BUDESONIDE INHALATION SUSPENSION

℞ only

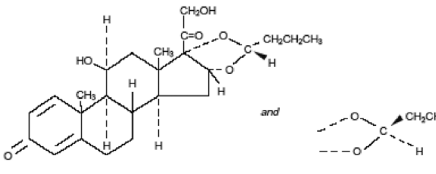
6815

6816

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

DESCRIPTION

Budesonide inhalation suspension 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 inhalation suspension is provided as a mixture of two epimers (22R and 22S) and it has the following structural formula:



$C_{25}H_{34}O_6$ M.W. 430.5

Budesonide inhalation suspension 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 x 10^3.

Budesonide inhalation suspension is a sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide inhalation suspension (micronized), and the inactive ingredients: citric acid monohydrate, disodium edetate, polysorbate 80, sodium chloride, tri-sodium citrate dihydrate and water for injection.

Two dose strengths are available in single-dose vials: 0.25 mg and 0.5 mg per 2 mL vial. For budesonide inhalation suspension, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari-LC-Jet Plus Nebulizer/Pari Master compressor system, under *in vitro* conditions, the mean delivered dose at the mouthpiece (% nominal dose) was approximately 17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less. Budesonide inhalation suspension should be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces (see **DOSAGE AND ADMINISTRATION**).

CLINICAL PHARMACOLOGY

Mechanism of Action

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

The activity of budesonide inhalation suspension 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 well 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 (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic- and non-allergic-mediated inflammation. The anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

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

Pharmacokinetics

Absorption

In asthmatic children 4 to 6 years of age, the total absolute bioavailability (i.e., lung + oral) following administration of budesonide inhalation suspension via jet nebulizer was approximately 6% of the labeled dose.

In children, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20 minutes after nebulization of a 1 mg dose. Systemic exposure, as measured by AUC and C_{max}, is similar for young children and adults after inhalation of the same dose of budesonide inhalation suspension.

Distribution

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

Metabolism

In vitro studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 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 difference between the *in vitro* and *in vivo* metabolic patterns has been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion/Elimination

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

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

Special Populations

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

Hepatic Insufficiency

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

Nursing Mothers

The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum concentration of budesonide for the 400 and 800 mcg doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after dosing. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two-dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide levels in plasma samples obtained from five infants at about 90 minutes after breast-feeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (< 0.02 nmol/L in four infants and < 0.04 nmol/L in one infant) (see **PRECAUTIONS, Nursing Mothers**).

Pharmacodynamics

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

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

Budesonide administered via a dry powder inhaler has been shown in various challenge models (including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate) to decrease bronchial hyper-responsiveness in asthmatic patients. The clinical relevance of these models is not certain.

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

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

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

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

CLINICAL TRIALS

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

Results of the 3 controlled clinical trials for recommended dosages of budesonide inhalation suspension (0.25 mg to 0.5 mg twice daily, up to a total daily dose of 1 mg) in patients, 12 months to 8 years of age, are presented below. Compared to placebo, budesonide inhalation suspension significantly decreased both nighttime and daytime symptom scores of asthma at doses of 0.25 mg twice daily, and 0.5 mg twice daily. Symptom reduction in response to budesonide inhalation suspension occurred across gender and age. Budesonide inhalation suspension significantly reduced the need for bronchodilator therapy at all the doses studied.

Improvements in lung function were associated with budesonide inhalation suspension treatment in the subgroup of patients capable of performing lung function testing. Significant improvements were seen in FEV_1 [budesonide inhalation suspension 0.5 mg twice daily] and morning PEF [budesonide inhalation suspension 0.25 mg twice daily and 0.5 mg twice daily] compared to placebo.

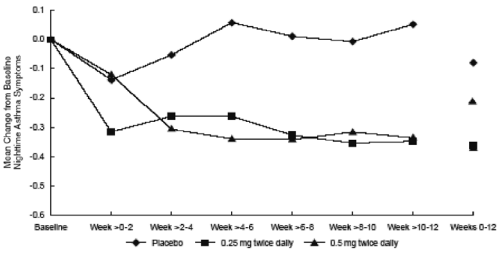
A numerical reduction in nighttime and daytime symptom scores (0 to 3 scale) of asthma was observed within 2 to 8 days, although maximum benefit was not achieved for 4 to 6 weeks after starting treatment. The reduction in nighttime and daytime asthma symptom scores was maintained throughout the 12 weeks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

Patients Previously Maintained on Inhaled Corticosteroid Therapy

The efficacy of budesonide inhalation suspension at doses of 0.25 mg and 0.5 mg twice daily was evaluated in 133 pediatric asthma patients, 4 to 8 years of age, previously maintained on inhaled corticosteroids (mean FEV_1 79.5% predicted; mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.04 to 1.18; mean baseline dose of beclomethasone dipropionate of 265 mcg/day, ranging between 42 to 1008 mcg/day; mean baseline dose of triamcinolone acetonide of 572 mcg/day, ranging between 200 to 1200 mcg/day). The changes from baseline to Weeks 0 to 12 in nighttime asthma symptom scores are shown in **Figure 1**. Nighttime asthma symptom scores were significantly improved in patients treated with budesonide inhalation suspension compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

Budesonide inhalation suspension at a dose of 0.5 mg twice daily significantly improved FEV_1, and both doses (0.25 mg and 0.5 mg twice daily) significantly increased morning PEF, compared to placebo.

Figure 1. A 12-Week Trial in Pediatric Patients Previously Maintained on Inhaled Corticosteroid Therapy Prior to Study Entry



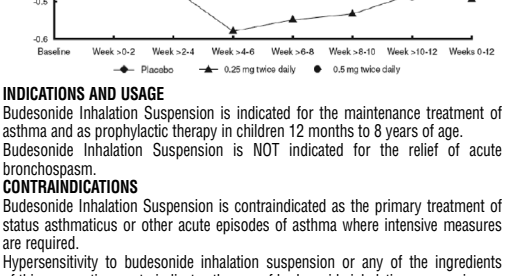
Patients Either Maintained on Bronchodilators Alone or Inhaled Corticosteroid Therapy

The efficacy of budesonide inhalation suspension at doses of 0.25 mg twice daily and 0.5 mg twice daily, was evaluated in pediatric patients 12 months to 8 years of age (mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.13 to 1.31).

Approximately 70% were not previously receiving inhaled corticosteroids. The changes from baseline to Weeks 0 to 12 in nighttime asthma symptom scores are shown in **Figure 2**. Budesonide inhalation suspension at doses of 0.25 mg and 0.5 mg twice daily, significantly improved nighttime asthma symptom scores compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

Budesonide inhalation suspension at a dose of 0.5 mg twice daily significantly improved FEV_1, and at doses of 0.25 mg and 0.5 mg twice daily significantly improved morning PEF, compared to placebo.

Figure 2. A 12-Week Trial in Pediatric Patients Either Maintained on Bronchodilators Alone or Inhaled Corticosteroid Therapy Prior to Study Entry



INDICATIONS AND USAGE

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

Budesonide Inhalation Suspension is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

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

Hypersensitivity to budesonide inhalation suspension or any of the ingredients of this preparation contraindicates the use of budesonide inhalation suspension.

WARNINGS

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

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

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

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for

further instructions. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to budesonide inhalation suspension. Lung function (FEV_1 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 budesonide inhalation suspension may unmask allergic or other immunologic conditions previously suppressed by the systemic corticosteroid therapy, e.g., rhinitis, conjunctivitis, eosinophilic conditions, eczema, and arthritis (see **DOSAGE AND ADMINISTRATION**).

Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressant doses of corticosteroids. In pediatric or adult patients who have not had these diseases, or who have not been properly vaccinated, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known.

The clinical course of chicken pox or measles infection in patients on inhaled corticosteroids has not been studied. However, a clinical study has examined the immune responsiveness of asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension (see **PRECAUTIONS, Pediatric Use**). If a patient on immunosuppressant doses of corticosteroids is exposed to chicken pox, 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.

Budesonide inhalation suspension is not a bronchodilator and is not indicated for the rapid relief of acute bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If acute bronchospasm occurs following dosing with budesonide inhalation suspension, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with budesonide inhalation suspension 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 budesonide inhalation suspension.

Hypersensitivity Reactions Including Anaphylaxis

Hypersensitivity reactions including anaphylaxis, rash, contact dermatitis, urticaria, angioedema, and bronchospasm have been reported with use of budesonide inhalation suspension . Discontinue budesonide inhalation suspension if such reactions occur (see **CONTRAINDICATIONS and ADVERSE REACTIONS**).

PRECAUTIONS

General

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function (see **DOSAGE AND ADMINISTRATION**).

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

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

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

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 budesonide inhalation suspension, each patient should be titrated to his/her lowest effective dose (see **PRECAUTIONS, Pediatric Use**).

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

In clinical trials with budesonide inhalation suspension, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. The incidences of localized infections of *Candida albicans* were similar between the placebo and budesonide inhalation suspension treatment groups. If these infections develop, they may require treatment with appropriate antifungal therapy and/or discontinuance of treatment with budesonide inhalation suspension.

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 budesonide inhalation suspension 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 instructions on the proper use of budesonide inhalation suspension and to attain the maximum improvement in asthma symptoms, the patient or the parent/guardian of the patient should receive, read, and follow the available patient information and instructions carefully.

- Patients should take budesonide inhalation suspension at regular intervals twice a day as directed, since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.
- The effects of mixing budesonide inhalation suspension with other nebulizable medications have not been adequately assessed. Budesonide inhalation suspension should be administered separately in the nebulizer.
- Budesonide inhalation suspension is not a bronchodilator, and its use is not intended to treat acute life-threatening episodes of asthma.
- Budesonide inhalation suspension should be administered with a jet nebulizer connected to a compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. The face mask should be properly adjusted to optimize delivery and to avoid exposing the eyes to the nebulized medication (see **DOSAGE AND ADMINISTRATION**).
- Ultrasonic nebulizers are not suitable for the adequate administration of budesonide inhalation suspension and, therefore, are not recommended (see **DOSAGE AND ADMINISTRATION**).
- Rinsing the mouth with water after each treatment may decrease the risk of development of local candidiasis. Corticosteroid effects on the skin can be avoided if the face is washed after the use of a face mask.
- Improvement in asthma control following treatment with budesonide inhalation suspension can occur within 2 to 8 days of beginning treatment, although maximum benefit may not be achieved for 4 to 6 weeks after starting treatment. If the asthma symptoms do not improve in that time frame, or if the condition worsens, the patient or the patient's parent/guardian should be instructed not to increase the dosage, but to contact the physician.
- Patients should not stop the use of budesonide inhalation suspension abruptly without consulting with their prescribing physician.
- Patients whose chronic 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.
- As always, care should be taken to avoid exposure to persons with chicken pox and measles. If exposure to such a person occurs, and the child has not had chicken pox or been properly vaccinated, a physician should be consulted without delay (see **WARNINGS** and **PRECAUTIONS, Pediatric Use**).
- 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.
- Patients or their parents/guardians considering use of budesonide inhalation suspension should consult with their physician if they are allergic to budesonide or any other orally inhaled corticosteroid.
- Physicians should be informed of other medications patients are taking as budesonide inhalation suspension may not be suitable in some circumstances and the physician may wish to use a different medicine.
- Budesonide inhalation suspension should be stored upright at controlled room temperature 20º to 25ºC (68º to 77ºF) and protected from light. Budesonide inhalation suspension should not be refrigerated or frozen.
- When an aluminum foil envelope has been opened, the shelf life of the unused vials is two weeks when protected from light. The date the envelope was opened should be recorded on the front of the envelope in the space provided.
- After opening the aluminum foil envelope, the unused vials should be returned to the envelope to protect them from light. Any individually opened vials must be used promptly.
- For proper usage of budesonide inhalation suspension and to attain maximum improvement, the available **Patient's Instructions for Use** should be read and followed.

Drug Interactions

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

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 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/m^2 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/m^2 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/m^2 basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m^2 basis).

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

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis).

Pregnancy

Teratogenic Effects

Pregnancy category B

As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (less than the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis) and 500 mcg/kg in rats (approximately 4 times the maximum recommended daily inhalation dose in adults on a mcg/m^2 basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/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 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 to 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 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10 to 12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).

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

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

Non-Teratogenic Effects

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

Nursing Mothers

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother (see **CLINICAL PHARMACOLOGY, Pharmacokinetics,** Special Populations, Nursing Mothers). No studies have been conducted in breastfeeding women with budesonide inhalation suspension; however, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar. Budesonide should be used in nursing women only if clinically appropriate. Prescribers should weigh the known benefits of breastfeeding for the mother and the infant against the potential risks of minimal budesonide exposure in the infant.

Pediatric Use

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

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

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

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5 to 12 years of age, those treated with budesonide administered via a dry powder inhaler 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 the budesonide dry powder inhaler 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 inhaled corticosteroids, including budesonide inhalation suspension, should be monitored routinely (e.g., 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 budesonide inhalation suspension, each patient should be titrated to his/her lowest effective dose.

An open-label non-randomized clinical study examined the immune responsiveness of varicella vaccine in 243 asthma patients 12 months to 8 years of age who

were treated with a total daily dose of budesonide inhalation suspension up to 1 mg (n = 151) or non-corticosteroid asthma therapy (n = 92) (i.e., beta$_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥ 5 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%) compared to patients treated with non-corticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Geriatric Use

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

ADVERSE REACTIONS

The following adverse reactions were reported in pediatric patients treated with budesonide inhalation suspension.

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

Adverse Events With ≥ 3% Incidence Reported By Patients On Budesonide

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

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

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

Incidence 1% to ≤ 3% (by Body System)

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

Body as a Whole
Allergic reaction, chest pain, fatigue, flu-like disorder

Respiratory System
Stridor

Resistance Mechanisms
Herpes simplex, external ear infection, infection

Central & Peripheral Nervous System
Dysphonia, hyperkinesia

Skin & Appendages
Eczema, pustular rash, pruritus

Hearing & Vestibular
Earache

Vision
Eye infection

Psychiatric
Anorexia, emotional lability

Musculoskeletal System
Fracture, myalgia

Application Site
Contact dermatitis

Platelet, Bleeding & Clotting
Purpura

White Cell and Resistance
Cervical lymphadenopathy

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

Cases of growth suppression have been reported for inhaled corticosteroids including post-marketing reports for budesonide inhalation suspension (see **PRECAUTIONS**, **Pediatric Use**).

Less frequent adverse events (<1%) reported in the published literature, long-term, open-label clinical trials, or from worldwide marketing experience with any formulation of inhaled budesonide include: immediate and delayed hypersensitivity reactions including anaphylaxis, rash, contact dermatitis, urticaria, angioedema, and bronchospasm (see **WARNINGS, Hypersensitivity Reactions Including Anaphylaxis**); symptoms of hypocorticism and hypercorticism; glaucoma, cataracts; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety, and psychosis; and bone disorders including avascular necrosis of the femoral head and osteoporosis.

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

Patients Not Receiving Systemic (Oral) Corticosteroids

Patients who require maintenance therapy of their asthma may benefit from treatment with budesonide inhalation suspension at the doses recommended above. Once the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose.

Patients Maintained on Chronic Oral Corticosteroids

Initially, budesonide inhalation suspension should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid may be initiated by reducing the daily or alternate daily dose. Further incremental reductions may be made after an interval of one or two weeks, depending on the response of the patient. Generally, these decrements should not exceed 25% of the prednisone dose or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for asthma instability, including objective measures of airway function, and for adrenal insufficiency (see **WARNINGS**).

During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, e.g., joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with budesonide inhalation suspension but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

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

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

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

Directions for Use

Illustrated **Patient's Instructions for Use** accompany each package of budesonide inhalation suspension.

HOW SUPPLIED

Budesonide inhalation suspension, 0.25 mg/2 mL is supplied in a sealed aluminum foil envelope containing one plastic strip of five single-dose vials. Each single-dose vial contains 2 mL of sterile liquid suspension, supplied in unit-dose cartons of 30 vials (6 pouches x 5 vials).

Budesonide inhalation suspension, 0.5 mg/2 mL is supplied in a sealed aluminum foil envelope containing one plastic strip of five single-dose vials. Each single-dose vial contains 2 mL of sterile liquid suspension, supplied in unit-dose cartons of 30 vials (6 pouches x 5 vials).

Storage

Store at 20º to 25ºC (68º to 77ºF) [See USP Controlled Room Temperature]. Store upright and protect from light.

When an envelope has been opened, the shelf life of the unused vials is 2 weeks when protected. After opening the aluminum foil envelope, the unused vials should be returned to the aluminum foil envelope to protect them from light. Any opened vial must be used promptly. Gently shake the vial using a circular motion before use. Keep out of reach of children. Do not freeze.

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