



Budesonide Inhalation Suspension

0.25 mg and 0.5 mg

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

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 and 0.5 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)

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

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

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.

2.2 Directions for Use

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.

Patient Information and Instructions for Use

Budesonide (baw DEH so nide) (budesonide) inhalation suspension 2 mL ampules containing 0.25 mg or 0.5 mg

For inhalation only. Do not swallow.

Only use budesonide inhalation suspension with a jet nebulizer machine that is connected to an air compressor. Do not use with an ultrasonic nebulizer.

What is budesonide inhalation suspension?

Budesonide inhalation suspension is an inhaled corticosteroid medicine. Budesonide inhalation suspension is a long-term maintenance medicine used to control and prevent asthma symptoms in children ages 12 months to 8 years.

Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms. Budesonide inhalation suspension helps reduce swelling and inflammation in the lungs, and helps keep the airways open to reduce asthma symptoms.

Budesonide inhalation suspension does not treat the sudden symptoms (wheezing, cough, shortness of breath, and chest pain or tightness) of an asthma attack. Always have a short-acting beta₂-agonist medicine (rescue inhaler) with you to treat sudden symptoms. If your child does not have an inhaled, short-acting bronchodilator, ask your healthcare provider to have one prescribed for your child.

WARNINGS AND PRECAUTIONS

Local 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)

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 [see *Contraindications* (4)].

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 corticosteroids: Risk of impaired adrenal function when transferring from oral steroids. Taper patients slowly from systemic corticosteroids if transferring to budesonide inhalation suspension. (5.5)

Hypercorticism 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 Nephron Pharmaceuticals Corporation at 1-800-443-4313 or FDA at 1-800-FDA-1088 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

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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

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Inhaled corticosteroids help to decrease inflammation in the lungs. Inflammation in the lungs can lead to asthma symptoms. Budesonide inhalation suspension helps reduce swelling and inflammation in the lungs, and helps keep the airways open to reduce asthma symptoms.

Budesonide inhalation suspension does not treat the sudden symptoms (wheezing, cough, shortness of breath, and chest pain or tightness) of an asthma attack. Always have a short-acting beta₂-agonist medicine (rescue inhaler) with you to treat sudden symptoms. If your child does not have an inhaled, short-acting bronchodilator, ask your healthcare provider to have one prescribed for your child.

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. In children or adults 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. If 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.

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 noncorticosteroid asthma therapy (n=92) (ie, beta₂-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (pELISA 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.

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 of the potential for adrenal insufficiency. In patients with 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 glucocorticosteroid 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 medical identification card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to 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.

5.6 Hypercorticism 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 of post-operatively or during periods of stress for evidence of inadequate adrenal response. It is possible that systemic corticosteroid effects such as hypercorticism, and adrenal suppression (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, each patient should be titrated to his/her lowest effective dose [see *Use in Specific Populations* (8.4)].

5.9 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, 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 instituted.

5.11 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled corticosteroids may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of inhaled corticosteroids. Healthcare providers should be alert to eosinophilic, vasculitis rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients. A causal relationship between budesonide and these underlying conditions has not been established.

5.12 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

Caution should be exercised when considering the concomitant use of budesonide suspension inhalation with ketoconazole, and other known strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin) because adverse effects related to increased systemic exposure to budesonide may occur [see *Drug Interactions* (7.1), *Clinical Pharmacology* (12.3)].

6 ADVERSE REACTIONS

Systemic and inhaled corticosteroid use may result in the following:

- Candida albicans* infection [see *Warnings and Precautions* (5.1)]
- Hypersensitivity reactions including anaphylaxis [see *Warnings and Precautions* (5.3)]
- Immunosuppression [see *Warnings and Precautions* (5.4)]
- Hypercorticism and adrenal suppression [see *Warnings and Precautions* (5.6)]

- Reduction in bone mineral density [see *Warnings and Precautions* (5.7)]
- Growth effects in pediatric patients [see *Warnings and Precautions* (5.8) and *Use in Specific Populations* (8.4)]

- Glaucoma, increased intraocular pressure and cataracts [see *Warnings and Precautions* (5.9)]
- Eosinophilic conditions and Churg-Strauss syndrome [see *Warnings and Precautions* (5.11)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The incidence of common adverse reactions is based on three double-blind, placebo-controlled, randomized U.S. clinical trials in which 945 patients, 12 months to 8 years of age, (98 patients >12 months and <2 years of age; 225 patients ≥2 and <4 years of age; and 622 patients ≥4 and ≤8 years of age) were treated with budesonide inhalation suspension (0.25 to 1 mg total daily dose for 12 weeks) 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 U.S. controlled clinical trials, regardless of relationship to treatment, in patients previously receiving bronchodilators and/or inhaled corticosteroids. This population included a total of 605 male and 340 female patients and 78.4% were Caucasian, 13.8% African American, 5.5% Hispanic and 2.3% Other.

Table 1 - Adverse Reactions occurring at an incidence of 2% in at least one active treatment group where the incidence was higher with budesonide inhalation suspension than placebo

Adverse Events	Vehicle Placebo (n=227) %	Budesonide Inhalation Suspension Total Daily Dose		
		0.25 mg (n=178) %	0.5 mg (n=223) %	1 mg (n=317) %
Respiratory System Disorder				
Respiratory Infection	36	34	35	38
Rhinitis	9	7	11	12
Coughing	5	5	9	8
Resistive Mechanism Disorders				
Otitis Media	11	12	11	9
Viral Infection	3	4	5	3
Moniliasis	2	4	3	4
Gastrointestinal System Disorders				
Gastroenteritis	4	5	5	5
Vomiting				