (RR=2.0) with use of oral systemic corticosteroids[5].

Finally, the sponsor has included a jointly issued position statement by ACOG and ACAAI[6] recommending that inhaled corticosteroids should be considered the prophylactic medications of choice for use in pregnant women with persistent asthma, unless they are well-controlled by cromolyn or nedocromil. The statement goes on to recommend that if an inhaled corticosteroid is to be newly initiated in a woman who is pregnant or is likely to become pregnant,

beclomethasone (BDP) or budesonide should generally be chosen. The Colleges base their recommendations on six studies regarding the gestational use of ICS that have been published since 1993, four dealing specifically with safety issues and two with efficacy. Three of the safety studies included a total of 573 pregnant women, 546 of whom had used BDP. The fourth study, the Swedish Medical Birth Registry[1] data, described the budesonide exposed pregnant women described in greater detail above.

2. Labeling Comments

- General Comment: For clarity, the sponsor should consider consolidating the results of the Swedish epidemiological study and its update into a single report rather than describing them separately.
- In paragraph 4, sentence 2, the dates should read 1995 – 1997.
- In paragraph 5, in sentence 1, the statement ... would be changed to "infants whose mothers were exposed to inhaled budesonide."
- In paragraph 5, in sentence 2, the statement ... should be changed to "infants whose mothers were exposed to inhaled budesonide during early pregnancy was ...
- The following sentence should be added to the beginning of paragraph 6: ...

3. Recommendations to be forwarded to Sponsor

We have completed our review of your submission SLR 012 for NDA 20-441 for Pulmicort Turbuhaler, which provides revised labeling to the Pregnancy Subsection of the current package insert. While we find the proposed supplement to be approvable, changes in the wording of the section will be required (see revisions in attachment) before a final action may be taken. As a general comment, we believe that the clarity of the section would be greatly improved by consolidating the report of the Swedish epidemiological study and its update, rather than reporting them separately. In addition, as requested during the telecon of 8 August 2001, please provide the following information:

- A discussion of whether the epidemiological study and other human exposure data provided in this submission would support a change for Pulmicort Turbuhaler from Pregnancy Category "C" to Pregnancy Category "B."

- Comparative human gestational exposure data between budesonide and other inhaled corticosteroid products, particularly for beclomethasone dipropionate.

We remind you that Pregnancy Subsection of the current package insert of NDA 20-929 for Pulmicort Respules should also be updated, consistent with the information in the PI of NDA 20-441.

We note the absence of class labeling with regard to the impact of orally inhaled corticosteroids on growth in children in the PI of NDA 20-441. Submit updated labeling for Pulmicort Turbuhaler incorporating this information.

4. References:

1. Kallen, B., H. Rydhstroem, and A. Aberg, "Congenital Malformations After the Use of Inhaled Budesonide in Early Pregnancy," *Obstetrics and Gynecology* 93; 3: March 1999.
2. Ericson, A. and B. Kallen, "Use Of Drugs During Pregnancy—Unique Swedish Registration Method That Can Be Improved," Information from the *Swedish Medical Products Agency* 1: 8-11, 1999.
3. Rodriguez-Pinilla, E. and M.L. Martinez-Frias, "Corticosteroids During Pregnancy and Oral Clefts: A Case-Control Study," *Teratology* 58:2-5, 1998.
4. NDA 20-441 SLR-012, Attachment 1, p.3.
5. Schatz M, Zeiger RS, Harden K, Hoffman CC, Chillingar L, Petitti D. "The Safety of Asthma and Allergy Medications during Pregnancy" *J Allergy Clin Immunol* 1997; 100:301-313.
6. Position Statement, American College of Obstetrics and Gynecology with the American College of Allergy, Asthma, and Immunology, "The Use of Newer Asthma and Allergy Medications during Pregnancy" *Annals of Allergy, Asthma, and Immunology* 2000, 84, 475-480.

MEDICAL TEAM LEADER REVIEW

Division of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION #:	NDA 20-441	APPLICATION TYPE:	Resubmission to NDA
SPONSOR:	AstraZeneca	PRODUCT/PROPRIETARY NAME:	Pulmicort Turbuhaler
INDICATION:	Maintenance Treatment of Asthma	USAN / Established Name:	Budesonide as dry powder formulation
CATEGORY OF DRUG:	Corticosteroid	ROUTE OF ADMINISTRATION:	Orally Inhaled
MEDICAL REVIEWER:	Purucker	REVIEW DATE:	14 November 2001

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date/ CDER Stamp Date:	Document ID #:	Submission type/Comments:
22 October 2001/ 23 October 2001	SLR-012-BZ	Response to approvable letter issued 20 August 2001. The supplement due date is 7 December 2001.

RELATED APPLICATIONS

Document Date:	Document ID #:	Comments:
16 February 2001	NDA 20-441 SLR 012	Pregnancy labeling supplement

Overview of Application/Review: This submission is comprised of a complete response to the approvable letter of 20 August 2001 regarding proposed revisions to the Pregnancy subsection of the PRECAUTIONS Section of the approved product label. The sponsor has provided an argument in favor of a change in Pregnancy Category from "C" to "B" for Pulmicort Turbuhaler. The data are supportive of this change, and the proposed labeling should be implemented following minor changes in wording.

Outstanding Issues: None.

Recommended Regulatory Action:

N drive location:

NDAs:

Efficacy / Label Supp.: ___X___ Approvable _____ Not Approvable

Signed: Medical Team Leader: _____ Date: _____

Division Director: _____ Date: _____

1. BACKGROUND

On 16 February 2001, the sponsor submitted a supplement (S-012) to NDA 20-441 for Pulmicort Turbuhaler proposing revised wording in the **Pregnancy** subsection of the **PRECAUTIONS** Section of the approved package insert. Included in the proposed revisions were data from two large Swedish epidemiological studies that failed to demonstrate increased risk for adverse pregnancy outcome with gestational exposure to budesonide (BDS; >2500 exposed pregnancies). The sponsor did not propose to remove or otherwise revise the text conveying information about the teratogenic and embryocidal effects of systemic BDS on fetuses of pregnant rabbits, or to change the Pregnancy Category, presently "C."

In the approvable letter dated 20 August 2001, the Division identified two issues that needed to be fully addressed before a final action could be taken. First, the sponsor was asked to discuss whether these human pregnancy exposure data for inhaled BDS would support a change from Pregnancy Category "C" to "B" (Comment 1a). Second, the sponsor was asked to submit human gestational exposure data, if available, comparing BDS to other inhaled corticosteroid (ICS) products, particularly beclomethasone dipropionate (BDP) because of its comparable duration of marketing (Comment 1b). The latter issue is important because if approved, this supplement would result in labeling of Pulmicort Turbuhaler as the first (and only) inhaled corticosteroid with a Pregnancy Category "B" classification. Inhaled BDP has been available as an orally inhaled product for the treatment of asthma for a duration (approximately two decades) comparable to BDS.

This submission constitutes a complete response to each of these two issues and is therefore fileable. The sponsor proposes to change the Pregnancy Category from "C" to "B," and has included supporting arguments and comparative data. There is a post-marketing surveillance update comprised of adverse pregnancy outcomes associated with BDS that the sponsor has not previously reported. The other changes to the **Pregnancy** subsection of the package insert (see below), were included in the original supplement. The sponsor has added a somewhat guarded interpretation of the potential significance of "positive" pre-clinical findings, given the "negative" human data. No other changes in the pre-clinical information have been proposed.

As a corollary, the sponsor has also chosen to address two additional comments that were not

considered central to the approvability of this supplement. First, wording in the submission has not been revised to consolidate the results of the two Swedish epidemiological studies (see Comment 2). Second, a separate labeling supplement to NDA 20-929 for Pulmicort Respules containing wording comparable to that proposed for Pulmicort Turbuhaler in the **Pregnancy** subsection is being prepared and will be submitted to that NDA.

2. APPROVED LABELING WITH SPONSOR'S PROPOSED MODIFICATIONS
   - Sponsor's proposed changes in ~~strikeout~~ and underline
   - FDA Reviewer's edits appear in red
   - Comments supporting FDA Reviewer's edits appear bulleted at the end of the section

Pregnancy

Teratogenic Effects: Pregnancy ~~Category C~~ 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 1/3 the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) and 500 mcg/kg/day in rats (approximately 3 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 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/m^2 basis).

~~There are no adequate and well controlled studies in pregnant women. Budesonide 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.

[redacted] ~~Studies in~~ 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 [redacted] (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 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%).

Ericson A, et al. Information from the *Swedish Medical Products Agen y*

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.

Labeling Comments

- In paragraph 4, sentence 1, "Studies *of* pregnant women…" is preferred over
- In paragraph 4, sentence 2, the dates should read 1995 – 1997 (see Kallen et al, *Obstet Gynecol* 93; 392-5, 1999; p.393 2nd paragraph under "Results" section).
- In paragraph 5, in sentence 1, the statement should be changed to "infants whose mothers were exposed to inhaled budesonide."
- In paragraph 5, in sentence 2, the statement should be changed to "infants whose mothers were exposed to inhaled budesonide..."

3. REVIEW

3.1 Response to Comment 1a

Provide a discussion of whether the epidemiological study and other human exposure data provided in this submission (S-012) would support a change for Pulmicort Turbuhaler

from Pregnancy Category "C" to Pregnancy Category "B."

The sponsor argues that there are sufficient data and experience with inhaled BDS during pregnancy to justify a change in the pregnancy category from a "Category C" to a "Category B."

As a general statement, the sponsor maintains that the safety of orally inhaled BDS is supported by its long duration of marketing (as three different products for ≥ 20 years) and its extensive worldwide patient exposure record (≥10 billion patient-days).

With regard to human pregnancy, the results of two large population based prospective cohort studies based on the Swedish Medical Birth Registry[1, 2] were submitted and reviewed with the initial supplement in this series (see MO review of 16 February 2001 supplement SLR-012). It was concluded by the sponsor and by the FDA reviewer that these studies indicated no increased risks for congenital malformations from the use of inhaled BDS during early pregnancy, although the power to detect an increase in the frequency of a specific malformation (orofacial cleft) was only approximately 50%. There was no clear "signal" of any other particular malformation.

The sponsor has submitted a synopsis of a recently completed study[3, 4] of pregnancy outcomes also utilizing the Swedish Medical Birth Registry. The study results are relevant to the safety of inhaled BDS with regard to pregnancy outcomes other than congenital malformations, and asthma medications other than inhaled corticosteroids. Limited data are available from this study because it has been published as an abstract[3] only, although the full-length article[4] has been submitted for publication and is presently under review, and a copy of this manuscript was submitted with the supplement. The data from this study are as follows:

During the period 1995 –1998, a total of 293,948 live, singleton births were identified and characterized by pregnancy duration, gender, birth weight, and length of the newborn. There were 7,719 mothers who reported the use of non-ICS asthma medications during early pregnancy and 2,968 who reported the use of inhaled BDS only during early pregnancy. The study also identified 207 mothers who reported the use of BDS during the entire pregnancy. According to the preliminary results, the use of inhaled BDS was not associated with clinically relevant effects on birth weight, birth length, premature birth rate, or incidence of stillbirth.

Other data in support of the Pregnancy Category change for Pulmicort Turbuhaler included post-marketing surveillance information. The sponsor updated the post-marketing surveillance to include all reports up to April 2001. An expanded search incorporating formulations of orally inhaled BDS other than Pulmicort Turbuhaler was also conducted, as was a search for adverse pregnancy outcomes other than congenital malformation (i.e. miscarriage, intrauterine death, or stillbirth). A total of 8 cases of congenital malformations of varying types and 6 cases of miscarriage/intrauterine death/stillbirth were located. Of this total, 4 of the latter category were miscarriages occurring prior to the 10th week of pregnancy, one was an intrauterine death at 16 weeks, and one was a stillbirth. The four miscarriages were reported in the FDA review of the prior submission through an internal search of the AERS database (MO review of S-012, p.6). Of the 8 cases of congenital malformation, two had been reported by the sponsor in the prior submission and 6 had been located via FDA review of the AERS database and reported in the prior review. There were no reports of orofacial cleft in either report.

3.2 Response to Comment 1b

Provide comparative human gestational exposure data between budesonide and other inhaled corticosteroid (ICS) products, particularly for beclomethasone dipropionate (BDP).

The sponsor was unable to locate any published reports where a direct comparison was made in a single study between BDS and other inhaled corticosteroids, specifically BDP, with regard to gestational outcomes. However, several reports of pregnancy outcome related to maternal exposure to a single ICS or other anti-asthma medication were included.

As noted above, there were three published studies of pregnancy outcomes associated with maternal exposure to inhaled BDS during pregnancy[1, 2, 3, 4] that together accounted for 2,968 pregnancies. By way of comparison, there were six studies reporting the outcomes for 1,019 women receiving all other inhaled corticosteroids combined during pregnancy. One of these six studies also included women receiving oral corticosteroids. About half of the total exposed population included in these reports, or 591 women, were treated with inhaled BDP. Slightly more than half of this number (395) could be accounted for in a single study[5]. In general, there did not appear to be any evidence of increased risk of adverse pregnancy outcome associated

with ICS in general or BDP in particular, although the numbers were very small, much smaller than for BDS, and therefore not powered to detect anything other than relatively large differences in outcome. A study of one database did appear to indicate an association of theophylline use with congenital malformations[5], an observation not corroborated in a 2nd report.[6]

3.3 Response to Comment 2

Consolidate the report of the Swedish epidemiological study and its update, rather than reporting them separately.

In summary, the sponsor argues that although the two epidemiological studies[1,2] both analyzed data obtained from the same registry (the Swedish Medical Birth Registry), they were independently conducted. The first study was sponsored by Astra Draco, Sweden and was authored by Kallen et al[1]. The second study was conducted independently by the Center for Epidemiology at the Medical Products Agency, and was authored by Ericson et al[2]. The sponsor maintains that the two studies had different objectives, different designs, different statistical models, and different sponsors and therefore should not be combined.

4. DISCUSSION AND RECOMMENDATIONS

According to 21 CFR 201.57 (f)(6)(i)(b), a Pregnancy Category B drug product is defined, in part, as a drug where an adverse effect has been shown in animal studies, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy, and there is no evidence of a risk in later trimesters. Evidence presented in the current submission is supportive that Pulmicort Turbuhaler satisfies these criteria. The evidence is comprised of the following:

1) ***Information from two epidemiological studies[1,2] of Swedish birth registries mined for pregnancy outcome data specifically related to congenital malformations.***

These two studies provide the primary basis for the new Pregnancy information labeling. The referenced studies identified 2,543 births in which maternal exposure to inhaled BDS occurred during early gestation. Rates of congenital malformations among the exposed group (3.6%) were similar to background rates (3.5%). The incidence of orofacial cleft, the most likely malformation based upon animal data, did not exceed the background rate, although

the study had only 50% power to detect a difference.

2) ***Information from an unpublished study[3,4] of this same registry mined for pregnancy outcome data unrelated to congenital malformations.***

   This study showed no clinically relevant differences in mean birth length, weight, duration of gestation, or incidence of stillbirths.

3) ***Information from this same unpublished study[3,4] that examined outcomes of pregnancies during which the mother used inhaled BDS for the entire duration of the pregnancy, as opposed to the first trimester only.***

   This study showed no clinically relevant difference in the aforementioned parameters for women who had used BDS throughout their pregnancies compared to women who used BDS early in pregnancy only or who used asthma medications other than ICS.

4) ***Information from AERS and other post-marketing surveillance systems concerning BDS.***

   The overall safety of inhaled BDS during pregnancy is further supported by the absence of a signal from the worldwide post-marketing surveillance system in addition to AERS.

5) ***Information from AERS, other post-marketing surveillance systems, and the peer-reviewed medical literature concerning other ICS.***

   The overall safety of inhaled BDS during pregnancy is also supported by the absence of a signal from the controlled clinical data and post-marketing surveillance of other ICS, which are of the same pharmacological class as BDS

Considered individually, each of the above data sources can be considered limited by the relatively small numbers of patients. However, taken in totality, the data are convincing that Pulmicort Turbuhaler satisfies the criteria for a Pregnancy Category "B" drug classification. This reviewer is in agreement with the change in Pregnancy Category from "C" to "B" for Pulmicort Turbuhaler. The proposed labeling changes should be implemented, following minor changes in wording indicated in this review.

5. REFERENCES:

1. Kallen, B., H. Rydhstroem, and A. Aberg, "Congenital Malformations After the Use of Inhaled Budesonide in Early Pregnancy," *Obstetrics and Gynecology 1999;* 93; 392-395.

2. Ericson, A. and B. Kallen, "Use Of Drugs During Pregnancy—Unique Swedish Registration Method That Can Be Improved," Information from the *Swedish Medical Products Agency* 1999; 1:99:8-11.
3. Gerhardsson de Verdier M. and E. Norjavaara "Normal Length and Weight in Children Whose Mothers Used Inhaled Budesonide. Abstract in *Eur Resp Journal* 2001; 18:254 (2551).
4. Gerhardsson de Verdier M. and E. Norjavaara "Normal Pregnancy Outcomes in a Population-Based Study Including 2,968 Pregnant Women Exposed to Budesonide." Manuscript submitted *ERS* 2001.
5. Rosa F. "Databases in the Assessment of the Effects of Drugs during Pregnancy." *J. Allergy Clin. Immunol. 1999;* 103:s360-s361.
6. Jadad, A.R., C Sigouin, P.T. Mohide, M. Levine, M. Fuentes. "Risk of Congenital Malformations Associated with Treatment of Asthma during Early Pregnancy" *Lancet 2000;* 355;119.

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

/s/

Mary Purucker
12/28/01 11:16:48 AM
MEDICAL OFFICER

Robert Meyer
12/28/01 03:24:22 PM
MEDICAL OFFICER

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/s/

Mary Purucker
8/20/01 01:13:29 PM
MEDICAL OFFICER

Robert Meyer
8/21/01 08:45:21 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-441/ S-012

ADMINISTRATIVE DOCUMENTS AND CORRESPONDENCE

AstraZeneca

Date: February 28, 2002

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 20-441
Pulmicort Turbuhaler® (budesonide inhalation powder)
Electronic Submission of Final Printed Labeling for Approved sNDA S-010 60 Dose 200 mcg Product and Approved sNDA S-012 Pregnancy Labeling

Dear Dr. Meyer:

Please refer to our approved New Drug Application for Pulmicort Turbuhaler® (budesonide inhalation powder), NDA 20-441, and to the following two Approved sNDAs. The sNDA S-010 was submitted December 22, 2000 for the 60-dose 200 mcg M0-ESP product and approved October 15, 2001. The sNDA S-012 was submitted February 16, 2001 to revise the pregnancy section of the package insert and was approved Dec 31, 2001. Reference is also made to the Division's request that AstraZeneca submit final printed labeling as indicated in the Approval Letters.

AstraZeneca is providing the final printed labeling for both sNDAs listed above as a single submission, in electronic format per the FDA Guidance Document entitled: " Providing Regulatory Submissions in Electronic Format – NDA", dated January 1999. The changes to the package insert for both approved sNDAs are included in one PI revision (Part# 808179-01).

This submission consists of one CD-ROM (approx. 1.12 MB) that contains the following files in a folder named "Labeling".

- labeltoc.pdf
- history.pdf
- current.pdf (Package Insert Part# 808179-00 as PDF of WORD PI)
- approved.pdf (Package Insert Part# 808179-01 as PDF of WORD PI)
- pi.pdf (Package Insert Part# 808179-01 as PDF of manufacturing PI)
- carton80835200.pdf (60 dose sample carton)
- label80835000.pdf (60 dose sample label/outsert of "Patient's Instructions for Use")

US Regulatory Affairs
AstraZeneca LP
1800 Concord Pike PO Box 8355 Wilmington DE 19803-8355

To assure that these files are virus free, virus scanning was accomplished using Norton AntiVirus Corporate Edition 7.03 with version 40219s as the virus definition file (date 2/19/02).

The confidentiality of this submission, and all information contained herein, is claimed by AstraZeneca under all applicable laws and regulations. Disclosure of any such information is not authorized without the prior written authorization of AstraZeneca.

Please direct any questions or requests for additional information to me, or in my absence, to Richard Jahn, Regulatory Project Manager, at (302) 885-8677.

Sincerely,

Richard Jahn for

Christopher M. Blango
Director, Regulatory Affairs
Telephone: (302) 885-1809
Fax: (302) 886-2822

Enclosure: CD-ROM – Archival Electronic Copy (for Central Document Room)
Desk Copy: Robert Meyer, M.D., Director
Division of Pulmonary and Allergy Drug Products
HFD-570 Room 10-B03 (Letter only)

Division of Pulmonary and Allergy Drug Products
CONSUMER SAFETY OFFICER REVIEW

Application Number: NDA 20-441/S-012

Name of Drug: Pulmicort Turbuhaler® (budesonide inhalation powder)

Sponsor: AstraZeneca PL

Material Reviewed:

Submission Date(s): BL Dated November 15, 2001 (Draft of changes to pregnancy section)
BL Dated December 28, 2001 (Package insert)
YY Dated September 28, 2001 (Current Package Insert)

Background

Labeling discussions with AstraZeneca took place November 14, 200 via telephone discussion and facsimilie transmission. Mr. Christopher Blango of AstraZeneca accepted Dr. Mary Puruker's proposed wording and submitted a document dated November 15, 2001 indicating the agreed upon wording for the Pregnancy section of the package insert. AtraZeneca followed up with a submission dated December 29, 2001, a complete copy of the final draft label, incorporating the agreed upon changes.

Review

Electronic submission of the Final Draft Label received December 28, 2001. A visual line-by-line comparison with the currently approved label found that this version contained all items agreed to as of November 15, 2001.

Conclusions

All appropriate changes have been implemented as discussed above.

Anthony M. Zeccola
Regulatory Management Officer

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/s/

Anthony Zeccola
12/28/01 02:50:05 PM
CSO

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

/s/

Mary Purucker
8/8/01 05:22:41 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-441/S-012

PRIOR APPROVAL SUPPLEMENT

AstraZeneca
P.O. Box 8355
Wilmington, DE 19803-8355

Attention: Eric Couture, Ph.D.
Director, Regulatory Affairs

Dear Dr. Couture:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Pulmicort Turbuhaler (budesonide inhalation powder)
NDA Number:	20-441
Supplement number:	S-012
Date of supplement:	February 16, 2001
Date of receipt:	February 20, 2001

This supplemental application proposes the following change(s): revision to the Pregnancy section of the package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 21, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Document Room 10B-03
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products, HFD-570
Attention: Document Room 10B-03
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call Ms.Gretchen Trout, Regulatory Project Manager, at (301) 827-1058.

Sincerely,

Sandra L. Barnes
Chief, Project Management Staff
Division of Pulmonary and Allergy Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

/s/

Gretchen Trout
2/27/01 01:27:28 PM
For S.Barnes