

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **BUDESONIDE INHALATION SUSPENSION** safely and effectively. See full prescribing information for **BUDESONIDE INHALATION SUSPENSION**.

BUDESONIDE INHALATION SUSPENSION

Initial U.S. Approval: 2000

INDICATIONS AND USAGE

Budesonide inhalation suspension is an inhaled corticosteroid indicated for:

- Maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age (1)

Limitations of Use:

Not indicated for the relief of acute bronchospasm (1)

DOSAGE AND ADMINISTRATION

Recommended dosing based on previous therapy (2). Start with the lowest recommended dose:

- Bronchodilators alone: 0.5 mg once daily or 0.25 mg twice daily
- Inhaled corticosteroids: 0.5 mg once daily or 0.25 mg twice daily up to 0.5 mg twice daily
- Oral corticosteroids: 0.5 mg twice daily or 1 mg once daily
- In symptomatic children not responding to non-steroidal therapy, a starting dose of 0.25 mg once daily may be considered
- If once-daily treatment does not provide adequate control, the total daily dose should be increased and/or administered as a divided dose. Once asthma stability is achieved, titrate the dose downwards.
- For inhalation use via compressed air driven jet nebulizers only (not for use with ultrasonic devices). Not for injection. (2.2)

DOSAGE FORMS AND STRENGTHS

Inhalation suspension: 0.25 mg/2 mL, 0.5 mg/2 mL, 1 mg/2 mL (3)

CONTRAINDICATIONS

- Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required (4)
- Hypersensitivity to any of the ingredients in budesonide inhalation suspension (4)

WARNINGS AND PRECAUTIONS

- Localized Infections:** Candida albicans infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth following inhalation (5.1)

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Maintenance Treatment of Asthma

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

Limitations of Use:

- Budesonide inhalation suspension is NOT indicated for the relief of acute bronchospasm.

2 DOSAGE AND ADMINISTRATION

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 either once daily or twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered either once daily or twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily	1 mg total daily dose

2.1 Dosing Recommendations

Dosing recommendations based on previous therapy are as follows:

- Bronchodilators alone: 0.5 mg once daily or 0.25 mg twice daily
- Inhaled corticosteroids: 0.5 mg once daily or 0.25 mg twice daily up to 0.5 mg twice daily
- Oral corticosteroids: 0.5 mg twice daily or 1 mg once daily

In symptomatic children not responding to non-steroidal therapy, a starting dose of 0.25 mg once daily may be considered. If once-daily treatment does not provide adequate control, the total daily dose should be increased and/or administered as a divided dose. In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved.

- Deterioration of Disease and Acute Asthma Episodes:** Do not use for the relief of acute bronchospasm (5.2)

- Hypersensitivity Reactions:** 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 (5.3)

- Immunosuppression:** Potential worsening of infections (e.g., existing tuberculosis, fungal, bacterial, viral, or parasitic infection, or ocular herpes simplex). Use with caution in patients with these infections. More serious or even fatal course of chickenpox or measles can occur in susceptible patients (5.4)

- Transferring Patients from Systemic Corticosteroid Therapy:** Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to budesonide inhalation suspension (5.5)

- Hypocorticism and Adrenal Suppression:** May occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, reduce budesonide inhalation suspension slowly. (5.6)

- Reduction in Bone Mineral Density with Long-term Administration:** Monitor patients with major risk factors for decreased bone mineral content (5.7)

- Effects on Growth:** Monitor growth of pediatric patients (5.8)

- Glaucoma and Cataracts:** Close monitoring is warranted (5.9)

- Paradoxical Bronchospasm:** Discontinue budesonide inhalation suspension and institute alternative therapy if paradoxical bronchospasm occurs (5.10)

- Eosinophilic Conditions and Churg-Strauss Syndrome:** Be alert to eosinophilic conditions (5.11)

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥3%) are respiratory infection, rhinitis, coughing, otitis media, viral infection, moniliasis, gastroenteritis, vomiting, diarrhea, abdominal pain, ear infection, epistaxis, conjunctivitis, rash (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd. at 1-866-604-3268 or FDA at 1-800-FDA-1088 or FDA or www.fda.gov/medwatch

DRUG INTERACTIONS

Strong Cytochrome P450 3A4 Inhibitors (e.g., ritonavir): Use with caution. May cause increased systemic corticosteroid effects (5.12, 7.1)

See 17 For PATIENT COUNSELING INFORMATION and FDA approved patient labeling

Revised: 6/2020

5.2 Deterioration of Disease and Acute Asthma Episodes

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

Patients should be instructed to contact their physician immediately if episodes of asthma not responsive to their usual doses of bronchodilators occur during the course of treatment with budesonide inhalation suspension. During such episodes, patients may require therapy with oral corticosteroids.

5.3 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* (4)].

5.4 Immunosuppression

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 children or adults. Patients who have not had these diseases, or been properly immunized, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affect 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. Infection has been reported in children who received intravenous immunoglobulin (IVIg), as appropriate, 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.

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. 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 budesonide inhalation suspension 0.25 mg to 1 mg daily (n=151) or non-corticosteroid asthma therapy (n=92) (i.e., beta₂-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (μg/LISA 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 (80%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

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.

5.5 Transferring Patients from Systemic Corticosteroid Therapy

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 at this 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 glucocorticosteroid systemically and does NOT provide the neuroendocrine actions that are 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 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 corticosteroids after transferring to budesonide inhalation suspension. 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.

Lung function (FEV₁ or AM PEFR), beta₂-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* (2)].

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

5.6 Hypocorticism and Adrenal Suppression

Budesonide inhalation suspension, will often help control asthma symptoms with less suppression of HPA function than therapeutically equivalent oral doses of prednisone. 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 hypocorticism, and adrenal suppression (including adrenal crisis) may appear in a small number of patients, particularly when budesonide is administered at higher than recommended doses over prolonged periods of time. If such effects occur, the dosage of budesonide inhalation suspension should be reduced slowly, consistent with accepted procedures for tapering of systemic corticosteroids and for management of asthma.

5.7 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term outcomes is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants and corticosteroids), should be monitored and treated with established standards of care.

5.8 Effects on Growth

Orally inhaled corticosteroids, including budesonide, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving budesonide inhalation suspension routinely (e.g., via stadiometry). To minimize the systemic effects of orally inhaled corticosteroids, including budesonide inhalation suspension, each patient should be titrated to higher lowest effective dose [see *Use in Specific Populations* (8.4)].

5.9 Glaucoma and Cataracts

Budesonide inhalation suspension, and cataracts have been reported following the long-term administration of inhaled corticosteroids, including budesonide. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

5.10 Paradoxical Bronchospasm and Upper Airway Symptoms

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 initiated.

- Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.
- Hypersensitivity to budesonide or any of the ingredients of budesonide inhalation suspension [see *Warnings and Precautions* (5.3), *Contraindications* (1)], *Adverse Reactions* (6.2)].

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- Allergic reactions. Tell your healthcare provider or get medical help right away if your child has:
 - skin rash, redness or swelling
 - severe itching
 - swelling of the face, mouth and tongue
 - trouble breathing or swallowing
 - chest pain
 - anxiety (feeling of doom)
- Immune system effects and a higher chance of infections. Your child is more likely to get infections when taking medicines that weaken the immune system. Symptoms of infection may include: fever, pain, aches, chills, feeling tired, nausea and vomiting. Tell your healthcare provider about any signs of infection while your child uses budesonide inhalation suspension.
- Adrenal insufficiency. Adrenal insufficiency is a condition in which the adrenal glands do not make enough steroid hormones. Symptoms of adrenal insufficiency include tiredness, weakness, nausea and vomiting, and low blood pressure.
- Decrease in bone mineral density (bone strength). Your healthcare provider may want to check your child for this during treatment with budesonide inhalation suspension.
- Slowed or delayed growth problems. Your child's healthcare provider may want to monitor your child's growth while using budesonide inhalation suspension.
- Eye problems, including glaucoma and cataracts. Your child's healthcare provider may suggest eye exams while using budesonide inhalation suspension.
- Increased wheezing right after taking budesonide inhalation suspension. Always have a fast-acting inhaled bronchodilator medicine with you to treat sudden wheezing.

Call your healthcare provider or get medical help right away if your child has any of the serious side effects listed above.

The most common side effects of budesonide inhalation suspension include:

- respiratory infections. Symptoms may include stuffy nose, sore nose and throat.
- runny nose
- cough
- viral infections
- viral irritation and inflammation of the stomach and intestine (gastroenteritis). Gastroenteritis symptoms may include: stomach ache, pain, diarrhea, nausea and vomiting, and loss of appetite.
- ear infections
- nosebleed
- pink eye (conjunctivitis)
- rash

Tell your healthcare provider if your child has any side effect that bothers him or her or that does not go away. For more information, ask your healthcare provider or pharmacist.

Call your healthcare provider for medical advice about side effects. You may report side effects to Cipla Ltd. at 1-866-604-3268 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

How should I store budesonide inhalation suspension?

- Store budesonide inhalation suspension in an upright position between 68°F to 77°F (20°C to 25°C).
- Keep budesonide inhalation suspension in the aluminum foil envelope to protect from light until ready to use.
- After a budesonide inhalation suspension ampule is opened it should be used right away.
- Budesonide inhalation suspension ampules can be stored for 2 weeks after opening the protective aluminum foil envelope.
- Throw away budesonide inhalation suspension ampules if not used within 2 weeks of opening the protective aluminum foil envelope.
- Do not refrigerate or freeze.

Keep budesonide inhalation suspension and all medicines out of the reach of children.

General Information about budesonide inhalation suspension

Medicines are sometimes prescribed for conditions other than those listed in a Patient Information leaflet. Do not use budesonide inhalation suspension for a condition for which it was not prescribed. Do not give budesonide inhalation suspension to other people, even if they have the same symptoms that you have. It may harm them.

This Patient Information leaflet summarizes the most important information about budesonide inhalation suspension. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about budesonide inhalation suspension that is written for health professionals.

What are the ingredients in budesonide inhalation suspension?

Active ingredient: budesonide

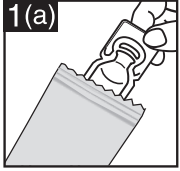
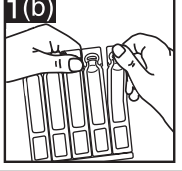
Inactive ingredients: disodium edetate, sodium chloride, sodium citrate dihydrate, citric acid monohydrate, polysorbate 80 and water for injection.

Patient Instructions for Use

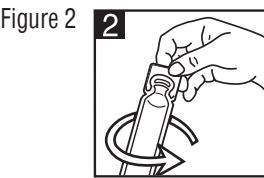
Important: Budesonide inhalation suspension is only for use with a jet nebulizer machine. Make sure you know how to use your jet nebulizer machine before your child uses budesonide inhalation suspension.

Budesonide inhalation suspension is a liquid that is turned into a mist by a nebulizer and inhaled into the lungs.

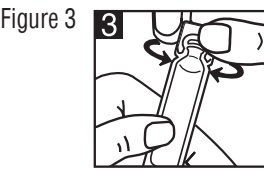
The face mask should be properly adjusted to optimize delivery and to avoid exposing the eyes to the nebulized medication. Corticosteroid effects on the skin can be avoided if the face is washed after the use of a face mask.

1 ampule in foil envelope	5 ampules in foil envelope
1. Budesonide inhalation suspension come in a sealed protective aluminum foil envelope. • Do not open the sealed pouch until you are ready to use a dose of budesonide inhalation suspension. • Open the sealed foil envelope and take out 1 single-dose ampule. See Figure 1(a).	1. Budesonide inhalation suspension come in a sealed protective aluminum foil envelope. • Do not open the sealed pouch until you are ready to use a dose of budesonide inhalation suspension. • Open the sealed foil envelope along the dotted line and take out 1 single-dose ampule from the strip. See Figure 1(b). • Record the date that you opened the foil on the back of the envelope in the space provided.
Figure 1(a) 	Return the unopened budesonide inhalation suspension ampules on the strip back into the foil envelope before storing. Figure 1(b) 

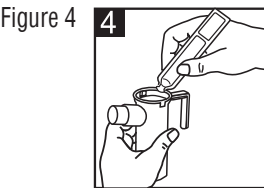
2. Gently shake the budesonide inhalation suspension ampule using a circular motion as shown in Figure 2.



3. Hold the budesonide inhalation suspension ampule upright without squeezing the ampule and open by twisting off the top as shown in Figure 3.



4. Place the open end of the budesonide inhalation suspension ampule into the nebulizer cup (reservoir) and slowly squeeze all of the medicine from the ampule into the nebulizer medicine cup as shown in Figure 4. Throw away the empty ampule.



5. Use your jet nebulizer as directed.

Manufactured by: Cipla Ltd., Indore SEZ, Pithampur, India
Manufactured for: Cipla USA, Inc.
10 Independence Boulevard, Suite 300, Warren, NJ 07059
Revised: 6/2020

In a study of asthmatic children 5-12 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 budesonide inhalation suspension, each patient 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 (see Dosage and Administration (2), Warnings and Precautions (5.8)).

5.8 Geriatric Use

Of the 215 patients in 3 clinical trials of budesonide inhalation suspension in adult patients, 85 (39%) 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.

5.9 Hepatic Impairment

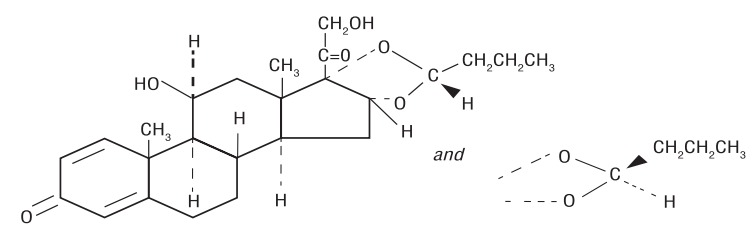
Formal pharmacokinetic studies using budesonide inhalation suspension have not been conducted in patients with hepatic impairment. However, since budesonide is predominantly cleared by hepatic metabolism, impairment of liver function may lead to accumulation of budesonide in plasma. Therefore, patients with hepatic disease should be closely monitored.

10 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, the pharmacokinetic effects such as hypercorticism or growth suppression may occur (see Warnings and Precautions (5.6)).

11 DESCRIPTION

Budesonide, the active component of budesonide inhalation suspension, is a corticosteroid designated chemically as (RS)-11 β ,16 α ,17, 21-tetrahydroxyprog-1,4-dien-3,20-dione cyclic 16, 17-acetal with butyraldehyde. Budesonide is provided as a mixture of two enantiomers (22R and 22S). The empirical formula of budesonide is C₂₄H₃₄O₆ 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 x 10³.

Budesonide inhalation suspension is a sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide (microsized), and the inactive ingredients disodium edetate, sodium chloride, sodium citrate dihydrate, citric acid monohydrate, polysorbate 80, and water for injection. Three dose strengths are available in single-dose ampules: 0.25 mg, 0.5 mg, and 1 mg per 2 mL ampule. For budesonide inhalation suspension, in use, 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, i.e., face masks or mouthpieces (see Dosage and Administration (2)).

12 CLINICAL PHARMACOLOGY

12.1 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 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 clinical significance of these findings is unknown.

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 enantiomer. 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 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 (65-85%) and the low potency of metabolites (see below).

12.2 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 administered budesonide, even though systemic budesonide exposure was comparable for both treatments, indicating that the inhaled treatment is working locally in the lung. Thus, the therapeutic effect of conventional doses of orally inhaled budesonide are largely explained by its direct action on the respiratory tract.

Improvement in the control of asthma symptoms following inhalation of budesonide inhalation suspension can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 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 hyperresponsiveness in asthmatic patients. The clinical relevance of these models is not certain.

Pre-treatment with budesonide administered as 1800 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.

HPA Axis Effects

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 at recommended doses. In the subgroup of children age 6 months to 2 years (n=21) receiving a total daily dose of budesonide inhalation suspension equivalent to 0.25 mg (n=5), 0.5 mg (n=5), 1 mg (n=4), or placebo (n=7), the mean change from baseline in ACTH-stimulated cortisol levels showed a decline in peak stimulated cortisol at 12 weeks compared to an increase in the placebo group. These mean differences were not statistically significant compared to placebo. Another 12-week study in 141 pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing was conducted. All patients were randomized to receive either 0.5 mg or 1 mg of budesonide inhalation suspension or placebo once daily. A total of 28, 17, and 37 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 <500 nmol/L at Week 12. In 4 of these patients receiving budesonide inhalation suspension, the cortisol values were near the cutoff level 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 (45-52%) urinary cortisol excretion compared to the run-in period. The highest recommended dose of budesonide inhalation suspension, 1 mg twice daily, 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 (see Warnings and Precautions (5.3)).

12.3 Pharmacokinetics

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

Metabolism

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

Excretion/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 4-6 years of age, the terminal half-life of budesonide after nebulization is 23 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 from 1 to 18 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 0.20 and 0.70 nmol/L, respectively, and occurred within 45 minutes after dosing. The estimated oral bioavailability 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 five 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 Use in Specific Populations (8.3)).

Drug-Drug Interactions

Inhibitors of cytochrome P450 enzymes

Ketoconazole: Ketoconazole, a strong inhibitor of cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4), the main metabolic enzyme for corticosteroids, increased plasma levels of orally ingested budesonide (see Warnings and Precautions (5.12), Drug Interactions (7.1)).

Cimetidine: At recommended doses, cimetidine, a non-specific inhibitor of CYP enzymes, had a slight but clinically insignificant effect on the pharmacokinetics of oral budesonide.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (approximately 0.5 and 0.1 times, respectively, the MRHMD in adults and children 12 months to 8 years of age on a mcg/m² basis). No tumorigenicity was seen in male rats at oral doses up to 25 mcg/kg (approximately 0.2 and 0.04 times, respectively, the MRHMD in adults and children 12 months to 8 years of age on a mcg/m² basis) and in female rats at oral doses up to 50 mcg/kg (approximately 0.5 and 0.1 times, respectively, the MRHMD in adults and children 12 months to 8 years of age 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 (approximately 0.5 and 0.1 times, respectively, the MRHMD in adults and children 12 months to 8 years of age 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 (approximately 0.5 and 0.1 times, respectively, the MRHMD in adults and children 12 months to 8 years of age on a mcg/m² basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings. In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (approximately equivalent to 0.5 and 0.1 times, respectively, the MRHMD in adults and children 12 months to 8 years of age 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.

Fertility and reproductive performance were unaffected in rats at subcutaneous doses up to 80 mcg/kg approximately equivalent to the MRHMD in adults on a mcg/m² basis. However, it caused a decrease in prenatally 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 approximately 0.2 times than the MRHMD in adults on a mcg/m² basis. No such effects were noted at 5 mcg/kg (approximately 0.05 times the MRHMD in adults on a mcg/m² basis).

14 CLINICAL STUDIES

Three double-blind, placebo-controlled, parallel group, randomized U.S. clinical trials of 12-week duration each were conducted in 1018 pediatric patients, 6 months to 8 years of age, 457 males and 381 females (798 Caucasian, 140 Blacks, 56 Hispanics, 3 Asians, 21 Others) with persistent asthma of varying disease duration (2 to 107 months) and severity. Doses of 0.25 mg, 0.5 mg, and 1 mg administered either once or twice daily were compared to placebo to provide information about appropriate dosing to cover a range of asthma severity. A Pari-LC-Jet Plus Nebulizer (with a face mask or mouthpiece) connected to a Pari Master compressor was used to deliver budesonide inhalation suspension to patients in the 3 U.S. controlled clinical trials. The co-primary endpoints were nighttime and daytime asthma symptom scores (0-3 scale). Improvements were addressed in terms of the primary efficacy variables of changes from baseline to the double-blind treatment period in nighttime and daytime asthma symptom scores (scale 0-3) as recorded in the patient diaries. Baseline was defined as the mean of the last seven days prior to randomization. The double-blind treatment period was defined as the mean over 12 week treatment period. Each of the five doses discussed below was studied in one or two, but not all, of the three of the U.S. studies.

Results of the 3 controlled clinical trials for recommended dosages of budesonide inhalation suspension (0.25 mg to 0.5 mg once or twice daily, or 1 mg once daily, up to a total daily dose of 1 mg) in 949 patients, 12 months to 8 years of age, are presented below. Statistically significant decreases in nighttime and daytime symptom scores of asthma were observed at budesonide inhalation suspension doses of 0.25 mg once daily (one study), 0.25 mg twice daily, and 0.5 mg twice daily compared to placebo. Use of budesonide inhalation suspension resulted in statistically significant decreases in either nighttime or daytime symptom scores, but not both, at doses of 1 mg once daily, and 0.5 mg once daily (one study). Symptom reduction in response to budesonide inhalation suspension occurred across gender and age. Statistically significant reductions in the need for bronchodilator therapy were also observed at all the doses of budesonide inhalation suspension studied.

Improvements in lung function were associated with budesonide inhalation suspension in the subgroup of patients capable of performing lung function testing. Statistically significant increases were seen in FEV₁, budesonide inhalation suspension 0.5 mg once daily and 1 mg once daily (one study); 0.5 mg twice daily and morning PEF (budesonide once or twice daily suspension; 1 mg once daily (one study); 0.5 mg twice daily; 0.5 mg twice daily) compared to placebo.

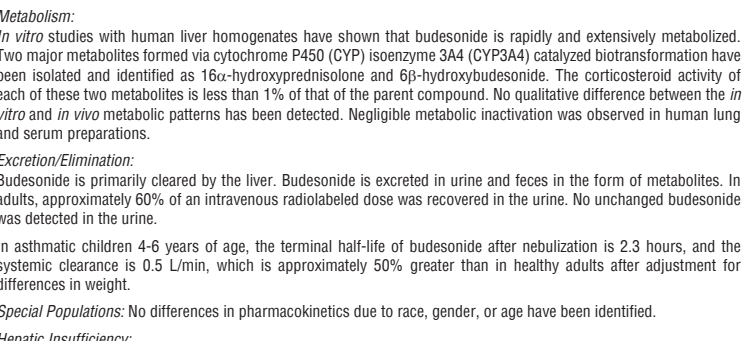
A numerical reduction in nighttime and daytime symptom scores (0-3 scale) of asthma was observed within 2-8 days, although maximum benefit was not achieved for 4-6 weeks after starting treatment. The reduction in nighttime and daytime asthma symptom scores was maintained throughout the 12 weeks of the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

Patients Not Receiving Inhaled Corticosteroid Therapy

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

Changes from baseline to the double-blind phase for the budesonide treatment groups compared to placebo were made using analysis of variance techniques. The model included terms for the respective changes from baseline as the dependent variable and terms for treatment, center and treatment by center interaction as exploratory variables (see Figures 1-3).

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

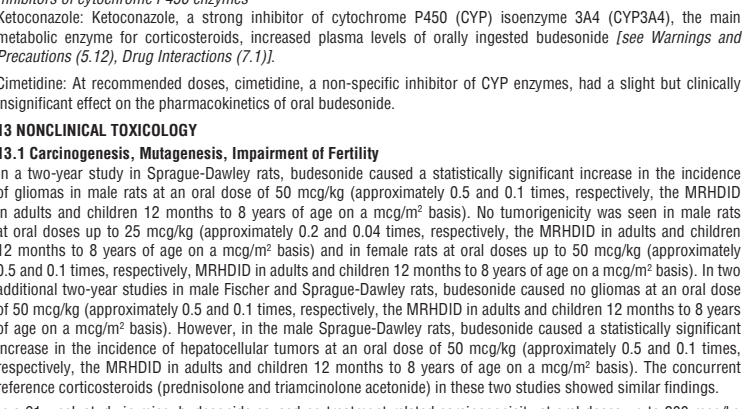


p-values: 0.25 mg qd 0.001, 0.5 mg qd 0.010, 1.0 mg qd 0.009

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 FEV₁ 79.5%, predicted; mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.04 to 1.18; mean baseline dose of beclomethasone dipropionate of 295 mcg/day, ranging between 42 to 1088 mcg/day; mean baseline dose of triamcinolone acetonide of 572 mcg/day, ranging between 200 to 1200 mcg/day). The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 2. Nighttime asthma symptom scores showed statistically significant decreases in patients treated with budesonide inhalation suspension compared to placebo. Similar decreases were also observed for daytime asthma symptom scores.

Statistically significant increases in FEV₁ compared to placebo were observed with budesonide inhalation suspension at a dose of 0.5 mg twice daily and in morning PEF for both doses (0.25 mg and 0.5 mg twice daily).

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



p-values: 0.25 mg bid 0.022, 0.5 mg bid 0.021

Patients Receiving Once-Daily or Twice-Daily Dosing

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

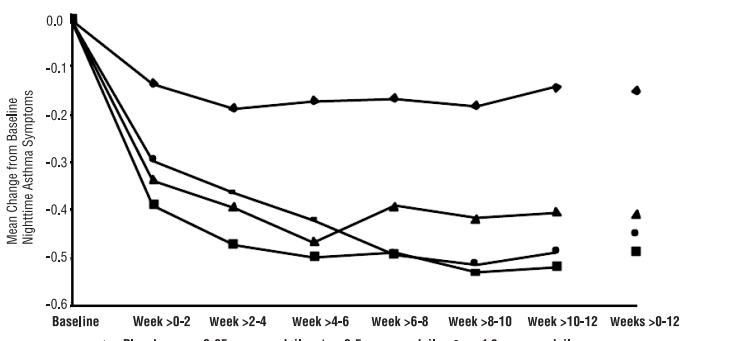
Budesonide inhalation suspension at a dose of 0.5 mg twice daily resulted in statistically significant increases compared to placebo in FEV₁ and at doses of 0.25 mg and 0.5 mg twice daily and 1 mg once daily statistically significant increases in morning PEF.

The evidence supports the efficacy of the same nominal dose of budesonide inhalation suspension administered on either a once-daily or twice-daily schedule. However, when all measures are considered together, the evidence is stronger for twice-daily dosing (see Dosage and Administration (2)).

Results of the 3 controlled clinical trials for recommended dosages of budesonide inhalation suspension (0.25 mg to 0.5 mg once or twice daily, or 1 mg once daily, up to a total daily dose of 1 mg) in 949 patients, 12 months to 8 years of age, are presented below. Statistically significant decreases in nighttime and daytime symptom scores of asthma were observed at budesonide inhalation suspension doses of 0.25 mg once daily (one study), 0.25 mg twice daily, and 0.5 mg twice daily compared to placebo. Use of budesonide inhalation suspension resulted in statistically significant decreases in either nighttime or daytime symptom scores, but not both, at doses of 1 mg once daily, and 0.5 mg once daily (one study). Symptom reduction in response to budesonide inhalation suspension occurred across gender and age. Statistically significant reductions in the need for bronchodilator therapy were also observed at all the doses of budesonide inhalation suspension studied.

Improvements in lung function were associated with budesonide inhalation suspension in the subgroup of patients capable of performing lung function testing. Statistically significant increases were seen in FEV₁, budesonide inhalation suspension 0.5 mg once daily and 1 mg once daily (one study); 0.5 mg twice daily and morning PEF (budesonide once or twice daily suspension; 1 mg once daily (one study); 0.5 mg twice daily; 0.5 mg twice daily) compared to placebo.

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



p-values: 0.25 mg qd 0.001, 0.5 mg qd 0.010, 1.0 mg qd 0.009

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 FEV₁ 79.5%, predicted; mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.04 to 1.18; mean baseline dose of beclomethasone dipropionate of 295 mcg/day, ranging between 4