

# Budemass Respule 0.5 mg and 1 mg

(Budesonide respirator Suspension)

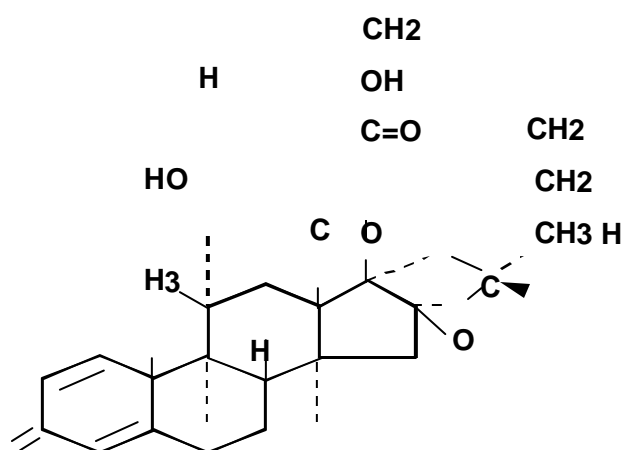
## Route of Administration-

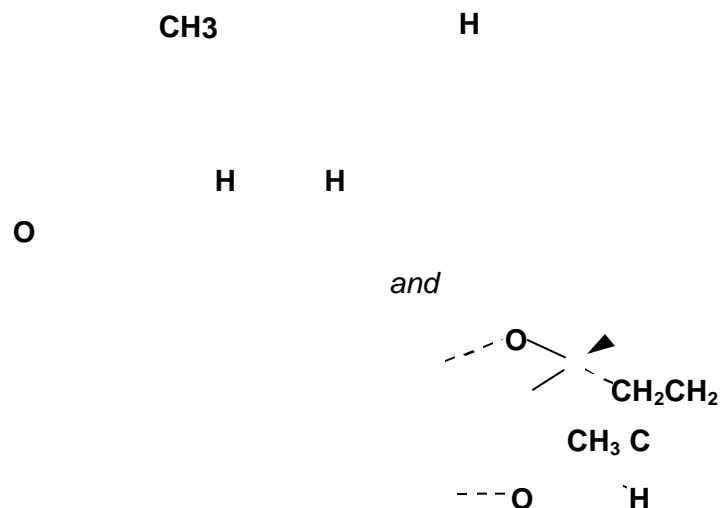
For inhalation use via compressed air driven jet nebulizers only (not for use with ultrasonic devices). Not for injection.

Read patient instructions before using.

## DESCRIPTION

Budesonide, the active component of BUDEMSS RESPULES, is a corticosteroid designated chemically as (RS)-11 $\beta$ , 16 $\beta$ , 17, 21-tetrahydroxypregna-1, 4-diene-3, 20-dione cyclic 16, 17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is C<sub>25</sub>H<sub>34</sub>O<sub>6</sub> and its molecular weight is 430.5. Its structural formula is:





BUDEMASE RESPULES (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  $1.6 \times 10^3$ .

BUDEMASE RESPULES is a sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide (micronized), and the inactive ingredients disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80 and Water for Injection. Two dose strengths are available in single-dose ampules or Respules: 0.5 mg and 1 mg per 2 mL Respule. For BUDEMASE RESPULES, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari-LC-Jet Plus Nebulizer/Pari Master compressor system, under *in vitro* conditions, the mean delivered dose at the mouthpiece (% nominal dose) was approximately 17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less. BUDEMASE RESPULES should be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces (see DOSAGE AND ADMINISTRATION).

### CLINICAL PHARMACOLOGY

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

subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The precise mechanism of corticosteroid actions on inflammation in asthma is not well known. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic- and non-allergic-mediated inflammation. The anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

### **Pharmacokinetics**

The activity of BUDEMSS RESPULES 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.

Budesonide is primarily cleared by the liver. In asthmatic children 4-6 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.

After a single dose of 1 mg budesonide, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20 minutes after nebulization in asthmatic children 4-6 years of age. The exposure (AUC) of budesonide following administration of a single 1 mg dose of budesonide by nebulization to asthmatic children 4-6 years of age is comparable to healthy adults given a single 2 mg dose by nebulization.

**Absorption:** In asthmatic children 4-6 years of age, the total absolute bioavailability (ie, lung + oral) following administration of BUDEMSS RESPULES via jet nebulizer was approximately 6% of the labeled dose.

The peak plasma concentration of budesonide occurred 10-30 minutes after start of nebulization.

**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 3A catalyzed biotransformation have been isolated and identified as 16 $\alpha$ -hydroxyprednisolone and 6 $\alpha$ -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:** Budesonide is excreted in urine and feces in the form of metabolites. In adults, approximately 60% of an intravenous radio labeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

**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 was affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide was, however, similar in cirrhotic patients and in healthy adults.

## Pharmacodynamics

The therapeutic effects of conventional doses of orally inhaled budesonide are largely explained by its direct local action on the respiratory tract. To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in adult patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered

dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels.

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

Budesonide decrease bronchial hyperresponsiveness in asthmatic patients.

The effects of BUDEMSS RESPULES 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 BUDEMSS RESPULES treatment at recommended doses. In the subgroup of children age 6 months to 2 years (n=21) receiving a total daily dose of BUDEMSS RESPULES 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.

The effects of BUDEMSS RESPULES 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 BUDEMSS RESPULES (1 and 2 mg twice daily) showed statistically significantly reduced (43-52%) urinary cortisol excretion compared to the run-in period. The highest recommended dose of BUDEMSS RESPULES, 1 mg total daily dose, did not show statistically significantly reduced urinary cortisol excretion compared to the run-in period.

BUDEMSS RESPULES, 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.

**INDICATIONS**

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

BUDEMSS RESPULES is NOT indicated for the relief of acute bronchospasm.

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**CONTRAINDICATIONS**

BUDEMSS RESPULES is contraindicated as the 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 this preparation contraindicates the use of BUDEMSS RESPULES.

**WARNINGS**

Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of 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 BUDEMSS RESPULES may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instructions. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Transfer of patients from systemic corticosteroid therapy to BUDEMSS RESPULES may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, eczema (see DOSAGE AND ADMINISTRATION).

Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressant doses of corticosteroids. In pediatric or adult patients who have not had these diseases, or who have not been properly vaccinated, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package insert for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

BUDEMSS RESPULES is not a bronchodilator and is not indicated for the rapid relief of acute bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If acute bronchospasm occurs following dosing with BUDEMSS RESPULES, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with BUDEMSS RESPULES should be discontinued and alternate therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with BUDEMSS RESPULES.

## **PRECAUTIONS**

### **General**

Inhaled corticosteroids may cause a reduction in growth velocity when administered to pediatric patients (see PRECAUTIONS, Pediatric Use).

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

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

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



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

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

In clinical trials with BUDESONIDE RESPULES, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. The incidences of localized infections of *Candida albicans* were similar between the placebo and BUDESONIDE RESPULES treatment groups. If symptomatic oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (ie, oral) antifungal therapy while still continuing with BUDESONIDE RESPULES therapy, but at times therapy with BUDESONIDE RESPULES may need to be interrupted under close medical supervision.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular *Herpes simplex*.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

### **Information for Patients**

For instructions on the proper use of BUDEMSS RESPULES and to attain the maximum improvement in asthma symptoms, the patient or the parent/guardian of the patient should receive, read, and follow the accompanying patient information and instructions carefully. In addition, patients being treated with BUDEMSS RESPULES should receive the following information and instructions. This information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects.

- Patients should take BUDEMSS RESPULES at regular intervals once or twice a day as directed by physician, since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.
- The effects of mixing BUDEMSS RESPULES with other nebulizable medications has not been adequately assessed.
- BUDEMSS RESPULES should be administered separately in the nebulizer.
- BUDEMSS RESPULES is not a bronchodilator, and its use is not intended to treat acute life threatening episodes of asthma.
- BUDEMSS RESPULES should be administered with a jet nebulizer connected to a compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. The face mask should be properly adjusted to optimize delivery and to avoid exposing the eyes to the nebulized medication (see DOSAGE AND ADMINISTRATION).
- Ultrasonic nebulizers are not suitable for the adequate administration of BUDEMSS RESPULES and, therefore, are not recommended (see DOSAGE AND ADMINISTRATION).
- Rinsing the mouth with water after each treatment may decrease the risk of development of local candidiasis. Corticosteroid effects on the skin can be avoided if the face is washed after the use of a face mask.
- Improvement in asthma control following treatment with BUDEMSS RESPULES can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks after starting treatment. If the asthma symptoms do not improve in that time frame, or if the condition worsens, the patient or the patient's parent/guardian should be instructed to contact the physician.
- Care should be taken to avoid exposure to chicken pox and measles. If exposure occurs, and the child has not had chickenpox or been properly vaccinated, a physician should be

consulted without delay.

- BUDEMSS RESPULES should be stored upright at controlled room temperature 20-25°C (68-77°F) and protected from light. BUDEMSS RESPULES should not be refrigerated or frozen.
- When an aluminum foil envelope has been opened, the shelf life of the unused RESPULES is two weeks when protected from light. The date the envelope was opened should be recorded on the back of the envelope in the space provided.
- After opening the aluminum foil envelope, the unused RESPULES should be returned to the envelope to protect them from light. Any individually opened RESPULES must be used promptly.
- For proper usage of BUDEMSS RESPULES and to attain maximum improvement, the accompanying Patient's Instructions for use should be read and followed.

### **Drug Interactions**

In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. Ketoconazole, a potent inhibitor of cytochrome P450 3A, may increase plasma levels of budesonide during concomitant dosing. The clinical significance of concomitant administration of ketoconazole with BUDEMSS RESPULES is not known, but caution may be warranted. Omeprazole did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of cytochrome P450, caused a slight decrease in budesonide clearance and a corresponding increase in its oral bioavailability.

### **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 (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m<sup>2</sup> basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than

the maximum recommended daily inhalation dose in adults and children on a mcg/m<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 (less than the maximum recommended daily inhalation dose in adults and children 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 (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m<sup>2</sup> basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

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

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m<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 (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

### **Pregnancy**

*Teratogenic Effects:* Pregnancy Category C □ As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (less than the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis) and 500

mcg/kg in rats (approximately 4 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m<sup>2</sup> basis).

There are no adequate and well-controlled studies in pregnant women. Budesonide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans. In addition, because there is a natural increase in corticosteroid production during pregnancy, most women will require a lower exogenous corticosteroid dose and many will not need corticosteroid treatment during pregnancy.

*Non-teratogenic Effects:* Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

### **Nursing Mothers**

It is not known whether budesonide is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised if budesonide is administered to nursing women.

### **Pediatric Use**

Safety and effectiveness of BUDEMSS RESPULES in children 12 months to 8 years of age have been established (see CLINICAL TRIALS and ADVERSE REACTIONS). Safety and effectiveness in children less than 12 months of age have not been established.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth

velocity associated with inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for “catch up” growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied. The growth of pediatric patients receiving inhaled corticosteroids, including BUDEMSS RESPULES, should be monitored routinely (eg, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapies.

To minimize the systemic effects of inhaled corticosteroids, including BUDEMSS RESPULES, each patient should be titrated to his/her lowest effective dose.

### **Geriatric Use**

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

### **ADVERSE REACTIONS**

The following adverse reactions were reported in pediatric patients treated with BUDEMSS RESPULES.

The incidence of common adverse reactions is based on three double-blind, placebo-controlled, 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 RESPULES (0.25 to 1 mg total daily dose for 12 weeks) or vehicle placebo. The incidence and nature of adverse events reported for BUDESONIDE RESPULES 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.

Adverse events with □ 3% Incidence Reported by Patients on Budesonide RESPULES

Adverse Events	Vehicle Placebo (n=227) %	BUDESONIDE RESPULES Total Daily Dose		
		0.25 mg (n=178) %	0.5 mg (n=223) %	1 mg (n=317) %
<b>Respiratory System Disorder</b>				
Respiratory Infection	36	34	35	38
Rhinitis	9	7	11	12
Coughing	5	5	9	8
<b>Resistance Mechanism Disorders</b>				
Otitis Media	11	12	11	9
Viral Infection	3	4	5	3
Moniliasis	2	4	3	4
<b>Gastrointestinal System Disorders</b>				
Gastroenteritis	4	5	5	5
Vomiting	3	2	4	4
Diarrhea	2	4	4	2
Abdominal Pain	2	3	2	3

<b>Hearing and Vestibular Disorders</b>				
Ear Infection	4	2	4	5
<b>Platelet, Bleeding, and Clotting Disorders</b>				
Epistaxis	1	2	4	3
<b>Vision Disorders</b>				



Conjunctivitis	2	<1	4	2
<b>Skin and Appendages Disorders</b>				
Rash	3	<1	4	2

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

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

#### **Incidence 1% to $\leq$ 3% (by body system)**

The information below includes all adverse events with an incidence of 1 to  $\leq$ 3%, in at least one BUDESONIDE RESPULES treatment group where the incidence was higher with BUDESONIDE RESPULES than with placebo, regardless of relationship to treatment.

Body as a whole: allergic reaction, chest pain, fatigue, flu-like disorder

Respiratory system: stridor

Resistance mechanisms: Herpes simplex, external ear infection, infection

Central & peripheral nervous system: dysphonia, hyperkinesia

Skin & appendages: eczema, pustular rash, pruritus

Hearing & vestibular: earache

Vision: eye infection

Psychiatric: anorexia, emotional lability

Musculo-skeletal system : fracture, myalgia

Application site: contact dermatitis

Platelet, bleeding & clotting: purpura

White cell and resistance: cervical lymphadenopathy

Cases of growth suppression have been reported for inhaled corticosteroids including post-marketing reports for BUDEMASS RESPULES (see PRECAUTIONS, Pediatric Use).

Less frequent adverse events (<1%) reported in the published literature, long-term, open-label clinical trials, or from marketing experience for inhaled budesonide include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, angioedema and bronchospasm; symptoms of hypocorticism and hypercorticism; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety and psychosis, and bone disorders including avascular necrosis of the femoral head and osteoporosis.

## **OVERDOSAGE**

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

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

## **DOSAGE AND ADMINISTRATION**

BUDEMASS RESPULES is indicated for use in asthmatic patients 12 months to 8 years of age. BUDEMASS RESPULES should be administered by the inhaled route via jet nebulizer connected to an air compressor. Individual patients will experience a variable onset and degree of symptom

relief. Improvement in asthma control following inhaled administration of BUDEMSS RESPULES can occur within 2-8 days of initiation of treatment, although maximum benefit may not be achieved for 4-6 weeks. The safety and efficacy of BUDEMSS RESPULES when administered in excess of recommended doses have not been established. In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved. The recommended starting dose and highest recommended dose of BUDEMSS RESPULES, based on prior asthma therapy, are listed in the following table.

<b>Previous Therapy</b>	<b>Recommended Starting Dose</b>	<b>Highest Recommended Dose</b>
<b>Bronchodilators alone</b>	0.5 mg total daily dose administered either once daily or twice daily in divided doses	0.5 mg total daily dose
<b>Inhaled Corticosteroids</b>	0.5 mg total daily dose administered either once daily or twice daily in divided doses	1 mg total daily dose
<b>Oral Corticosteroids</b>	1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily	1 mg total daily dose

In symptomatic children not responding to non-steroidal therapy, a starting dose of 0.25 mg once daily of BUDEMSS RESPULES may also be considered.

If once daily treatment with BUDEMSS RESPULES does not provide adequate control of asthma symptoms, the total daily dose should be increased and/or administered as a divided dose.

### **Patients Not Receiving Systemic (Oral) Corticosteroids**

Patients who require maintenance therapy of their asthma may benefit from treatment with BUDEMSS RESPULES at the doses recommended above. Once the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose. For the patients who do not respond adequately to the starting dose, consideration should be given to administering the total daily dose as a divided dose, if a once daily dosing schedule was followed. If necessary, higher doses, up to the maximum recommended doses, may provide additional asthma control.

### **Patients Maintained on Chronic Oral Corticosteroids**

Initially, BUDEMSS RESPULES should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid may be initiated by reducing the daily or alternate daily dose. Further incremental reductions may be made after an interval of one or two weeks, depending on the response of the patient. Generally, these decrements should not exceed 25% of the prednisone dose or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for asthma instability, including objective measures of airway function, and for adrenal insufficiency (see WARNINGS). During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with BUDEMSS RESPULES but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

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

The effects of mixing BUDEMSS RESPULES with other nebulizable medications has not been adequately assessed. BUDEMSS RESPULES should be administered separately in the nebulizer (see PRECAUTIONS, Information for Patients).

### **Directions for Use**

Illustrated *Patient Instructions for Use* accompany each package of BUDEMSS RESPULES.

### **HOW SUPPLIED**

BUDEMSS RESPULES is supplied in sealed aluminum 3 layer foil envelopes containing one plastic strip of five single-dose Respules together with patient instructions for use. There are 25 Respules in a carton. Each single-dose Respule contains 2 mL of sterile liquid suspension.

BUDEMSS RESPULES is available in two strengths, each containing 2 ml:

Budemass 0.5 Mg Respules	0.5 mg/2 ml
Budemass 1 mg Respules	1 mg/2 ml

### **Storage**

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