**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, the therapeutic activity of budesonide is 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 availability, budesonide was 85-90% bound to plasma proteins (85-95%) and the low potency of metabolites (see below).

**CLINICAL PHARMACOLOGY**

**Absorption:**

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

**Distribution:**

In asthmatic children 4-6 years of age, the volume of distribution at steady-state of budesonide was 21.4 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 ng/mL) achieved with, and exceeding, recommended doses. Budesonide showed little or no binding to corticosteroid-binding globulin. Budesonide rapidly equilibrates with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

**Metabolism:**

In vitro studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoforms CYP2C9 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16b-hydroxybudesonide and 11b-hydroxybudesonide. The glucocorticoid activity of each of these two metabolites is less than 1% that of the parent compound. No qualitative difference between the in vitro and in vivo metabolic patterns has been detected. Nephilic glucocorticoid 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 as metabolites. In adults, approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine. In healthy young children 4-6 years of age, the terminal elimination phase 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.

**Immunosuppression:**

Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were not affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The pharmacokinetic pharmacodynamics of budesonide were similar in corticosteroid 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 87 lactating women with asthma from 1 to 6 months postpartum. Systemic exposure of the mother to budesonide was comparable to that seen 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 0.79 ng/mL, respectively, and occurred within 45 minutes after dosing. The estimated oral daily dose of budesonide from breast milk to the infant (approximately 0.007 and 0.014 mcg/kg/day for the 400 and 800 dose regimens used in this study, which represents approximately 0.3% to 1% of the dose ingested by the mother. Budesonide levels in milk samples obtained from five infan
ts given 800 mcg of oral budesonide once daily (treated about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant) (see PRECAUTIONS, Nursing Mothers).

**Pharmacodynamics**

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

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

Budesonide administered via a dry powder inhaler has been shown in various challenge models (including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate) to depress antigen-induced hyperresponsiveness. The clinical relevance of these models is not certain.

Pre-treatment with budesonide administered as 1600 mcg daily (800 mcg twice daily) via a dry powder inhaler for 2 weeks reduced the acute (early-phase) reaction and delayed (late-phase) reaction decrease in FEV1 following inhaled allergen challenge. Pre-treatment effects of PULMICORT RESPULES on the hypothalamic-pituitary-adrenal (HPA) axis were studied in three, 12-week, double-blind, placebo-controlled studies in 293 pediatric patients, 6 years to 8 years of age, with persistent asthma. For most patients, the ability to increase cortisol levels in response to stress, as assessed by a dexamethasone suppression test, remained intact with PULMICORT RESPULES treatment at recommended doses. In the subgroup of patients with asthma who were 6-8 years of age, the terminal half-life of budesonide after nebulization was approximately 2.3 hours, whereas the terminal half-life of budesonide for the 400 and 800 mcg doses was 0.39 and 0.79 ng/mL, respectively, and occurred within 45 minutes after dosing. The estimated oral daily dose of budesonide from breast milk to the infant (approximately 0.007 and 0.014 mcg/kg/day for the 400 and 800 mg/kg/day for the 400 and 800 dose regimens used in this study, which represents approximately 0.3% to 1% of the dose ingested by the mother. Budesonide levels in milk samples obtained from five infants given 800 mcg of oral budesonide once daily (treated about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant) (see PRECAUTIONS, Nursing Mothers).

**Pulmicort Respules® (budesonide inhalation suspension) 0.25 mg, 0.5 mg, and 1 mg Rx only**

**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, the therapeutic activity of budesonide is approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The activity of PULMICORT RESPULES is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was twice 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 (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 the 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 controlled delivery systems including inhaled-dry powder devices. A decrease in inhaler and the inhalation suspension for nebulization. This is explained by a combination of a relatively rapid lung deposition and a first pass hepatic degradation of orally absorbed drug (85-95%) and the low potency of metabolites (see below).

**Pharmacokinetics**

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

Distribution: In asthmatic children 4-6 years of age, the volume of distribution at steady-state of budesonide was 21.4 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 ng/mL) achieved with, and exceeding, recommended doses. Budesonide showed little or no binding to corticosteroid-binding globulin. Budesonide readily equilibrates with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism: In vitro studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoforms CYP2C9 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16b-hydroxybudesonide and 11b-hydroxybudesonide. The glucocorticoid activity of each of these two metabolites is less than 1% that of the parent compound. No qualitative difference between the in vitro and in vivo metabolic patterns has been detected. Nephilic glucocorticoid 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 as metabolites. In adults, approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine. In healthy young children 4-6 years of age, the terminal elimination phase 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 not affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The pharmacokinetic pharmacodynamics of budesonide were similar in corticosteroid patients and in healthy adults.

Nursing Mothers: The disposition of budesonide when delivered by inhalation from a dry powder
Patients Previously Maintained on Inhaled Corticosteroids

The efficacy of PULMICORT RESPULES at doses of 0.25 mg and 0.5 mg twice daily was evaluated in 133 pediatric asthma patients, 4 to 8 years of age, previously maintained on inhaled corticosteroids (mean FEV1, 79.5% predicted; mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.04 to 1.18; mean baseline dose of beclomethasone dipropionate of 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 0-12 in nighttime asthma symptom scores are shown in Figure 2. Nighttime asthma symptom scores were significantly improved in patients treated with PULMICORT RESPULES compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

PULMICORT RESPULES at a dose of 0.5 mg twice daily significantly improved FEV1, and both doses (0.25 mg and 0.5 mg twice daily) significantly increased morning PEF compared to placebo.

Patients Receiving Once-Daily or Twice-Daily Dosing

The efficacy of PULMICORT RESPULES at doses of 0.25 mg once daily, 0.5 mg twice daily, and 1 mg once daily 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 1.36) were evaluated in this study. Patients who were not previously receiving inhaled corticosteroids. The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 3. PULMICORT RESPULES at doses of 0.25 mg and 0.5 mg twice daily, and 1 mg once daily, significantly improved nighttime asthma symptom scores compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

PULMICORT RESPULES at a dose of 0.5 mg twice daily significantly improved FEV1, and at doses of 0.25 mg and 0.5 mg twice daily and 1 mg once daily significantly improved morning PEF compared to placebo.

The evidence supports the efficacy of the same nominal dose of PULMICORT RESPULES administered on either a once-daily or twice-daily schedule. However, when all measures are considered together, the evidence is stronger for twice-daily dosing (see DOSAGE AND ADMINISTRATION).

INDICATIONS

PULMICORT RESPULES is indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age. PULMICORT RESPULES is NOT indicated for the relief of acute bronchospasm.

PULMICORT RESPULES (budesonide inhalation suspension) 0.25 mg, 0.5 mg, and 1 mg

CONTRAINDICATIONS

PULMICORT 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 PULMICORT 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 active inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA)-axis function. Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn.

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

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

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to PULMICORT RESPULES. It is not known if budesonide is functionally equivalent to betamethasone, 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.

Patients or family members of patients from systemic corticosteroid therapy to PULMICORT RESPULES may unmask allergic or other immunologic conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, eosinophilic conditions, eczema, and arthritis (see DOSAGE AND ADMINISTRATION).

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

The clinical course of chicken pox or measles infection in patients on inhaled corticosteroids has not been studied. However, a clinical study has examined the immune responsiveness of asthma patients. 12 months to 8 years of age who were treated with PULMICORT RESPULES (see PRECAUTIONS, Pediatric Use).

If a patient on immunosuppressant doses of corticosteroids is exposed to chicken pox, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG) may be indicated. (See the respective package inserts for complete VZIG and IVIG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PULMICORT 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 PULMICORT RESPULES, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with PULMICORT 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 PULMICORT RESPULES.

PRECAUTIONS

General

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 dose equalization or even improvement of respiratory function (see DOSAGE AND ADMINISTRATION).

Because budesonide is absorbed into the circulation and may be systemically active, particularly at higher doses, suppression of HPA function may be associated with the use of PULMICORT RESPULES. As with other inhaled corticosteroids, including PULMICORT RESPULES, each patient should be titrated to his/her lowest effective dose (see PRECAUTIONS, Pediatric Use).

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

Oral inhaled corticosteroids, including budesonide, may cause a reduction in growth velocity when administered to pediatric patients. A reduction in growth velocity may occur as a result of inadequate control of asthma or from use of corticosteroids for treatment. The potential effects of prolonged treatment on growth velocity should be weighed against the benefits of treatment and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including PULMICORT RESPULES, each patient should be titrated to his/her lowest effective dose (see PRECAUTIONS, Pediatric Use).

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

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

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.
Patients being treated with PULMICORT 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 effects or intended effects. For instructions on the proper use of PULMICORT RESPULES and to attain the maximum improvement in asthma symptoms, the patient should receive, read, and follow the accompanying patient information and instructions carefully.

Patients should take PULMICORT RESPULES at regular intervals once or twice a day as directed. The 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 PULMICORT RESPULES with other nebulizable medications have not been determined. Only one medication should be inhaled at a time from a PULMICORT RESPULES nebulizer.

PULMICORT RESPULES is not a bronchodilator, and its use is not intended to treat acute life-threatening episodes of asthma.

PULMICORT 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 nebulizer (see DOSAGE AND ADMINISTRATION).

Ultrasonic nebulizers are not suitable for the adequate administration of PULMICORT 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 PULMICORT RESPULES can occur within 2–8 days of beginning treatment, although maximum benefit may not be achieved for 4–6 weeks after initiating treatment.

If the asthma symptoms or any signs of pregnancy (such as a change in the time frame, urine condition, or condition of the patient or the patient's parent/guardian) should not be instructed not to increase the dosage, but to contact the physician.

PULMICORT RESPULES should not be used in patients where the pregnancy is known.

Patients whose chronic systemic corticosteroids have been reduced or withdrawn should be monitored closely for an increase in asthma symptoms or any signs of pregnancy.

As always, care should be taken to avoid exposure to persons with chicken pox and measles. If exposure to such a person occurs, and the child has not had chicken pox or been previously vaccinated, a physician should be consulted without delay (see WARNINGS, and PRECAUTIONS). (Pediatric Use).

Long-term use of inhaled corticosteroids, including budesonide, may increase the risk of some eye complications (e.g., cataracts). Regular eye examinations should be considered.

Patients or their parents/guardians considering use of PULMICORT RESPULES should consult with their physician if they are allergic to budesonide or any other orally inhaled corticosteroid.

Pulmonary function tests or other determination of the dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypoadrenalism or hypothyroidism.

The potential growth effects of inhaled corticosteroids, including PULMICORT RESPULES, should be monitored routinely (e.g., via stadiometry). The potential growth effects of inhaled corticosteroids, including PULMICORT RESPULES, should be monitored routinely (e.g., via stadiometry). The potential growth effects of inhaled corticosteroids, including PULMICORT RESPULES, should be monitored routinely (e.g., via stadiometry).

Concomitant use of oral corticosteroids should be managed according to the patient's needs. The growth effects of inhaled corticosteroids, including PULMICORT RESPULES, should be monitored routinely (e.g., via stadiometry). The potential growth effects of inhaled corticosteroids, including PULMICORT RESPULES, should be monitored routinely (e.g., via stadiometry).

Non-teratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving long-term inhaled corticosteroids. Corticosteroid effects on the skin can be avoided if the face is washed after the use of a face mask.

In the absence of data and exposure in pregnant women, the use of PULMICORT RESPULES during pregnancy is not recommended. However, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be small. PULMICORT RESPULES should be used in nursing women if clinically appropriate. Prescribers should weigh the known benefits of breastfeeding for the mother and for the infant against the potential risks of minimal budesonide exposure in the infant.

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered by inhalation are not available. A warning card indicating that the baby may need suppression, and the physician may wish to use a different medicine.

PHARMACOLOGY, Pharmacodynamics, CLINICAL TRIALS and ADVERSE REACTIONS).

Pediatric Use

Safety in children six months to 12 months of age has been evaluated. Safety and effectiveness in children 12 months to 8 years of age have not been established. (see CLINICAL PHARMACOLOGY, Pharmacodynamics, CLINICAL TRIALS and ADVERSE REACTIONS).

An 12-week study in 141 pediatric patients 6 to 12 months of age with mild to moderate asthma or persistent wheezing was conducted. The results in this patient population were similar to those obtained in adult patients using PULMICORT RESPULES. A 12-week study in 62 patients with asthma or persistent wheezing was conducted in a similar population using PULMICORT RESPULES. The dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be small. PULMICORT RESPULES should be used in nursing women if clinically appropriate. Prescribers should weigh the known benefits of breastfeeding for the mother and the infant against the potential risks of minimal budesonide exposure in the infant.

In a study of asthmatic children 5-12 years of age, those treated with budesonide administered via a dry powder inhaler 200 mcg twice daily (n=311) had a 1.1-centimeter reduction in growth velocity compared with those receiving placebo (n=418) at the one year difference between these two treatment groups did not increase further over three years of additional treatment. By the end of the study, budesonide dry powder inhaler and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be further confounded by the unique use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving inhaled corticosteroids, including PULMICORT RESPULES, should be monitored routinely (see DOSAGE AND ADMINISTRATION). The effects of prolonged treatment should be weighed against clinical benefits obtained and the risks associated with alternative therapeutic regimens. To minimize the possibility of cataractogenicity, including PULMICORT RESPULES, each patient should be titrated to his/her lowest effective dose.

An open-label non-randomized clinical study examined the immunomodulatory action of variella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with PULMICORT RESPULES (500 mcg/d or non-steroidal anti-inflammatories (NSAID)). No significant effect of PULMICORT RESPULES was observed on patients with non-steroidal anti-inflammatory therapy (90%). No patient treated with PULMICORT RESPULES developed chicken pox as a result of vaccinating for variella.
2 mL ampules containing 0.25 mg, 0.5 mg, or 1 mg
FOR INHALATION ONLY.

- Your doctor has prescribed PULMICORT RESPULES. It contains a medication called budesonide, which is a synthetic corticosteroid. It is important that your child take PULMICORT RESPULES using a compressed air driven jet nebulizer as instructed.
- Use this nebulizer therapy as directed at the same time each day, even during symptom-free periods. DO NOT STOP TREATMENT OR REDUCE THE DOSE EVEN IF YOUR CHILD FEELS BETTER, unless told to do so by your doctor.
- DO NOT let your child inhale more doses or use this medication more often than instructed.
- This medication is intended to help prevent and control asthma symptoms. It is NOT intended to provide rapid relief of breathing difficulties during an asthma attack.
- Your doctor may prescribe additional medication (such as bronchodilators) for emergency relief if an acute asthma attack occurs. Please contact your doctor if:
  - an asthma attack does not respond to the additional medication,
  - your child requires more of the additional medication than usual.
- If your child uses another medication by inhalation, consult your healthcare provider for instructions on when to use it in relation to using PULMICORT RESPULES.
- PULMICORT RESPULES has not been studied when mixed with other nebulizable medications. PULMICORT RESPULES should be given separately in the nebulizer.

Tell your doctor before starting to take this medication if your child:
- Is allergic to budesonide or any other inhaled corticosteroid,
- Is taking any other medications,
- Has any infections,
- Has or had tuberculosis,
- Has osteoporosis,

- Has recently been around anyone with chicken pox or measles,
- Is planning to have surgery,
- Has been taking an oral corticosteroid medicine like prednisone. You may have to follow specific instructions to avoid health risks associated with stopping the use of these types of medicines.

In some circumstances, this medicine may not be suitable and your doctor may wish to prescribe a different medicine. Make sure that your doctor knows what other medicines your child is taking, including prescription and non-prescription medicines, as well as any vitamins or dietary and herbal supplements.

As with all inhaled corticosteroids, you should be aware of the following side effects:
- Increased wheezing right after taking PULMICORT RESPULES. Always have a short-acting bronchodilator medicine with you to treat sudden wheezing. Short-acting bronchodilator medicines help to relax the muscles around the airways in your lungs. Wheezing happens when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- Immune system effects and a higher chance of infections.
- Eye problems including glaucoma and cataracts. Eye examinations should be considered while using PULMICORT RESPULES.
- Your child’s growth should be checked regularly while taking PULMICORT RESPULES because of the potential for slowed growth.

Based on clinical trials, the most common side effects reported by patients using PULMICORT RESPULES are:
- Respiratory infections
- Ear infections
- Runny nose

These are not all of the possible side effects of PULMICORT RESPULES. For more information, ask your doctor or pharmacist.

PULMICORT RESPULES should be used with a compressed air driven jet nebulizer following the manufacturer’s instructions. The mist produced is then inhaled through either a mouthpiece or face mask. The treatment generally takes five to ten minutes. Treatment is complete when mist no longer comes out of the mouthpiece or face mask. The face mask should be properly adjusted to optimize delivery and to avoid exposing the eyes to the nebulized medication.

Patients should take PULMICORT RESPULES at regular intervals once or twice a day, as directed, since its effectiveness depends on regular use. Improvement in the control of asthma symptoms with PULMICORT RESPULES can occur within 2–8 days. It may take up to 4–6 weeks before maximum improvement is seen.

If your child misses a dose by more than several hours, just take the next regularly scheduled dose when it is due. DO NOT DOUBLE the dose.
1. Assemble the nebulizer according to the instructions supplied by the manufacturer.

2. Open the sealed aluminum foil envelope along the dotted line and remove one (1) single-dose ampule from the strip (Figure 1). Record the date that you open the foil on the back of the envelope in the space provided.

   Place the unused Respules™ ampules remaining on the strip back into the aluminum foil envelope before storing. This will protect the medication from light. PULMICORT RESPULES should be stored upright at room temperature, 68–77°F (20–25°C). Do not refrigerate or freeze.

3. Gently shake the RESPULES ampule using a circular motion as shown in Figure 2.

4. Hold the RESPULES ampule upright without squeezing and open by twisting off the top (Figure 3).

5. Place the open end of the RESPULES ampule into the nebulizer cup and slowly squeeze out all of the contents as shown in Figure 4.

6. If using a face mask, make sure that the mask fits tightly so that the mist does not get into the child's eyes. Turn on the compressor to begin nebulizing the medication. Use the nebulizer as directed. Continue the treatment with PULMICORT RESPULES until mist is no longer coming out of the mouthpiece/face mask (usually about 5 to 10 minutes).

7. Throw away the empty RESPULES ampule. See the CLEANING OF EQUIPMENT and STORING YOUR PULMICORT RESPULES sections for additional information.

NOTE:
1. As with other inhaled corticosteroids, rinse your child's mouth with water after each dose to reduce the risk of developing thrush.
2. Wash your child's face after treatment to avoid possible skin irritation.

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HOW TO USE PULMICORT RESPULES

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CLEANING OF EQUIPMENT

The nebulizer cup and the mouthpiece or the face mask should be cleaned according to the instructions supplied by the manufacturer.

STORING YOUR PULMICORT RESPULES

PULMICORT RESPULES should be stored in an upright position at temperatures between 68 and 77°F (20 and 25°C) in the aluminum foil envelope to protect from light. Do not freeze.

When the foil envelope is opened, the unused RESPULES ampules should be used within 2 weeks. After opening the aluminum foil package, the unused RESPULES ampules should be returned to the foil envelope to protect them from light. Any individually opened RESPULES ampule must be used promptly.

Remember to record the date you open the foil on the back of the envelope in the space provided.

Store PULMICORT RESPULES, like all medications, in a secure place out of the reach of children.

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FURTHER INFORMATION ABOUT PULMICORT RESPULES

This leaflet does not contain the complete information about this medication. If you have any questions, you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished the medication.

REMEMBER: This medication has been prescribed for your child by your doctor. DO NOT give this medication to anyone else.

USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.

If your child is exposed to chicken pox or measles, consult your doctor.

For additional information about PULMICORT RESPULES, please visit our website: pulmicortrespules.com or call the AstraZeneca Information Center, Monday through Friday, 8 am – 7 pm ET, excluding holidays:

1-800-236-9933

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Manufactured for:
AstraZeneca LP, Wilmington, DE 19850
By: AstraZeneca AB, Södertälje, Sweden
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Adverse Events with ≥ and <2 years of age; 225 patients

The information below includes all adverse events with an incidence of 1 to 10%. It includes both those events occurring with PULMICORT RESPULES and those occurring in placebo-controlled trials of PULMICORT RESPULES, if the information is not available from the controlled trials. Such information is also provided for PULMICORT RESPULES (0.25 mg to 1 mg total daily dose for 12 weeks) when administered as a single daily dose or divided doses. 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 PULMICORT RESPULES than with placebo.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Vehicle/Placebo (n=227) %</th>
<th>PULMICORT RESPULES Total Daily Dose 0.25 mg (n=178)</th>
<th>0.5 mg (n=223)</th>
<th>1 mg (n=217)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory System Disorder</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory Infection</td>
<td>36</td>
<td>24</td>
<td>35</td>
<td>39</td>
</tr>
<tr>
<td>Coughing</td>
<td>17</td>
<td>9</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td><strong>Respiratory Mechanism Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic Rhinitis</td>
<td>11</td>
<td>12</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Viral Infection</td>
<td>6</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td><strong>Gastrointestinal System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>6</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>3</td>
<td>2</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td><strong>Hearing and Vestibular Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ear Infection</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Pain, Bleeding, and Clotting Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2</td>
<td>&lt;1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Skin and Appendages Disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>&lt;1</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

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 6 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 PULMICORT RESPULES (0.25 mg to 1 mg total daily dose for 12 weeks) or vehicle placebo. The incidence and nature of adverse events reported for PULMICORT RESPULES were 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 650 male and 240 female patients.

Adverse Events with ≥ 3% Incidence Reported by Patients on PULMICORT RESPULES

In symptomatic children not responding to non-steroidal therapy, a starting dose of 0.25 mg once daily of PULMICORT RESPULES may also be considered. If the desired clinical effect is not 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 necessary, higher doses, up to the maximum recommended doses, may provide additional asthma control.

Patients Maintained on Oral Corticosteroids

Initially, PULMICORT RESPULES should be used concurrently with the patient’s usual maintenance dose of systemic corticosteroid. After approximately one week of 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 to two weeks, depending on the response of the patient. Generally, these decrements should not exceed 25% of the prednisone equivalent 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 musculoskeletal pain, lassitude, and depression; despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with PULMICORT 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.

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

The effects of mixing PULMICORT RESPULES with other nebulizable medications have not been adequately assessed. PULMICORT RESPULES ampules should not be returned to the aluminum foil envelope to protect them from light. Any opened RESPULES ampule must be used promptly. Gently shake the RESPULES ampule using a circular motion before use. Keep out of reach of children. Do not store in freezing temperatures. Store in a dry place. Used RESPULES ampules and any unused RESPULES ampules should be returned to the aluminum foil envelope. RESPULES ampules must be destroyed when they are opened.

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PULMICORT RESPULES is supplied in sealed aluminum foil envelopes containing one plastic sterile single-dose RESPULES ampule. Each single-dose RESPULES ampule contains 2 mL of sterile liquid suspension.

Storage

PULMICORT 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 ampules is 2 weeks when protected. After opening the aluminum foil envelope, the used single-dose RESPULES ampules must be returned to the aluminum foil envelope to protect them from light. Any opened RESPULES ampule must be used promptly. Gently shake the RESPULES ampule using a circular motion before use. Keep out of reach of children. Do not freeze.

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