

# 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)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 1 INDICATIONS AND USAGE

- 1.1 Maintenance Treatment of Asthma

### 2 DOSAGE AND ADMINISTRATION

- 2.1 Dosing Recommendations
- 2.2 Directions for Use

### 3 DOSAGE FORMS AND STRENGTHS

### 4 CONTRAINDICATIONS

### 5 WARNINGS AND PRECAUTIONS

- 5.1 Local Effects
- 5.2 Deterioration of Disease and Acute Asthma Episodes
- 5.3 Hypersensitivity Reactions Including Anaphylaxis
- 5.4 Immunosuppression
- 5.5 Transferring Patients from Systemic Corticosteroid Therapy
- 5.6 Hypercorticism and Adrenal Suppression
- 5.7 Reduction in Bone Mineral Density
- 5.8 Effects on Growth
- 5.9 Glaucoma and Cataracts
- 5.10 Paradoxical Bronchospasm and Upper Airway Symptoms
- 5.11 Eosinophilic Conditions and Churg-Strauss Syndrome
- 5.12 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

### 6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Post-marketing Experience

### 7 DRUG INTERACTIONS

- 7.1 Inhibitors of Cytochrome P450 3A4

### 8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

### 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 beta<sub>2</sub>-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

REVISED: 10/2024

## 8.2 Lactation

4.2 Pediatric Use

8.5 Geriatric Use

8.6 Hepatic Impairment

## 10 OVERDOSAGE

## 11 DESCRIPTION

## 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

## 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

## 14 CLINICAL STUDIES

## 16 HOW SUPPLIED / STORAGE AND HANDLING

## 17 PATIENT COUNSELING INFORMATION

17.1 Administration with a jet nebulizer

17.2 Oral Candidiasis

17.3 Not for Acute Symptoms

17.4 Hypersensitivity Including Anaphylaxis

17.5 Immunosuppression

17.6 Hypercorticism and Adrenal Suppression

17.7 Reduction in Bone Mineral Density

17.8 Reduced Growth Velocity

17.9 Ocular Effects

17.10 Use Daily

\* Sections or subsections omitted from the full prescribing information are not listed.

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 *Patient Counseling Information* (17.1)].

A Pari-LC-Jet Plus Nebulizer (with face mask or mouthpiece) with sterile 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.

Lung function (FEV<sub>1</sub> 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* (2)].

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

**5.6 Hypercorticism and Adrenal Suppression**  
Budesonide inhalation suspension, will often help control asthma symptoms with less suppression of HPA function than the 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

- be inactive for a long period of time
- have a family history of osteoporosis
- does not eat well (poor nutrition)
- takes bone thinning medicines (such as anticonvulsant medicines or corticosteroids) for a long time.

- has an eye problem such as increased pressure in the eye, glaucoma or cataracts.
- has liver problems.
- is planning to have surgery.
- has any other medical conditions.

is pregnant or plans to become pregnant. It is not known if budesonide inhalation suspension will harm your unborn baby.

is breast-feeding or plans to breast-feed. Budesonide inhalation suspension can pass into breast milk. You and your healthcare provider should decide if you will use budesonide inhalation suspension or breast-feed.

Tell your healthcare provider about all the medicine your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using budesonide inhalation suspension with certain other medicines may affect each other causing side effects. Especially tell your healthcare provider if your child takes:

- corticosteroids
- anti-seizure medicine (anticonvulsants)
- medicines that suppress the immune system (immunosuppressant)
- ketonazole (Nizoral)
- certain medicines that can affect how your liver breaks down medicine.

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

Patients should be instructed to contact their physician immediately if episodes of asthma not responsive to their usual doses of bronchodilator 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 using corticosteroids. 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, beta<sub>2</sub>-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. When transferring asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled 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.

Lung function (FEV<sub>1</sub> 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* (2)].

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

**5.6 Hypercorticism and Adrenal Suppression**  
Budesonide inhalation suspension, will often help control asthma symptoms with less suppression of HPA function than the 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

- be inactive for a long period of time
- have a family history of osteoporosis
- does not eat well (poor nutrition)
- takes bone thinning medicines (such as anticonvulsant medicines or corticosteroids) for a long time.

- has an eye problem such as increased pressure in the eye, glaucoma or cataracts.
- has liver problems.
- is planning to have surgery.
- has any other medical conditions.

is pregnant or plans to become pregnant. It is not known if budesonide inhalation suspension will harm your unborn baby.

is breast-feeding or plans to breast-feed. Budesonide inhalation suspension can pass into breast milk. You and your healthcare provider should decide if you will use budesonide inhalation suspension or breast-feed.

Tell your healthcare provider about all the medicine your child takes, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Using budesonide inhalation suspension with certain other medicines may affect each other causing side effects. Especially tell your healthcare provider if your child takes:

- corticosteroids
- anti-seizure medicine (anticonvulsants)
- medicines that suppress the immune system (immunosuppressant)
- ketonazole (Nizoral)
- certain medicines that can affect how your liver breaks down medicine.

Ask your healthcare provider or pharmacist for a list of these medicines, if you are not sure.

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

budesonide (micronized), and the inactive ingredients citric acid, edetate disodium dihydrate, polysorbate 80, sodium chloride, sodium citrate, and water for injection. Two dose strengths are available in single-dose ampules: 0.25 mg and 0.5 mg per 2 mL ampule. 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 (5% 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* (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 than 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 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 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 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).

### 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 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 hyperresponsiveness 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 FEV<sub>1</sub> 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=8), or placebo (n=3), 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. 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 ATCH-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 [see *Warnings and Precautions* (5.5)].

### 12.3 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<sub>max</sub>, 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 *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 *Use in Specific Populations* (8.2)].

#### 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 MRHDID in adults and children 12 months to 8 years of age on a mcg/m<sup>2</sup> 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 MRHDID in adults and children 12 months to 8 years of age on a mcg/m<sup>2</sup> basis) and in female rats at oral doses up to 50 mcg/kg (approximately 0.5 and 0.1 times, respectively, the MRHDID in adults and children 12 months to 8 years of age on a mcg/m<sup>2</sup> 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 MRHDID in adults and children 12 months to 8 years of age on a mcg/m<sup>2</sup> 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 MRHDID in adults and children 12 months to 8 years of age on a mcg/m<sup>2</sup> basis). The concurrent reference corticosteroids (prednisone 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 and 0.1 times, respectively, the MRHDID in adults and children 12 months to 8 years of age on a mcg/m<sup>2</sup> 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 rate hepatocyte culture.

Fertility and reproductive performance were unaffected in rats at an oral dose of 50 mcg/kg (approximately equivalent to the MRHDID in adults on a mcg/m<sup>2</sup> 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 approximately 0.2 times than the MRHDID in adults a mcg/m<sup>2</sup> basis. No such effects were noted at 5 mcg/kg (approximately 0.04 times the MRHDID in adults on a mcg/m<sup>2</sup> basis).

## 14 CLINICAL STUDIES

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, 657 males and 361 females (798 Caucasians, 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 to 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 to 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 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 once or twice daily, or 1 mg once daily, up to a total daily dose of 1 mg) in 946 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 studies.

Improvements in lung function were associated with budesonide inhalation suspension treatment in the subgroup of patients capable of performing lung function testing. Statistically significant increases were seen in FEV<sub>1</sub> [budesonide inhalation suspension 0.5 mg once daily and 1 mg once daily (one study); 0.5 mg twice daily] and morning PEF [budesonide inhalation suspension 1 mg once daily (one study), 0.25 mg twice daily; 0.5 mg twice daily] compared to placebo.

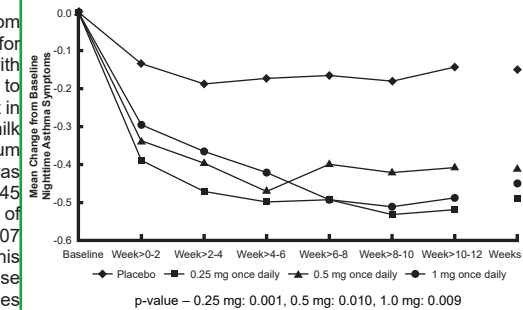
A numerical reduction in nighttime and daytime symptom scores (0 to 3 scale) of asthma was observed within 2 to 8 days, although maximum benefit was not achieved for 4 to 6 weeks after starting treatment. The reduction in nighttime and daytime asthma symptom scores was maintained throughout the 12 weeks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

### Patients 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

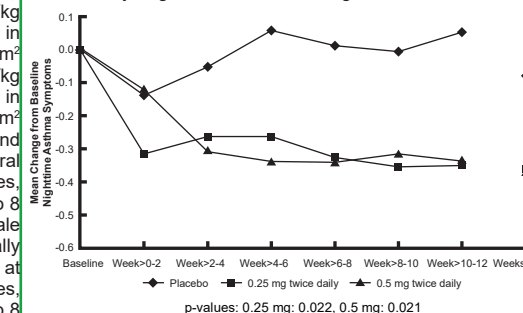


### Patients Previously Maintained on Inhaled Corticosteroids

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<sub>1</sub>, 79.5% predicted; mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.04 to 1.18; mean baseline dose of beclomethason 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 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 FEV<sub>1</sub>, 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. Night time Asthma Changes from Baseline



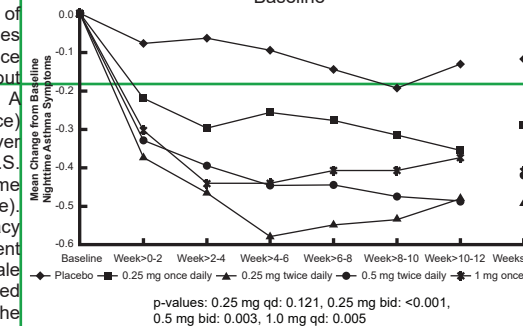
### Patients Receiving Once-Daily or Twice-Daily Dosing

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 to 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 FEV<sub>1</sub>, 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. When all measures are considered together, the evidence is stronger for twice-daily dosing [see *Dosage and Administration* (2)].

Figure 3: A 12-Week Trial in Pediatric Patients Either Maintained on Bronchodilators Alone or Inhaled Corticosteroid Therapy Prior to Study Entry. Nighttime Asthma Changes from Baseline



## 16 HOW SUPPLIED/STORAGE AND HANDLING

Budesonide inhalation suspension is supplied in sealed aluminum foil envelopes containing one plastic strip of five single-dose ampules or in individually wrapped single-dose ampules, together with patient instructions for use. There are 30 ampules in a carton. Each single-dose ampule contains 2 mL of sterile liquid suspension.

Budesonide inhalation suspension is available in two strengths, each containing 2 mL:

NDC 0487-9601-30 0.25 mg/2 mL  
30 ampules per carton/5 ampules per foil pouch.

### 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. Budesonide inhalation solution comes 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 envelope along the dotted line and take out 1 single-dose ampule from the strip. See Figure 1.
- Remove the side that you opened the foil on the envelope in the space provided.
- If your prescription was filled with individually wrapped, single-dose ampules, open the sealed aluminum foil envelope and remove the ampule (Figure 1a).

Return the unopened budesonide inhalation suspension ampules on the strip back into the foil envelope before storing.

Active ingredient: budesonide.

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



Figure 1



Figure 1a

NDC 0487-9601-01 0.25 mg/2 mL

30 ampules, each in an individual foil pouch.

NDC 0487-9701-30 0.5 mg/2 mL

30 ampules per carton/5 ampules per foil pouch.

NDC 0487-9701-01 0.5 mg/2 mL

30 ampules, each in an individual foil pouch.

Budesonide inhalation suspension should be stored upright at controlled room temperature 20°C to 25°C (68°F to 77°F) [see USP], and protected from light. When an envelope has been opened, the shelf life of the unused ampules is 2 weeks when protected. After opening the aluminum foil envelope, the unused ampules should be returned to the aluminum foil envelope to protect them from light. Any opened ampule must be used promptly. Gently shake the ampule using a circular motion before use. Keep out of reach of children. Do not freeze.

## 17 PATIENT COUNSELING INFORMATION

### 17.1 Administration with a Jet Nebulizer

Patients should be advised that 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. 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 *Dosage and Administration* (2)].

### 17.2 Oral Candidiasis

Patients should be advised that localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e. oral) antifungal therapy while still continuing therapy with budesonide inhalation suspension, but at times therapy with budesonide inhalation suspension may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised [see *Warnings and Precautions* (5.1)].

### 17.3 Not for Acute Symptoms

Budesonide inhalation suspension is not meant to relieve acute asthma symptoms and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta<sub>2</sub>-agonist such as albuterol.

(The healthcare professional should provide that patient with such medication and instruct the patient in how it should be used). Patients should be clearly instructed to notify their healthcare professional immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta<sub>2</sub>-agonist
- Need for more inhalations than amount of inhaled, short, acting beta<sub>2</sub>-agonists
- Significant decrease in lung function as outlined by the physician

Patients should not stop therapy with budesonide inhalation suspension without physician/provider guidance since symptoms may recur after discontinuation [see *Warnings and Precautions* (5.2)].

### 17.4 Hypersensitivity 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); *Warning and Precautions* (5.3)].

### 17.5 Immunosuppression

Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chickenpox or measles and, if exposed, to consult their physician without delay. 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. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex [see *Warnings and Precautions* (5.4)].

### 17.6 Hypercorticism and Adrenal Suppression

Patients should be advised that budesonide inhalation suspension may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to budesonide inhalation suspension [see *Warnings and Precautions* (5.6)].

### 17.7 Reduction in Bone Material Density

Patients who are at an increased risk for decreased BMD should be advised that the use of corticosteroids may pose an additional risk [see *Warnings and Precautions* (5.7)].

### 17.8 Reduced Growth Velocity

Patients should be informed that orally inhaled corticosteroids, including budesonide, may cause a reduction in growth velocity when administered to pediatric patients. Healthcare professionals should closely follow the growth of children and adolescents taking corticosteroids by any route [see *Warnings and Precautions* (5.8)].