

Effective Date: 07/12/2006

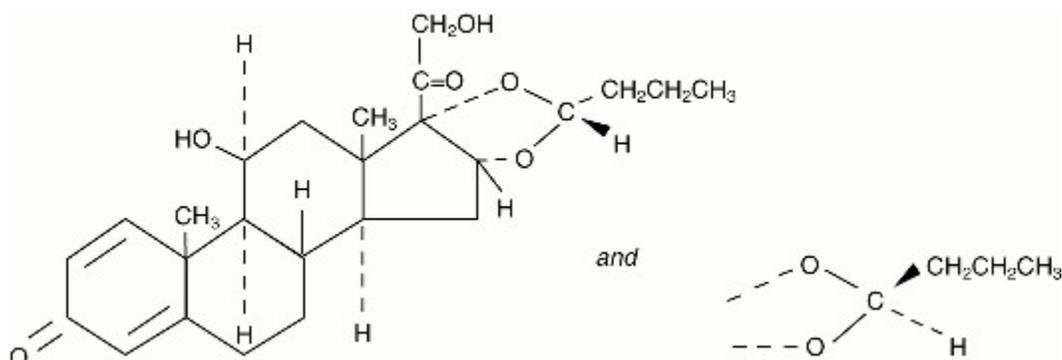
PULMICORT FLEXHALER 180 mcg
(budesonide inhalation powder, 180 mcg)

PULMICORT FLEXHALER 90 mcg
(budesonide inhalation powder, 90 mcg)

For Oral Inhalation Only

DESCRIPTION

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



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

PULMICORT FLEXHALER is an inhalation-driven multi-dose dry powder inhaler containing a formulation of 1 mg per actuation of micronized budesonide and micronized lactose (which may contain trace or residual levels of milk proteins). Each actuation of PULMICORT FLEXHALER 180 mcg delivers 160 mcg budesonide from the mouthpiece

and each actuation of PULMICORT FLEXHALER 90 mcg delivers 80 mcg budesonide from the mouthpiece (based on *in vitro* testing at 60 L/min for 2 sec). Each PULMICORT FLEXHALER 180 mcg contains 120 actuations and each PULMICORT FLEXHALER 90 mcg contains 60 actuations.

In vitro testing has shown that the dose delivery for PULMICORT FLEXHALER is dependent on airflow through the device, as evidenced by a decrease in the fine particle dose at a flow rate of 30 L/min to a value that is approximately 40-50% of that produced at 60 L/min. At a flow rate of 40 L/min, the fine particle dose is approximately 70% of that produced at 60 L/min. 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 asthmatic children age 6 to 17 (N=516, FEV₁ 2.29 [0.97–4.28]) peak inspiratory flow (PIF) through PULMICORT FLEXHALER was 72.5 [19.1 – 103.6] L/min). Inspiratory flows were not measured in the adult pivotal study. Patients should be carefully instructed on the use of this drug product to assure optimal dose delivery.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

The activity of PULMICORT FLEXHALER 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 precise mechanism of corticosteroid actions on inflammation in asthma is not known. Inflammation is an important component in the pathogenesis of asthma. 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 FLEXHALER or inhaled budesonide. 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

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 and using a different budesonide containing dry-powder inhaler) with an absolute systemic availability of 39% of the metered dose. Peak steady-state plasma concentrations of budesonide delivered from PULMICORT FLEXHALER in adults with asthma (n=39) occurred at approximately 10 minutes post-dose and averaged 0.6 and 1.6 nmol/L at doses of 180 mcg once daily and 360 mcg twice daily, respectively.

In asthmatic patients, budesonide showed a linear increase in AUC and C_{max} with increasing dose after both a single dose and repeated dosing of inhaled budesonide.

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 FLEXHALER. Budesonide showed little or no binding to corticosteroid binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism

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

Excretion/Elimination

The 22R form of budesonide 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. Budesonide was excreted in urine and feces in the form of metabolites. Approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

Special Populations

No clinically relevant pharmacokinetic differences have been identified due to race, sex, 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.

Peak steady-state plasma concentrations of budesonide delivered via PULMICORT FLEXHALER in children and adolescents with asthma (n=14) occurred at approximately 15 to 30 minutes post-dose and averaged 0.4 and 1.5 nmol/L at doses of 180 mcg once daily and 360 mcg twice daily, respectively.

Hepatic Insufficiency

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

Drug-Drug Interactions

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

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

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

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

The effects of inhaled budesonide 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 inhaled budesonide 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 with 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 of inhaled budesonide twice daily 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 taking 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 inhaled budesonide when administered at doses ranging from 100 to 800 mcg twice daily. In patients who had previously been oral steroid-dependent, use of inhaled budesonide at doses ranging from 100 to 800 mcg twice daily was associated with higher stimulated cortisol response compared with baseline following 1 year of therapy.

The administration of inhaled budesonide via a different dry-powder inhaler 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 inhaled budesonide on growth is not fully known.

Clinical Studies

The safety and efficacy of PULMICORT FLEXHALER were evaluated in two 12-week, double-blind, randomized, parallel-group, placebo-controlled clinical studies conducted at sites in the United States and Asia involving 1137 patients aged 6 to 80 years with mild to

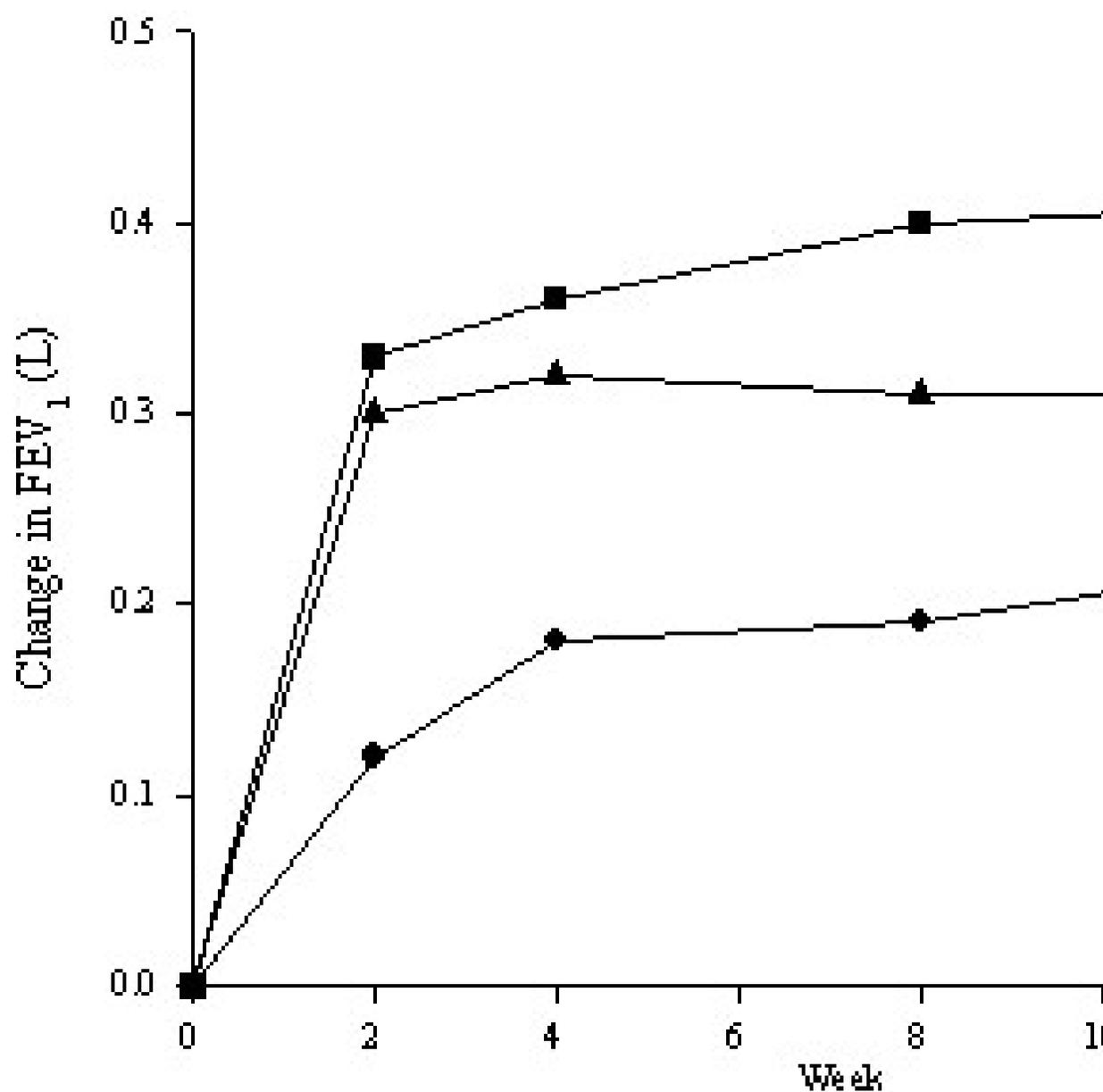
moderate asthma. Study 1 evaluated PULMICORT FLEXHALER 180 mcg, PULMICORT TURBUHALER® 200 mcg, and placebo, each administered as 1 inhalation once daily or 2 inhalations twice daily in patients 18 years of age and older with mild to moderate asthma previously treated with inhaled corticosteroids. The delivered dose of PULMICORT FLEXHALER 180 mcg and PULMICORT TURBUHALER 200 mcg are the same; each delivers 160 mcg from the mouthpiece. Study 2 evaluated PULMICORT FLEXHALER 90 mcg, 2 inhalations once daily or 4 inhalations twice daily, PULMICORT TURBUHALER 200 mcg, 1 inhalation once daily or 2 inhalations twice daily, and placebo in pediatric patients aged 6 to 17 years with mild to moderate asthma. Both of the studies had a 2-week placebo treatment run-in period followed by a 12-week randomized treatment period. The primary endpoint was the difference between baseline and the mean of the treatment-period FEV₁ (adults) or FEV₁ % predicted (children).

Adult Patients with Asthma (Study 1)

This study enrolled 621 patients aged =18 to 80 years with mild-to-moderate asthma (mean baseline % predicted FEV₁ 64.3%) whose symptoms were previously controlled on inhaled corticosteroids. Mean change from baseline in FEV₁ in the PULMICORT FLEXHALER 180 mcg, 2 inhalations twice-daily group was 0.28 liters, as compared to 0.10 liters in the placebo group (p<0.001). Secondary endpoints of morning and evening peak expiratory flow rate, daytime asthma symptom severity, nighttime asthma symptom severity, daily rescue medication use, and the percentage of patients who met predefined asthma related withdrawal criteria showed differences from baseline favoring PULMICORT FLEXHALER over placebo. The responses of PULMICORT FLEXHALER compared with PULMICORT TURBUHALER tended to be lower.

12-Week Trial in Adult Patients with Mild to Moderate Asthma (Study 1)

Mean Change from Baseline in FEV₁ (L)



	N	N	N	N
PULMICORT FLEXHALER 180 mcg	130	127	115	111
PULMICORT TURBUHALER 200 mcg	129	124	122	118
Placebo	119	113	84	78

- ▲ PULMICORT FLEXHALER 180 mcg, 2 inhalations twice daily
- PULMICORT TURBUHALER 200 mcg, 2 inhalations twice daily
- ◆ Placebo

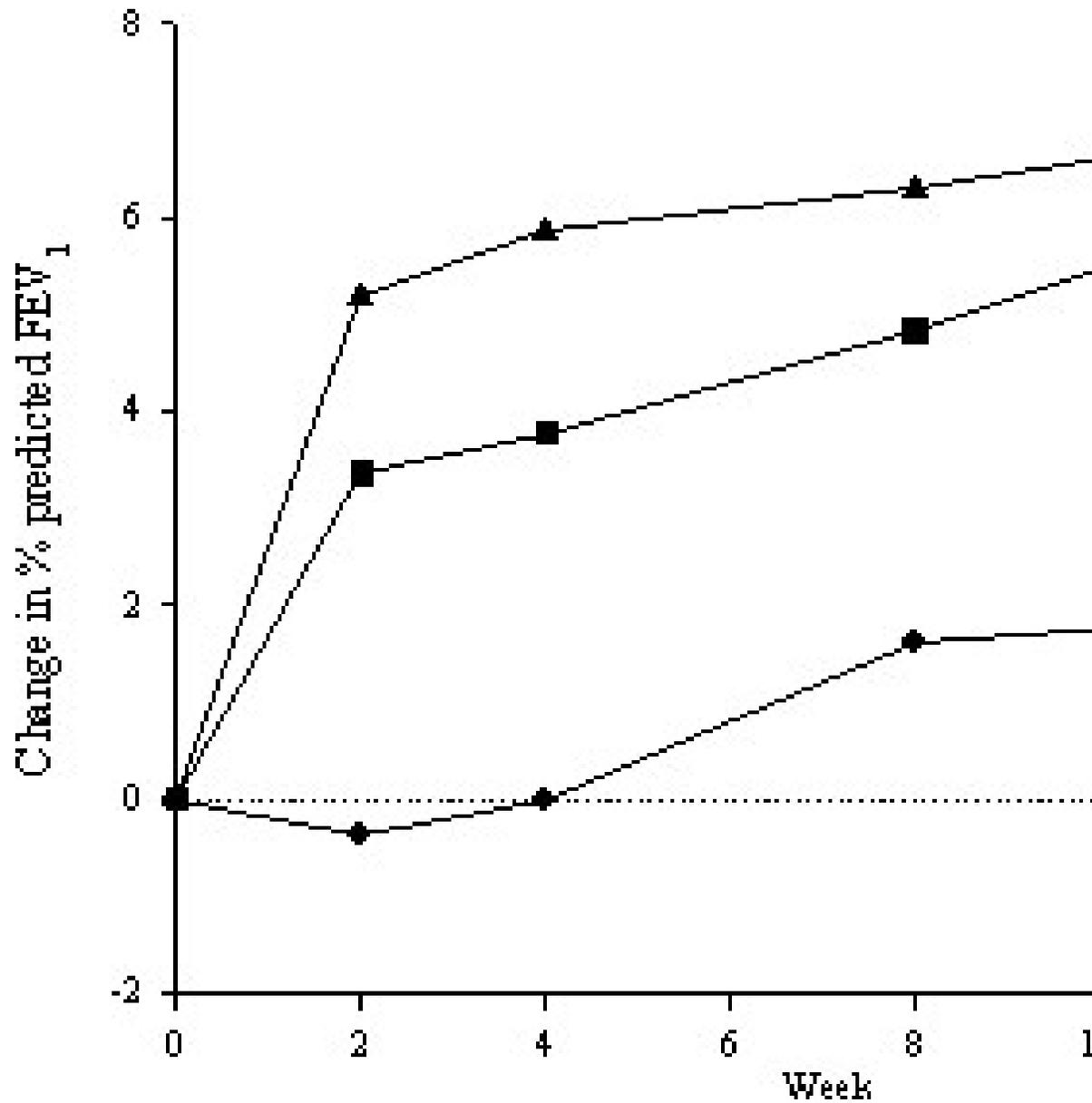
* Average over treatment period: values are adjusted treatment means for the average period using last observation carried forward (primary endpoint).
 Comparison of PULMICORT FLEXHALER 180 mcg, 2 inhalations twice daily

Pediatric and Adolescent Patients with Asthma (Study 2)

This study enrolled 516 patients aged 6 to 17 years with mild asthma (mean baseline % predicted FEV₁ 84.9%). The study population included patients previously treated with inhaled corticosteroids for no more than 30 days before the study began (4%) and patients who were naïve to inhaled corticosteroids (96%). Mean change from baseline in % predicted FEV₁ during the 12-week treatment period in the PULMICORT FLEXHALER 90 mcg, 4 inhalations twice daily treatment group was 5.6 compared with 0.2 in the placebo group (p<0.001). Secondary endpoints of morning and evening PEF showed differences from baseline favoring PULMICORT FLEXHALER over placebo.

12-Week Trial in Pediatric Patients With Mild Asthma (Study 2)

Mean Change from Baseline in Percent Predicted FEV₁



	N	N	N	N
PULMICORT FLEXHALER 90 mcg	93	84	87	81
PULMICORT TURBUHALER 200 mcg	99	97	95	91
Placebo	104	94	94	91

- ▲ PULMICORT FLEXHALER 90 mcg, 4 inhalations twice daily
- PULMICORT TURBUHALER 200 mcg, 2 inhalations twice daily
- ◆ Placebo

* Average over treatment period: values are adjusted treatment means for the average treatment period using last observation carried forward (primary endpoint).

Comparison of PULMICORT FLEXHALER 90 mcg, 4 inhalations twice daily vs placebo over the treatment period: $p < 0.001$

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

PULMICORT FLEXHALER is contraindicated in patients with known hypersensitivity to any component of the formulation.

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to PULMICORT FLEXHALER 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 hypothalamic-pituitary-adrenal (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 FLEXHALER 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.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to PULMICORT FLEXHALER. Lung function (FEV₁ or AM PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to PULMICORT FLEXHALER may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, arthritis, eosinophilic conditions, and eczema.

Patients who are on drugs that 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 FLEXHALER 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 FLEXHALER, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with PULMICORT FLEXHALER 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 FLEXHALER. 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 (see DOSAGE AND ADMINISTRATION).

In responsive patients, PULMICORT FLEXHALER may permit control of asthma symptoms with less suppression of HPA-axis function than therapeutically equivalent oral doses of prednisone. Since budesonide is absorbed into the circulation and can be systemically active, the beneficial effects of PULMICORT FLEXHALER 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 FLEXHALER.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with PULMICORT FLEXHALER 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, reduced bone mineral density, and adrenal suppression may appear in a small number of patients,

particularly at higher doses. If such changes occur, PULMICORT FLEXHALER should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic steroids.

Orally inhaled corticosteroids, including budesonide, may cause a reduction in growth velocity when administered to pediatric patients. A reduction in growth velocity may occur as a result of inadequate control of asthma or from use of corticosteroids for treatment. The potential effects of prolonged treatment on growth velocity should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including PULMICORT FLEXHALER, each patient should be titrated to his/her lowest effective dose (see PRECAUTIONS, Pediatric Use).

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

In clinical trials with PULMICORT FLEXHALER, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. These infections may require treatment with appropriate antifungal therapy and/or discontinuance of treatment with PULMICORT FLEXHALER.

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

Patients being treated with PULMICORT FLEXHALER 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. For proper use of PULMICORT FLEXHALER and to attain maximum improvement, the patient should read and follow the accompanying *Patient's Instructions for Use*.

- Patients should use PULMICORT FLEXHALER 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.
- Patients should be advised that PULMICORT FLEXHALER is not a bronchodilator and is not intended to treat acute or life-threatening episodes of asthma.
- Patients should be advised that the effectiveness of PULMICORT FLEXHALER depends on proper use of the device and inhalation-administering technique:
 1. PULMICORT FLEXHALER must be in the upright position (mouthpiece on top) during loading in order to provide the correct dose.
 2. PULMICORT FLEXHALER must be primed when the unit is used for the very first time. To prime the unit, it must be held in an upright position and the brown grip turned fully in one direction as far as it will go, then twisted fully back again in the other direction as far as it will go. One of the twisting movements will produce an audible click. This procedure must be repeated.
 3. To load the first dose, the grip must be turned fully in one direction and then fully in the other direction until it clicks.
 4. After the first dose, it is not necessary to prime the unit. However, it must be loaded in the upright position immediately prior to use as described above.
 5. Patients should be advised not to shake the inhaler.
- Patients should place the mouthpiece between the lips and inhale forcefully and deeply. The powder is then delivered to the lungs.
- Patients should not exhale through PULMICORT FLEXHALER.
- Due to the small volume of powder, patients may not sense the presence of any medication entering the lungs when inhaling from PULMICORT FLEXHALER. This lack of sensation does not indicate that the patient is not receiving benefit from PULMICORT FLEXHALER.

- Patients should be advised that rinsing the mouth with water without swallowing after each dosing may decrease the risk of the development of oral candidiasis.
- Patients should be instructed that they will receive a new PULMICORT FLEXHALER unit each time they refill their prescription. Patients should be advised to discard the whole device after the labeled number of inhalations has been used. The dose indicator window tells how many doses are left in the inhaler. The inhaler is empty when the number zero (“0”) on the red background reaches the middle of the window.
- PULMICORT FLEXHALER should not be used with a spacer.
- The mouthpiece should not be bitten or chewed.
- Replace the cover securely after each opening.
- Patients should keep PULMICORT FLEXHALER clean and dry at all times.
- Patients should be advised that improvement in asthma control following inhalation of budesonide 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 not to increase the dosage, but to contact the physician.
- Patients whose systemic corticosteroids have been reduced or withdrawn should be instructed to carry a warning card indicating that they may need supplemental systemic corticosteroids during periods of stress or an asthma attack that does not respond to bronchodilators.
- Patients should be advised not to stop the use of PULMICORT FLEXHALER abruptly.
- Patients should be warned to avoid exposure to chicken pox or measles and if they are exposed, to consult their physicians without delay.
- Long-term use of inhaled corticosteroids, including budesonide, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.

- Women considering the use of PULMICORT FLEXHALER should consult with their physician if they are pregnant or intend to become pregnant, or if they are breast-feeding a baby.
- Patients considering use of PULMICORT FLEXHALER should consult with their physician if they are allergic to budesonide or any other orally inhaled corticosteroid.
- Patients should inform their physician of other medications they are taking as PULMICORT FLEXHALER may not be suitable in some circumstances and the physician may wish to use a different medicine.

Drug Interactions

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in rats and mice using oral administration to evaluate the carcinogenic potential of budesonide.

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 (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50

mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). The concurrent reference corticosteroids (prednisone and triamcinolone acetonide) in these two studies showed similar findings.

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 (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis).

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

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (less than the maximum recommended human daily inhalation dose on a mcg/m² basis).

At 20 mcg/kg/day (less than the maximum recommended human daily inhalation dose on a mcg/m² basis), decreases in maternal body weight gain, prenatal viability, and viability of the young at birth and during lactation were observed. No such effects were noted at 5 mcg/kg (less than the maximum recommended human daily inhalation dose in adults on a mcg/m² basis).

Pregnancy

Teratogenic Effects: Pregnancy category B

As with other glucocorticoids, budesonide produced fetal loss, decreased pup weight, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg/day in rabbits (less than the maximum recommended human daily inhalation dose on a mcg/m² basis) and 500 mcg/kg/day in rats (approximately 3 times the maximum recommended human daily inhalation dose on a mcg/m² basis). No teratogenic or embryocidal effects were observed in rats when budesonide was administered by inhalation at doses up to 250 mcg/kg/day

(equivalent to the maximum recommended human daily inhalation dose on a mcg/m² basis).

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

Studies of pregnant women, however, have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (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 with 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 FLEXHALER 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 FLEXHALER in pediatric patients below 6 years of age have not been established.

Clinical studies with inhaled budesonide included 704 patients 6 to 17 years of age (n=204 treated with PULMICORT FLEXHALER). The frequency of adverse events observed with PULMICORT FLEXHALER in pediatric patients 6 to 17 years of age was similar to that of patients 18 to 80 years of age.

Controlled clinical studies have shown that orally inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with orally inhaled corticosteroids including the impact on final adult height are unknown. The potential for "catch up" growth following discontinuation of treatment with orally inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with PULMICORT TURBUHALER 200 mcg twice daily (n=311) had a 1.1-centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of four years, children treated with PULMICORT TURBUHALER and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving orally inhaled corticosteroids, including PULMICORT FLEXHALER, should be monitored routinely (eg, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks and benefits associated with alternative therapies. To minimize the systemic effects of inhaled corticosteroids, including PULMICORT FLEXHALER, each patient should be titrated to his/her lowest effective dose.

Geriatric Use

Of the total number of patients in controlled clinical studies receiving inhaled budesonide, 153 (n=11 treated with PULMICORT FLEXHALER) were 65 years of age or older and one was age 75 years or older. No overall differences in safety were observed between these patients and younger patients. Clinical studies did not include sufficient numbers of patients aged 65 years and over to determine differences in efficacy between elderly and younger patients. Other reported clinical or medical surveillance experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The following adverse reactions were reported in patients treated with PULMICORT FLEXHALER 180 or 90 mcg in two double-blind, placebo-controlled clinical trials in which 226 patients age 6-80 years, previously receiving bronchodilators, inhaled corticosteroids, or both, were treated with PULMICORT FLEXHALER, administered as 360 mcg twice daily for 12 weeks.

The following table shows the incidence of adverse events (whether considered drug-related or non-drug-related by the investigators) that occurred at a rate of $\geq 1\%$ in the PULMICORT FLEXHALER group and were more common than in the placebo group.

Adverse Events with a $\geq 1\%$ Incidence and with incidence greater than placebo, reported by patients on PULMICORT FLEXHALER 180 or 90 mcg

Adverse Event	PULMICORT FLEXHALER 360 mcg twice daily N=226 %	Placebo N=230 %
Nasopharyngitis	9.3	8.3
Nasal congestion	2.7	0.4
Pharyngitis	2.7	1.7
Rhinitis allergic	2.2	1.3
Viral upper respiratory tract infection	2.2	1.3
Nausea	1.8	0.9
Viral gastroenteritis	1.8	0.4
Otitis media	1.3	0.9
Oral candidiasis	1.3	0.4
Average exposure duration (days)	76.2	68.2

Long-Term Safety

Non-placebo controlled long-term studies in children (at doses up to 360 mcg daily), and adolescent and adult subjects (at doses up to 720 mcg daily), treated for up to one year with PULMICORT FLEXHALER, revealed a similar pattern and incidence of adverse events.

Adverse Event Reports from Other Sources

The following other adverse events occurred in placebo-controlled clinical trials with similar or lower budesonide doses with PULMICORT TURBUHALER with an incidence of =1% in the budesonide group and were more common than in the placebo group:

=3%: respiratory infection, sinusitis, headache, pain, back pain, fever.

=1-3%: neck pain, syncope, abdominal pain, dry mouth, vomiting, weight gain, fracture, myalgia, hypertonia, migraine, ecchymosis, insomnia, infection, taste perversion, voice alteration.

Higher doses of PULMICORT TURBUHALER 800 mcg twice daily resulted in an increased incidence of voice alteration, flu syndrome, dyspepsia, gastroenteritis, nausea, and back pain, compared with doses of 400 mcg twice daily.

In a 20-week trial in adult asthmatics who previously required oral corticosteroids, the effects of inhaled budesonide with 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. In considering these data, the increased average duration of exposure for inhaled budesonide patients (78 days for inhaled budesonide vs. 41 days for placebo) should be taken into account. Adverse events, whether considered drug-related or non-drug-related by the investigators, reported in more than five patients in the budesonide group and which occurred more frequently with budesonide than placebo are given (% inhaled budesonide and % placebo): asthenia (9% and 2%), headache (12% and 2%), pain (10% and 2%), dyspepsia (8% and 0%), nausea (6% and 0%), oral candidiasis (10% and 0%), arthralgia (6% and 0%), cough increased (6% and 2%), respiratory infection (32% and 13%), rhinitis (6% and 2%), sinusitis (16% and 11%).

Rare adverse events reported in the published literature or from worldwide marketing experience with any formulation of inhaled budesonide include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema and bronchospasm; symptoms of hypocorticism and hypercorticism; glaucoma, cataracts; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety and psychosis.

OVERDOSAGE

The potential for acute toxic effects following overdose of PULMICORT FLEXHALER is low. If used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism may occur (see PRECAUTIONS). Another budesonide-containing dry powder inhaler at 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 280 times the maximum recommended daily inhalation dose in adults and approximately 330 times the maximum recommended daily inhalation dose in children on a mcg/m² basis). There were no deaths following the administration of an inhalation dose of 68 mg/kg in rats

(approximately 380 times the maximum recommended daily inhalation dose in adults and approximately 450 times the maximum recommended daily inhalation dose in children on a mcg/m² basis). The minimal oral lethal dose was 200 mg/kg in mice (approximately 560 times the maximum recommended daily inhalation dose in adults and approximately 670 times the maximum recommended daily inhalation dose in children on a mcg/m² basis) and less than 100 mg/kg in rats (approximately 560 times the maximum recommended daily inhalation dose in adults and approximately 670 times the maximum recommended daily inhalation dose in children based on a mcg/m² basis).

Post-marketing experience showed that acute overdose of inhaled budesonide commonly remained asymptomatic. The use of excessive doses (up to 6400 mcg daily) for prolonged periods showed systemic corticosteroid effects such as hypercorticism.

DOSAGE AND ADMINISTRATION

PULMICORT FLEXHALER 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, budesonide has a relatively rapid onset of action for an inhaled corticosteroid. Improvement in asthma control following inhaled administration of budesonide 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 FLEXHALER when administered in excess of recommended doses have not been established.

A definitive comparative therapeutic ratio between PULMICORT FLEXHALER and PULMICORT TURBUHALER has not been established. For patients who have been on PULMICORT TURBUHALER the dose of PULMICORT FLEXHALER may not be predicted by the dose of that product. The clinical response of PULMICORT FLEXHALER compared with PULMICORT TURBUHALER tends to be lower (see Clinical Studies). Any patient who is switched from PULMICORT TURBUHALER to PULMICORT FLEXHALER should be dosed appropriately, taking into account the dosing recommendations, and titrating the dose as dictated by the clinical response.

Adults (age 18 and older): The recommended starting dosage is 360 mcg twice daily. In some patients, a starting dosage of 180 mcg twice daily may be adequate. The maximum dosage should not exceed 720 mcg twice daily.

Children (age 6 to 17): The recommended starting dosage is 180 mcg twice daily. In some patients a starting dosage of 360 mcg twice daily may be appropriate. The maximum dosage should not exceed 360 mcg twice daily.

Dose Titration

As with any inhaled corticosteroid, physicians are advised to select the dosage of PULMICORT FLEXHALER that would be appropriate based upon the patient's disease severity and titrate the dosage of PULMICORT FLEXHALER downward over time to the lowest level that maintains proper asthma control. In adult patients who are well controlled, a dosage of 180 mcg twice daily may be considered. In some adult patients, a starting dosage of 180 mcg twice daily may be adequate. If the 180 mcg twice daily dosage of PULMICORT FLEXHALER in adults does not provide adequate control, the dosage should be increased.

Patients Maintained on Chronic Oral Corticosteroids

Clinical studies with PULMICORT FLEXHALER did not evaluate patients on oral corticosteroids. However, clinical studies with therapeutic doses of PULMICORT TURBUHALER did show efficacy in the management of asthmatics dependent or maintained on systemic corticosteroids. If a patient is already on a systemic corticosteroid for asthma control, PULMICORT FLEXHALER should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. The patient's asthma should be reasonably stable before withdrawal of oral corticosteroids is initiated. After approximately one week, gradual withdrawal of the systemic corticosteroid may be 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 FLEXHALER 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.

Directions for Use

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

Patients should be instructed to prime PULMICORT FLEXHALER 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 (see further instructions in PRECAUTIONS, Information for Patients).

HOW SUPPLIED

PULMICORT FLEXHALER 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 PULMICORT FLEXHALER inhaler cannot be refilled and should be discarded when empty.

PULMICORT FLEXHALER is available in two strengths: 180 mcg/dose, 120 doses (NDC 0186-0916-12) with a target fill weight of 225 mg (range 200-250), and 90 mcg/dose, 60 doses (NDC 0186-0917-06) with a target fill weight of 165 mg (range 140-190).

The dose indicator window shows how many doses are left in the inhaler. The inhaler is empty when the number zero ("0") on the red background reaches the middle of the window. If the unit is used beyond the point at which the zero reaches the middle of the window, the correct amount of medication may not be obtained and the unit should be discarded.

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

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