

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-929/S-013

APPROVAL LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-929/S-013

AstraZeneca Pharmaceuticals
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

Attention: Christopher Blango
Director, Regulatory Affairs

Dear Mr. Blango:

Please refer to your supplemental new drug application dated August 30, 2002, received September 3, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pulmicort Respules (budesonide inhalation suspension).

We also acknowledge receipt of your submissions dated November 26, 2002 and January 22, February 12, and 20, 2003.

This supplemental new drug application proposes changes to the CLINICAL PHARMACOLOGY, Pharmacodynamics, and PRECAUTIONS, Pediatric Use sections of the label to include information on children 6 to 12 months of age.

We completed our review of this application, as amended. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the submitted labeling (package insert submitted February 20, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-929/S-013." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Colette Jackson, Project Manager, at (301) 827-5584.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, MD, Ph.D.
Acting Director
Division of Pulmonary and Allergy Drug Products, HFD-570
Office of Drug Evaluation II
Center For Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Badrul Chowdhury
2/26/03 01:44:16 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-929/S-013

APPROVED LABELING

721851-XX

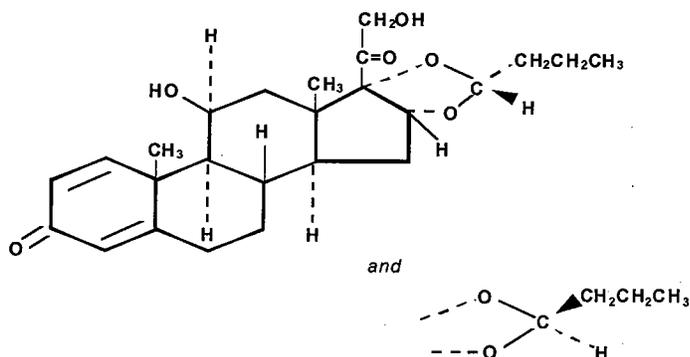
Pulmicort Respules
(budesonide inhalation suspension)
0.25 mg and 0.5 mg

Rx only

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 PULMICORT RESPULES[®], is a corticosteroid designated chemically as (RS)-11 β , 16 α , 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 C₂₅H₃₄O₆ and its molecular weight is 430.5. Its structural formula is:



Budesonide is a white to off-white, tasteless, odorless powder that is practically insoluble in water and in heptane, sparingly soluble in ethanol, and freely soluble in chloroform. Its partition coefficient between octanol and water at pH 7.4 is 1.6×10^3 .

PULMICORT 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 (Respules™): 0.25 mg and 0.5 mg per 2 mL RESPULE. For PULMICORT 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. PULMICORT RESPULES should be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Mechanism of Action

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil 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.

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 Pulmicort Turbuhaler® (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 (85-95%) and the low potency of metabolites (see below).

Pharmacokinetics

The activity of PULMICORT 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 PULMICORT 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 α -hydroxyprednisolone and 6 β -hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns has been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion: 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.

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.

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.

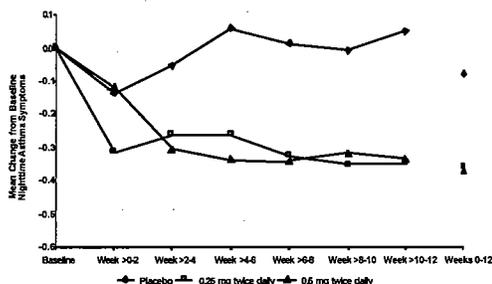
Improvement in the control of asthma symptoms following inhalation of PULMICORT RESPULES can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks.

Budesonide administered via Turbuhaler 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 via Turbuhaler 1600 mcg daily (800 mcg twice daily) for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV₁ following inhaled allergen challenge.

The 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 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 PULMICORT RESPULES treatment at recommended doses. In the subgroup of children age 6 months to 2 years (n=21) receiving a total daily dose of PULMICORT 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. 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 PULMICORT RESPULES or placebo once daily. A total of 28, 17, and 31 patients in the PULMICORT RESPULES 0.5 mg, 1 mg, and placebo arms respectively, had an evaluation of serum cortisol levels post-ACTH stimulation both at baseline and at the end of the study. The mean change from baseline to Week 12 ACTH-stimulated minus basal plasma cortisol levels did not indicate adrenal suppression in patients treated with PULMICORT RESPULES versus placebo. However, 7 patients in this study (4 of whom received PULMICORT RESPULES 0.5 mg, 2 of whom received PULMICORT RESPULES 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 PULMICORT RESPULES, the cortisol values were near the cutoff value of 500 nmol/L.

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



Patients Receiving Once-Daily or Twice-Daily Dosing

The efficacy of PULMICORT RESPULES at doses of 0.25 mg once daily, 0.25 mg twice daily, 0.5 mg twice daily, and 1 mg once daily, was evaluated in 469 pediatric patients 12 months to 8 years of age (mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.13 to 1.31). Approximately 70% were not previously receiving inhaled corticosteroids. The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 3. 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).

The effects of PULMICORT 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 PULMICORT 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 PULMICORT RESPULES, 1 mg total daily dose, did not show statistically significantly reduced urinary cortisol excretion compared to the run-in period.

PULMICORT 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.

CLINICAL TRIALS

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, 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 PULMICORT RESPULES to patients in the 3 U.S. controlled clinical trials. The co-primary endpoints were nighttime and daytime asthma symptom scores (0-3 scale). Each of the five 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. Compared to placebo, PULMICORT RESPULES significantly decreased both nighttime and daytime symptom scores of asthma at doses of 0.25 mg once daily (one study), 0.25 mg twice daily, and 0.5 mg twice daily. PULMICORT RESPULES significantly decreased 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 PULMICORT RESPULES occurred across gender and age. PULMICORT RESPULES significantly reduced the need for bronchodilator therapy at all the doses studied.

Improvements in lung function were associated with PULMICORT RESPULES in the subgroup of patients capable of performing lung function testing. Significant improvements were seen in FEV₁ [PULMICORT RESPULES 0.5 mg once daily and 1 mg once daily (one study); 0.5 mg twice daily] and morning PEF [PULMICORT RESPULES 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 (0-3 scale) of asthma was observed within 2-8 days, although maximum benefit was not achieved for 4-6 weeks after starting treatment. The reduction in nighttime and daytime asthma symptom scores was maintained throughout the 12 weeks of the double-blind trials.

Patients Not Receiving Inhaled Corticosteroid Therapy

The efficacy of PULMICORT RESPULES 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 improved significantly in the patients treated with PULMICORT RESPULES compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

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

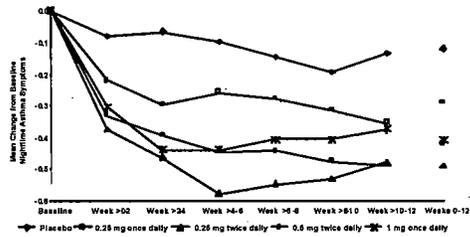


Patients Previously Maintained on Inhaled Corticosteroids

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.

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



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.

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 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 PULMICORT 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 PULMICORT RESPULES may unmask allergic conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, and 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 inserts for complete VZIG and IG 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

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 PULMICORT 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 PULMICORT 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, PULMICORT 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 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 mouth, 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 localized infections of *Candida albicans* were similar between the placebo and PULMICORT 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 PULMICORT RESPULES therapy, but at times therapy with PULMICORT 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 PULMICORT 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 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 or intended effects.

- Patients should take PULMICORT RESPULES at regular intervals once or twice a day as directed, 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 PULMICORT RESPULES with other nebulizable medications have not been adequately assessed. PULMICORT RESPULES should be administered separately in the 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 nebulized medication (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 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 chicken pox or been properly vaccinated, a physician should be consulted without delay.
- PULMICORT RESPULES should be stored upright at controlled room temperature 20-25°C (68-77°F) and protected from light. PULMICORT 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 PULMICORT 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 PULMICORT 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/m² 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/m² basis). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

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/m² 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/m² basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m² 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/m² basis) and 500 mcg/kg in rats (approximately 4 times the maximum recommended daily inhalation dose in adults on a mcg/m² 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/m² 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 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 been established (see CLINICAL PHARMACOLOGY, Pharmacodynamics, CLINICAL TRIALS and ADVERSE REACTIONS).

A 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 PULMICORT RESPULES or placebo once daily. Adrenal axis function was assessed with an ACTH stimulation test at the beginning and end of the study, and mean changes from baseline in this variable did not indicate adrenal suppression in patients who received PULMICORT RESPULES versus placebo. However, on an individual basis, 7 patients in this study (6 in the PULMICORT RESPULES treatment arms and 1 in the placebo arm) experienced a shift from having a normal baseline stimulated cortisol level to having a subnormal level at Week 12 (see CLINICAL PHARMACOLOGY, Pharmacodynamics). Pneumonia was observed more frequently in patients treated with PULMICORT RESPULES than in patients treated with placebo, (N = 2, 1, and 0) in the PULMICORT RESPULES 0.5 mg, 1 mg, and placebo groups, respectively.

A dose dependent effect on growth was also noted in this 12-week trial. Infants in the placebo arm experienced an average growth of 3.7 cm over 12 weeks compared with 3.5 cm and 3.1 cm in the PULMICORT RESPULES 0.5 mg and 1 mg arms respectively. This corresponds to estimated mean (95% CI) reductions in 12-week growth velocity between placebo and PULMICORT RESPULES 0.5 mg of 0.2 cm (-0.6 to 1.0) and between placebo and PULMICORT RESPULES 1 mg of 0.6 cm (-0.2 to 1.4). These findings support that the use of PULMICORT RESPULES in infants 6 to 12 months of age may result in systemic effects and are consistent with findings of growth suppression in other studies with inhaled corticosteroids.

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 PULMICORT 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 PULMICORT RESPULES, each patient should be titrated to his/her lowest effective dose.

Geriatric Use

Of the 215 patients in 3 clinical trials of PULMICORT 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 PULMICORT 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 \geq 12 months and $<$ 2 years of age; 225 patients \geq 2 and $<$ 4 years of age; and 622 patients \geq 4 and \leq 8 years of age) were treated with PULMICORT RESPULES (0.25 to 1 mg total daily dose for 12 weeks) or vehicle placebo. The incidence and nature of adverse events reported for PULMICORT 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 \geq 3% Incidence Reported by Patients on PULMICORT RESPULES

| Adverse Events | Vehicle Placebo (n=227) % | PULMICORT RESPULES Total Daily Dose | | |
|---|------------------------------------|--|------------------------|----------------------|
| | | 0.25 mg (n=178) % | 0.5 mg (n=223) % | 1 mg (n=317) % |
| Respiratory System Disorder | | | | |
| Respiratory Infection | 36 | 34 | 35 | 38 |
| Rhinitis | 9 | 7 | 11 | 12 |
| Coughing | 5 | 5 | 9 | 8 |
| Resistance Mechanism Disorders | | | | |
| Otitis Media | 11 | 12 | 11 | 9 |
| Viral Infection | 3 | 4 | 5 | 3 |
| Moniliasis | 2 | 4 | 3 | 4 |
| Gastrointestinal System Disorders | | | | |
| Gastroenteritis | 4 | 5 | 5 | 5 |
| Vomiting | 3 | 2 | 4 | 4 |
| Diarrhea | 2 | 4 | 4 | 2 |
| Abdominal Pain | 2 | 3 | 2 | 3 |
| Hearing and Vestibular Disorders | | | | |
| Ear Infection | 4 | 2 | 4 | 5 |
| Platelet, Bleeding, and Clotting Disorders | | | | |
| Epistaxis | 1 | 2 | 4 | 3 |
| Vision Disorders | | | | |
| Conjunctivitis | 2 | <1 | 4 | 2 |
| Skin and Appendages Disorders | | | | |
| 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 PULMICORT RESPULES than with placebo.

The following adverse events occurred with an incidence of 3% or more in at least one PULMICORT 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 ≤3% (by body system)

The information below includes all adverse events with an incidence of 1 to ≤3%, in at least one PULMICORT RESPULES treatment group where the incidence was higher with PULMICORT 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
Musculoskeletal system: fracture, myalgia
Application site: contact dermatitis
Platelet, bleeding & clotting: purpura
White cell and resistance: cervical lymphadenopathy

The incidence of reported adverse events was similar between the 447 PULMICORT RESPULES-treated (mean total daily dose 0.5 to 1 mg) and 223 conventional therapy-treated pediatric asthma patients followed for one year in three open-label studies.

Cases of growth suppression have been reported for inhaled corticosteroids including post-marketing reports for PULMICORT 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 effects following overdose of PULMICORT 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/m² 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/m² 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/m² 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/m² basis).

DOSAGE AND ADMINISTRATION

PULMICORT RESPULES is indicated for use in asthmatic patients 12 months to 8 years of age. PULMICORT 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 PULMICORT 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 PULMICORT 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 PULMICORT RESPULES, based on prior asthma therapy, are listed in the following table.

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

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 once-daily treatment with PULMICORT 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 PULMICORT 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, PULMICORT 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 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 should be administered separately in the nebulizer (see PRECAUTIONS, Information for Patients).

Directions for Use

Illustrated *Patient's Instructions for Use* accompany each package of PULMICORT RESPULES.

HOW SUPPLIED

PULMICORT RESPULES is supplied in sealed aluminum foil envelopes containing one plastic strip of five single-dose RESPULES together with patient instructions for use. There are 30 RESPULES in a carton. Each single-dose RESPULE contains 2 mL of sterile liquid suspension.

PULMICORT RESPULES is available in two strengths, each containing 2 mL:

| | |
|------------------|--------------|
| NDC 0186-1988-04 | 0.25 mg/2 mL |
| NDC 0186-1989-04 | 0.5 mg/2 mL |

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 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.

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Rev. XX/XX

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

| | | | |
|--------------------|--------------------------------|-------------|----------------------------------|
| APPLICATION: | NDA #20-929 | TRADE NAME: | Pulmicort Respules |
| APPLICANT/SPONSOR: | AstraZeneca | USAN NAME: | Budesonide Inhalation suspension |
| MEDICAL OFFICER: | Curtis J Rosebraugh MD, MPH | | |
| TEAM LEADER: | Lydia Gilbert-McClain, MD | CATEGORY: | Corticosteroid |
| DUE DATE: | | ROUTE: | Inhaled |

SUBMISSIONS REVIEWED IN THIS DOCUMENT

| <u>Document Date</u> | <u>CDER Stamp Date</u> | <u>Submission</u> | <u>Comments</u> |
|----------------------|------------------------|-------------------|--|
| 30 Aug 2002 | 03 Sept 2002 | sNDA | |
| 14 Dec 1998 | | | Written Request for Pediatric Studies in infants between the ages of 6 and 12 months |

RELATED APPLICATIONS

| <u>Document Date</u> | <u>Application Type</u> | <u>Comments</u> |
|----------------------|-------------------------|--------------------------------------|
| 8 Aug 2000 | NDA 20-929 | Approval date for Pulmicort Respules |

REVIEW SUMMARY: The primary objective of this study was to evaluate the safety of once-daily administration of Pulmicort Respules (0.5 and 1.0 mg) compared with placebo for the treatment of mild to moderate asthma or recurrent or persistent wheezing in infants between the ages of 6 and 12 months. The primary safety variable was assessment of adrenal function as assessed by the mean change from baseline at Week 12 in basal and 1-hour post adrenocorticotrophic hormone (ACTH) stimulated cortisol levels or changes in urinary cortisol excretion. Secondary objectives included evaluating body length changes and evaluating the efficacy of Pulmicort Respules and placebo by comparing nighttime and daytime asthma symptom scores, use of breakthrough medication, number of treatment failures, and subject discontinuations, and physician's global assessment of each subject's asthma status.

The results of this study do not indicate a population mean suppressive effect on adrenal function in subjects aged 6 to 12 months with once-daily dosages of 0.5 or 1.0 mg BIS, although there may be individual subjects with increased sensitivity and possible adrenal suppression. The safety profile of BIS was comparable to that already existing in labeling except for higher percentages of Tooth disorder, Nervousness, Pneumonia, and Urticaria in the BIS group compared to placebo. A dose-dependent decrease in growth velocity was seen in the BIS groups compared to placebo which suggests that at these doses the drug may have systemic effects.

This submission fulfills the requirements of the Written Request and this application is approvable with need for label revisions to gain full approval.

OUTSTANDING ISSUES: See Above

RECOMMENDED REGULATORY ACTION

| | | |
|------------------|--|--|
| IND/NEW STUDIES: | <input type="checkbox"/> SAFE TO PROCEED | <input type="checkbox"/> CLINICAL HOLD |
| NDA/SUPPLEMENTS: | <input type="checkbox"/> FILEABLE | <input type="checkbox"/> NOT FILEABLE |
| | <input type="checkbox"/> APPROVAL | <input checked="" type="checkbox"/> APPROVABLE |
| OTHER ACTION: | | <input type="checkbox"/> NOT APPROVABLE |

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NDA #20-929, Pulmicort Respules

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1. ABBREVIATIONS

BIS- Budesonide Inhalation Suspension (generic name for Pulmicort Respules)

ITT-Intent to Treat

ACTH-adrenocorticotrophic hormone

LOCF- last observed value carried forward

ANCOVA-analysis of covariance

sNDA-Supplemental New Drug Application

List of Tables

CLINICAL REVIEW OF SNDA #20-929**EXECUTIVE SUMMARY****1. RECOMMENDATIONS****1.1. Recommendation on Approvability**

This supplemental NDA has been submitted in accordance with the December 14, 1998 Written Request as a supplement to the already approved drug product Pulmicort Respules®. The sponsor is not seeking changes in the INDICATIONS section of the labeling. Rather, the sponsor is requesting changes to the CLINICAL PHARMACOLOGY, Pharmacodynamics, and PRECAUTIONS, Pediatric Use label sections. The study report submitted in this application completes the requirements of the Written Request and this application is approvable based on appropriate revision of the proposed labeling changes.

1.2. Recommendation on Phase 4 Studies and/or Risk Management Steps

Not Applicable

2. SUMMARY OF CLINICAL FINDINGS**2.1. Background and Administrative Issues**

Pulmicort Respules for nebulization was approved August 8, 2000 for use in asthmatic patients 12 months to 8 years of age. As part of a Written Request issued December 14, 1999, the sponsor has submitted this sNDA reporting additional safety information on the use of Pulmicort Respules in subjects 6 months to 12 months in age.

2.2. Brief Overview of Clinical Program

The primary objective of this study was to evaluate the safety of once-daily administration of Pulmicort Respules (0.5 and 1.0 mg) compared with placebo for the treatment of mild to moderate asthma or recurrent or persistent wheezing in infants between the ages of 6 and 12 months. The primary safety variable was assessment of adrenal function as assessed by the mean change from baseline at Week 12 in basal and 1-hour post adrenocorticotrophic hormone (ACTH) stimulated cortisol levels or changes in urinary cortisol excretion. Secondary objectives included evaluation of body length changes and evaluating the efficacy of Pulmicort Respules and placebo by comparing nighttime and daytime asthma symptom scores, use of breakthrough medication, number of treatment failures, and subject discontinuations, and physician's global assessment of each subject's asthma status.

2.3. Efficacy

Efficacy was a secondary objective of this study and was assessed by comparing differences between treatment groups in the following variables: nighttime asthma symptom scores,

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daytime asthma symptom scores, use of breakthrough medication, percentage of symptom-free days, number of treatment failures, number of subject discontinuations, and investigator's global assessment of each subject's asthma status at the end of the study.

In general the Budesonide Inhalation Suspension (BIS) treatment groups demonstrated greater improvement trends of mean values (not statistically significant) in subjective parameters (AM & PM symptom scores, Symptom-free days, investigator global assessment), but not in the objective parameters (Withdrawals, breakthrough medication use) with the exception of treatment failures which occurred less frequently in the active treatment groups 15 % and 18% for BIS 0.5 mg and BIS 1.0 mg respectively) compared to placebo (22%). Definitive efficacy conclusions can not be made from these results. Approximately twice the percentage of subjects randomized to the BIS 0.5 mg treatment group (29%) had prior corticosteroid use compared to the BIS 1.0 mg and placebo groups (16% and 14% respectively) suggesting that subjects in the BIS 0.5 mg group were sicker and more likely to have treatment failures. The results of the asthma symptom score also suggest a more favorable response in the BIS 0.5 mg group compared with the BIS 1.0 mg group.

2.4. Safety

The primary safety variable was adrenal function as determined by plasma cortisol levels (pre- and 1-hour post- ACTH) and overnight urinary free cortisol levels at Visits 2 (randomization) and 6 (Week 12). Subnormal adrenal function by plasma cortisol levels was defined as a post-ACTH plasma cortisol value less than 500 nmol/L at either Visit 2 or Visit 6. Urinary cortisol excretion was measured as the ~~_____~~ cortisol levels from overnight timed urine samples. Subjects who did not undergo the cosyntropin stimulation test were to provide timed urine samples. Other secondary safety variables included the incidence and severity of adverse events, changes from baseline in hematology and chemistry laboratory, body length/height and body weight and oropharyngeal and nasal fungal cultures.

Body length was measured ~~_____~~

The mean values of the three different groups did not indicate any difference in adrenal responsiveness of the populations to the ACTH stimulation test. Using a combination of the serum and urine analysis groups, there were seven subjects that had subnormal responses to adrenal stimulation with six in the BIS group and one in the placebo group. In the serum analysis group, there were 5 individuals (maybe 6 depending on labeling errors), all exposed to BIS, that did not have an adequate response (as pre-defined as a post-ACTH infusion level >500 nmol/L) to cosyntropin. This may indicate that, while populations may expect no adrenal suppression, there are individuals within those populations that may have increased sensitivity to exogenous corticosteroid than the group mean and this sensitivity must be kept in mind by practicing physicians when approaching therapy for the individual patient. It is

Executive Summary

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NDA #20-929, Pulmicort Respules

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also important to note that the BIS 1.0 mg group only contained data from 17 subjects of the 29 originally randomized (compared to 28 for the BIS 0.5mg and 31 for the placebo groups) which could introduce a considerable bias if the excluded subjects did not reflect the group mean.

A total of 6 subjects (5 in the BIS 0.5 mg group and 1 in the placebo group) had urinary cortisol testing at Visits 2 and 6. The data from this aspect of adrenal evaluation has a great deal of variability and questionable validity of the single placebo comparator and as such should not be used to make any HPA function conclusions for labeling purposes.

Overall Mean body length increases were 3.1, 3.5 and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. There appears to be dose ordering growth suppression. In order to see if there was a possible drop-out bias, the biostatistics reviewer, Dr. Jim Gebert investigated growth for an "evaluable group" consisting of subjects that had all data points and completed the study. This group demonstrated the same trend with mean body length increases of 3.3 cm, 3.5 cm and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. While this is not statistically significant ($p=0.2861$ BIS 1.0 mg vs. placebo) this study was not powered with any pre-specified criteria and this trend does seem to indicate that increasing the dose will decrease growth velocity. This should not be surprising, as this is an expected effect of corticosteroids. This finding should be reflected in the label, not as a criticism of the drug, but as a reminder to practitioners that they should always use the lowest effective dose and not be lulled into an erroneous sense of security that because they are giving a corticosteroid by inhalation there will not be systemic effects. There was no relationship between mean body length and abnormal responses to ACTH stimulation.

Three subjects (2 in the BIS 1.0 mg for asthma and pneumonia and 1 in the BIS 0.5 mg group for rash) had treatment discontinued prematurely as the result of an adverse event. Adverse events of Tooth disorder, Pharyngitis, Nervousness, Pneumonia and Urticaria were reported more frequently in the active treatment arms compared to placebo and except for pharyngitis are not presently in the Label for PULMICORT Respules.

2.5. Dosing

The Pulmicort Respules product is currently approved at dosages of 0.5 mg – 1 mg total daily dose in patients 12 months to 8 years of age. The sponsors studied Pulmicort Respules 0.5 mg and 1 mg once a day in this study.

2.6. Special Populations

This study was performed in infants 6 months to 12 months in age. Overall, most subjects were Caucasian (70%) and male (62%).

CLINICAL REVIEW

1. INTRODUCTION AND BACKGROUND

1.1. Established and Proposed Trade Name of Drug, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established Trade Name: Pulmicort Respules™

Drug Class: Corticosteroid

Indication: Pulmicort Respules is already approved for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age. The sponsor is not seeking additions to the INDICATIONS section of the label.

Dose/regimens/Age Groups: The dosages used in this study of infants 6 to months of age were 0.5 mg and 1.0 mg once a day.

1.2. State of Armamentarium for Indication(s)

Budesonide Inhalation Solution (Pulmicort Respules®) is the only inhaled corticosteroid formulated for nebulization in the U.S. It is the only corticosteroid approved for asthma in patients down to 1 year of age.

1.3. Important Milestones in Product Development

14 Dec 1998: Written Request

8 Aug 2000: Approval of NDA 20-929 for Pulmicort Respules

03 Sept 2002: CDER stamp date for sNDA

1.4. Other Relevant Information

Not Applicable

1.5. Important Issues with Pharmacologically Related Agents

Not Applicable

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2. CLINICALLY RELEVANT FINDINGS FROM OTHER REVIEWS

2.1. Chemistry, Manufacturing and Controls

Cross-referenced to review of NDA 20-929 dated 8 Aug 2000.

2.2. Animal Pharmacology and Toxicology

Cross-referenced to review of NDA 20-929 dated 8 Aug 2000.

2.3. Microbiology

Cross-referenced to review of NDA 20-929 dated 8 Aug 2000.

2.4. Statistics

Not Applicable

3. HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

3.1. Pharmacokinetics

Cross-referenced to review NDA 20-929 dated 8 Aug 2000.

3.2. Pharmacodynamics

Cross-referenced to review of NDA 20-929 dated 8 Aug 2000.

4. DESCRIPTION OF CLINICAL DATA AND SOURCES

4.1. Sources of Clinical Data

Sources of data were this sNDA submission dated August 30, 2002 with a CDER stamp date of September 03, 2002.

4.2. Overview of Clinical Trials

There was one clinical trial submitted in this package titled: Study #SD-004-0732: "A Safety and Efficacy Study of Two Dosage Levels of Pulmicort® Respules™ (budesonide inhalation suspension, 0.5 or 1.0 mg/day) versus Placebo in Infants Between the Ages of Six and Twelve Months with Mild to Moderate Asthma". This was a 12-week, multicenter, randomized, double-blind, placebo-controlled study of 2 doses of Pulmicort Respules (Budesonide Inhalation Suspension referred to further as BIS 0.5 mg and 1.0 mg) and placebo. It was planned that 144 subjects would be randomized throughout approximately 50 clinical sites to obtain 90 subjects completing the study.

4.3. Postmarketing Experience

There have been no adverse marketing experiences with this product.

4.4. Literature Review

The following literature was reviewed during the course of this application:

Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *NEJM*. 2000; 343(15):1064-1069.

Wohl MEB, Majzoub JA. Asthma, steroids, and growth. *NEJM* 2000; 343(15): 1113

Simons FER. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *NEJM*. 1997; 337(23):1659-1665

The Childhood Asthma Management Program Research Group. *NEJM*. 2000; 343(15):1054-1063

Purucker M, Malozowski S. Letter to Editor. *NEJM*. 2001; 344(8):607

Ilowite J. Letter to Editor. *NEJM*. 2001; 344(8):607

Skoner DP. Growth effects of asthma and asthma therapy. *Curr Opin Pulm Med*. 2002; 8(1):45-9

Brand PL. Inhaled corticosteroids reduce growth. Or do they? *Eur Respir J*. 2001; 17(2):287-94

Carson SH, Taeusch HW Jr, Avery ME. Inhibition of lung cell division after hydrocortisone injection into fetal rabbits. *J Appl Physiol* 1973; 34:660-663

Massaro GD, Massaro D. Formation of alveoli in rats: postnatal effect of prenatal dexamethasone. *Am Physiol* 1992; 263:L37-L41

Muglia LJ, Bae DS, Brown TT, et al. Proliferation and differentiation defects during lung development in corticotrophin-releasing hormone-deficient mice. *Am J Respir Cell Mol Biol* 1999; 20:181-188

5. CLINICAL REVIEW METHODS

5.1. Conduct of the Review

Assessment of this NDA was initiated with a review of the sponsor's overall clinical program for this drug. Minutes of meetings and teleconferences with the sponsor were reviewed, as well as notes from previous reviewers. Financial disclosure statements were reviewed. A literature review on inhaled corticosteroids and growth in children was performed. Input was obtained from other disciplines, especially statistics and biopharmaceutics. Medical officer comments are written in *Italics*. References to pages in the application are in square brackets [].

5.2. Materials Consulted and Documentation

Not applicable

5.3. Data Quality and Integrity

The quality and integrity of the data was intact.

5.4. Ethical Standards

Ethical standards were maintained throughout the study and were reviewed and agreed upon prior to study initiation by all local IRB reviewing bodies at each participating site.

5.5. Financial Disclosure

As required by 21 CFR part 54, the sponsor submitted financial disclosure information for all investigators participating in the study. Three investigators responded positively to having a financial interest. ~~_____~~ / responded to having Significant Equity Interests in AstraZeneca LP. ~~_____~~ / was listed as the primary investigator at center ~~_____~~ and enrolled ~~_____~~ patients in the study. ~~_____~~ / the primary investigator at Center ~~_____~~ / also responded positively to having Significant Equity interests. ~~_____~~ enrolled ~~_____~~ patient into the trial. ~~_____~~ / also at Center ~~_____~~ / enrolled ~~_____~~ patients in the study and responded positively to receiving significant payments from AstraZeneca LP. In total therefore, 12 (8%) of the 141 randomized subjects were enrolled at centers with investigators with financial interests in AstraZeneca. This number should not have a significant impact on the interpretation of the safety results.

6. INTEGRATED REVIEW OF EFFICACY

6.1. Brief Statement of Conclusions

Efficacy evaluation was not a primary outcome in this study and no efficacy conclusions will be reflected in the label. Efficacy was evaluated by examination of asthma symptom scores (AM and PM), physician's global assessments, withdrawal/treatment failure, use of breakthrough medication, percentage of symptom-free days, and investigator's global assessment of each subject's asthma status at the end of the study. In general the BIS treatment groups demonstrated greater improvement trends of mean values in AM and PM symptom scores, symptom-free days, and investigator global assessment. For the "Harder" (objective) endpoints in the study -withdrawal rates, treatment failure and use of breakthrough medication, only treatment failures showed a favorable response in the active treatment groups compared to placebo. The sponsor asserts that assessing efficacy in this population is difficult, since there are no standard methods for measurement of lung function and only few objective parameters. In general the BIS treatment groups demonstrated mean trends of greater improvement in the subjective parameters listed above, but not in the objective parameters (except for treatment failures) and not to the extent that any definitive conclusions can be made.

Reviewer Comment: This reviewer is struck by the somewhat "Harder" endpoints of withdrawal rates and breakthrough medication use being essentially equivalent. This would indicate that the placebo group had an equivalent outcome to the active treatment group. This conclusion must be somewhat tempered by the fact that some subjects in the placebo group received additional/breakthrough inhaled corticosteroids other than BIS. Having said that however, it does give caution to clinicians to carefully assess whether infant patients do need inhaled steroids or not for wheezing that may or may not be asthma. There are animal studies that give cause for concern about the use of inhaled steroids in infants. In babies, the number of branching structures of airways and conducting vessels are complete in early gestation, while alveoli increase by a factor of six after birth, mostly in the first two years (Wohl and Majzoub)¹. In glucocorticoid-deficient mice, the administration of corticosteroids during a period of alveolar development results in decrease lung-cell mass and the presence of too few abnormally large alveoli (Muglia, Bae, Brown)², (Carson, Taesch and Avery)³, (Massaro and Massaro)⁴. Therefore, the long-term consequence of steroid use in this age population on subsequent lung/organ development is unknown and was not part of this study's design. Clinicians should therefore be judicious in their use of steroid inhalation

¹ Wohl MEB, Majzoub JA. Asthma, steroids, and growth. NEJM 2000; 343 (15): 1113

² Muglia LJ, Base DS, Brown TT, et.al. Proliferation and differentiation defects during lung development in corticotrophin-releasing hormone-deficient mice. Am J Respir Cell Mol Biol 1999; 20: 181-188

³ Carson SH, Taesch HW Jr, Avery ME. Inhibition of lung cell division after hydrocortisone injection into fetal rabbits. J Appl physiol 1973; 34:660-663

⁴ Massaro GD, Massaro D. Formation of alveoli in rats: prenatal effect of prenatal dexamethasone. Am Physiol 1992; 263: L37 - L41

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therapy especially when there are studies like the present one that do not demonstrate better outcome measures than placebo by "Harder" objective endpoints.

6.2. General Approach to the Efficacy Review

This application includes one study for efficacy review and therefore only the results of this study were reviewed. The efficacy endpoints in this study are supportive only for the listed age categories.

6.3. Summary of Trials by Indication

Not Applicable

6.3.1. Studies for Indication #1

Not Applicable

6.3.2. Studies for Indication #2

Not Applicable

6.4. Efficacy Discussion and Conclusions

AM and PM Symptom Scores: The BIS 0.5 mg group had a greater mean improvement than placebo for AM and PM symptom scores whereas the BIS 1.0 mg group was indistinguishable from placebo. Both active treatment groups experienced a greater mean number of symptom free days compared to placebo (BIS 0.5=11.3 mean days, BIS 1.0=5.8 mean days) but did not achieve statistical significance.

Physician Global Assessments: Physician global assessments rated asthma symptomatology as a "Great Deal Better" or "Somewhat Better" for 90% and 85% of subjects in the BIS 0.5 mg and BIS 1.0 mg groups, respectively, compared with 67% of placebo-treated subjects.

Withdrawals: There were no significant differences in withdrawal rates of the ITT population between groups during the double-blind period with 7 (14.6%), 8 (18.2%) and 7 (14.3%) of subjects withdrawing from the BIS 0.5 mg, BIS 1.0 mg and Placebo groups respectively.

Treatment Failure: Treatment failure was defined as the use of an additional asthma/breakthrough maintenance therapy for uncontrolled asthma symptoms or the use of prednisone for an asthma exacerbation. Treatment failure occurred in 7 (14.6%), 8 (18.2%) and 11 (22.4%) subjects in the BIS 0.5 mg, BIS 1.0 mg and placebo groups respectively. It is interesting to note that under the summary of prior medication use [Vol. 001/Pg 224], total glucocorticoid use was 29.2%, 15.9% and 14.3% for the BIS 0.5 mg, BIS 1.0mg and placebo groups respectively indicating that almost twice as many subjects with prior corticosteroid use were randomized into the BIS 0.5 mg group.

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Reviewer Comment: *This may indicate that the subjects in the BIS 0.5 mg group were sicker on average.*

Breakthrough Medication Use: The percentage of total days on study treatment without use of breakthrough medication was not statistically significant for either of the BIS dosage groups compared with placebo (72.8, 76.6 and 72.3 days for placebo, 0.5 mg, and 1.0 mg groups respectively).

7. INTEGRATED REVIEW OF SAFETY

7.1. Brief Statement of Findings

The primary purpose of this study was to evaluate the effects of BIS 0.5 mg and 1.0 mg on adrenal function in a 6 to 12 month of age population with wheezing. Adrenal function was assessed before and at the end of the 12-week treatment period by measuring changes in plasma cortisol levels in response to the 1-hour cosyntropin (ACTH) stimulation test or by changes in urinary free cortisol excretion obtained from overnight timed urine samples. The mean values of the three different groups did not indicate any difference in adrenal responsiveness of the populations to the ACTH stimulation test. However, there were seven subjects that had subnormal responses to adrenal stimulation with six in the BIS group and one in the placebo group (the one subject in the placebo group is probably a labeling error). There were 5 individuals (maybe 6 depending on labeling errors), all exposed to BIS, that did not have an adequate response (as pre-defined as a post-ACTH infusion level >500 nmol/L) to cosyntropin. This may indicate that, while populations may expect no adrenal suppression, there are individuals within those populations that may have increased sensitive to exogenous corticosteroid than the group mean and this sensitivity must be kept in mind by practicing physicians when approaching therapy for the individual patient. It is also important to note that the BIS 1.0 mg group only contained 17 subjects (compared to 28 for the BIS 0.5mg and 31 for the placebo groups) which could introduce a considerable bias if the excluded subjects did not reflect the group mean.

A total of 6 subjects (5 in the BIS 0.5 mg group and 1 in the placebo group) had urinary cortisol testing at Visits 2 and 6. The data from this aspect of adrenal evaluation has a great deal of variability and questionable validity of the single placebo comparator and as such should not be used to make any HPA function conclusions for labeling purposes. Regarding adverse events, three subjects (2 in the BIS 1.0 mg for asthma and pneumonia and 1 in the BIS 0.5 mg group for rash) had treatment discontinued prematurely as the result of an adverse event. Adverse events of Tooth disorder, Pharyngitis, Nervousness, Pneumonia and Urticaria occurred in higher percentages in the active treatment arms compared to placebo and are not presently contained in the Label for the Respules.

While there did not seem to group mean differences in adrenal suppression, the same cannot be said of Body Length changes. Overall Mean body length increases were 3.1, 3.5 and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. There appears to be dose ordering growth suppression. In order to see if there was a possible drop-out bias, Dr. Gebert investigated growth for an "evaluable group" consisting of subjects that had all data points and completed the study. This group demonstrated the same trend with mean changes of 3.3 cm, 3.5 cm and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. While this is not statistically significant ($p=0.2861$ BIS 1.0 mg vs. placebo) this study was not powered with any pre-specified criteria and this trend does seem to indicate that increasing the dose will decrease growth velocity. This should not be surprising, as this is an expected effect of corticosteroids. This effect should be placed in the label, not as a criticism of the drug, but as a reminder to practitioners that they should always use the lowest effective dose and not be

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lulled into an erroneous false sense of security that because they are giving a corticosteroid by inhalation there will not be systemic consequences.

7.2. Methods and Content (Materials Utilized in Review)

A literature review on growth velocity in pediatric subjects receiving inhaled corticosteroids was performed. Safety information from the study was reviewed

7.3. Description of Patient Exposure

A total of 101 subjects had basal and ACTH-stimulated plasma cortisol values at baseline (33, 29, and 39 in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups respectively).

7.4. Safety Findings from Clinical Studies

7.4.1.1. Safety Outcomes

7.4.1.1.1. ACTH-stimulated plasma cortisol

A total of 101 subjects had basal and ACTH-stimulated plasma cortisol values at baseline (33, 29, and 39 in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups respectively). The mean basal and ACTH-stimulated plasma cortisol values at baseline averaged 244.7 nmol/L and 631.4 nmol/L across all treatment groups, respectively. The mean change from baseline to Visit 6 in ACTH-stimulated minus basal plasma cortisol levels did not indicate apparent suppression as monitored by mean values. [vol. 001/Pg. 093]

Reviewer Comment: Note that data from only 17 subjects (compared to 29 at baseline) was collected at the final visit.

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Study SD-004-0732: Summary of change from Baseline in Mean Plasma Cortisol Values (nmol/L) at Week 12 (Evaluable Population^a)

| Parameter | Treatment Group | N | Baseline Mean | Visit 6 Mean (SE) | Change from Baseline Mean (SE) | Change from Baseline Adjusted Mean (SE) ^b | Adjusted Mean Difference from Placebo (SE) ^b | 95% CI | ANCOVA P-Value | Wilcoxon P-Value |
|--|-----------------|----|---------------|-------------------|--------------------------------|--|---|--------------|----------------|------------------|
| Plasma Cortisol (Pre-Stimulation) | Placebo | 31 | 268 | 234 (24.5) | -33.3 (26.4) | -17.8 (22.0) | | | | |
| | BIS 0.5 mg | 28 | 233 | 231 (25.8) | -2.3 (20.8) | -6.3 (23.0) | 11.6 (31.8) | -51.9, 75.0 | 0.718 | 0.671 |
| | BIS 1.0 mg | 17 | 202 | 244 (32.1) | 42.2 (44.8) | 20.4 (29.7) | 38.3 (37.2) | -36.0, 112.5 | 0.307 | 0.168 |
| Plasma Cortisol (Post-Stimulation) | Placebo | 31 | 647 | 650 (31.6) | 2.8 (32.0) | 5.6 (30.4) | | | | |
| | BIS 0.5 mg | 28 | 646 | 674 (40.0) | 27.9 (41.0) | 30.0 (31.9) | 24.4 (44.1) | -63.5, 112.2 | 0.582 | 0.891 |
| | BIS 1.0 mg | 17 | 627 | 661 (33.4) | 33.5 (46.7) | 24.8 (41.0) | 19.2 (51.1) | -82.6, 121.0 | 0.708 | 0.940 |
| Plasma cortisol (Post-Minus Pre-Stimulation) | Placebo | 31 | 379 | 415 (38.4) | 36.1 (48.9) | 19.8 (36.1) | | | | |
| | BIS 0.5 mg | 28 | 412 | 443 (43.7) | 30.2 (44.3) | 37.9 (38.0) | 18.0 (52.5) | -86.6, 122.7 | 0.732 | 0.832 |
| | BIS 1.0 mg | 17 | 426 | 417 (37.0) | -8.7 (62.6) | 8.4 (48.8) | -11.4 (60.8) | -133, 109.8 | 0.852 | 0.140 |

^a included subjects with a baseline plasma cortisol value ≥ 500 nmol/L and who did not receive a steroid within the 4 weeks prior to final cortisol testing

^b Mean adjusted for baseline

Reviewer Comment: Noted that the BIS 1.0 mg group only contained 17 subjects which could introduce a considerable bias if the excluded subjects did not reflect the mean report.

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Few subjects had shifts from a baseline post-ACTH-stimulation plasma cortisol value ≥ 500 nmol/L to a Week 12 post-ACTH plasma cortisol value of < 500 nmol/L (4 (14%), 2 (12%), and 1 (3%) in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups respectively. For 5 of the 7 subjects with a subnormal ACTH-stimulated plasma cortisol value at Week 12 the end-of-treatment post-ACTH-stimulated plasma cortisol value was below the cut-off value of 500 nmol/L (18 $\mu\text{g/dL}$)(values of / — / all exposed to BIS 0.5mg and / — / both exposed to BIS 1.0mg). For the remaining 2 subjects (BIS 0.5 and Placebo) the post-stimulation value was very low, 155nmol/L and 109 nmol/L (pre-stimulation values were / — / and / — /). The sponsor speculates that these low values may be due to sampling or labeling errors.

Reviewer Comment: While the mean values of the three different groups did not indicate any difference in adrenal responsiveness of the populations, there were 5 individuals (maybe 6 depending on labeling errors), all exposed to BIS, that did not have an adequate response to cosyntropin. This may indicate that, while the general patient population may not have adrenal suppression, there are individuals that may have increased sensitivity to exogenous corticosteroid suppression and this must be kept in mind by practicing physicians when treating individual patients.

7.4.1.1.2. Urinary Cortisol

A total of 6 subjects (5 in the BIS 0.5 mg group and 1 in the placebo group) had urinary cortisol testing at Visits 2 and 6. The mean change from baseline at Week 12 was 52.2 ug/g among subjects in the BIS 0.5 mg group compared to a -44.8 mean change for the placebo subject. See table below. [Vol. 001/Pg. 102]

| Study SD-004-0732: Urinary Cortisol Data (Evaluable Population) | | | | |
|---|---------|-----------|-------------------------------|---------|
| Treatment Group | Sex/Age | Race | Urinary Cortisol Value (ug/g) | |
| | | | Visit 2 | Visit 6 |
| BIS 0.5 mg | F/6 | Caucasian | 13.7 | 10.0 |
| BIS 0.5 mg | M/11 | Caucasian | 21.0 | 34.8 |
| BIS 0.5 mg | M/9 | Black | 5.9 | 181.6 |
| BIS 0.5 mg | F/7 | Caucasian | 12.9 | 8.1 |
| BIS 0.5 mg | M/8 | Caucasian | 28.1 | 108.0 |
| Placebo | F/6 | Black | 62.6 | 17.8 |

Review Comment: The data from this aspect of adrenal evaluation has a great deal of variability as demonstrated by the subject on Placebo who had a minus mean change which would fulfill the criteria for abnormal response. Since there is not a placebo control group and because of the wide range of variability (perhaps reflecting the difficulty in collecting proper urine samples in this age group) this data should not be used to make any HPA function conclusions for labeling purposes.

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Frequency of Adverse Events with discrepancies between active arms and placebo are listed in the table below. [vol. 001/pgs 112-114]

| Study SD-004-0732: Frequency of Adverse Events with discrepancy reporting of BIS compared to placebo | | | |
|--|----------------------|----------------------|-------------------|
| | BIS 0.5 mg (N=48) | BIS 1.0 mg (N=44) | Placebo (N=49) |
| Otitis Media | 23 (47.9%) | 12 (27.3%) | 20 (40.8%) |
| Fever | 12 (25.0%) | 10 (22.7%) | 17 (34.7%) |
| Asthma Aggravated | 4 (8.3%) | 4 (9.1%) | 8 (16.3%) |
| Tooth Disorder | 6 (12.5%) | 7 (15.9%) | 2 (4.1%) |
| Coughing | 4 (8.3%) | 2 (4.5%) | 6 (12.2%) |
| Conjunctivitis | 7 (14.6%) | 0 (0.0%) | 4 (8.2%) |
| Pharyngitis | 7 (14.6%) | 0 (0.0%) | 2 (4.1%) |
| Rhonchi | 1 (2.1%) | 1 (2.3%) | 6 (12.2%) |
| Dermatitis Fungal | 2 (4.2%) | 2 (4.5%) | 4 (8.2%) |
| Nervousness | 3 (6.3%) | 1 (2.3%) | 0 (0.0%) |
| Pneumonia | 2 (4.2%) | 1 (2.3%) | 0 (0.0%) |
| Urticaria | 1 (2.1%) | 1 (2.3%) | 0 (0.0%) |
| Lymphadenopathy | 0 (0.0%) | 0 (0.0%) | 2 (4.1%) |
| Dysphonia | 1 (2.1%) | 0 (0.0%) | 0 (0.0%) |

Three subjects (2 in the BIS 1.0 mg for asthma and pneumonia and 1 in the BIS 0.5 mg group for rash) had treatment discontinued prematurely as the result of an adverse event.

Reviewer Comment: Tooth disorder, Pharyngitis, Nervousness, Pneumonia and Urticaria are not presently in the Label ✓

! Noted is the lower frequency of Asthma aggravation, rhonchi, dermatitis fungal and lymphadenopathy in the active treatment group compared to placebo..

7.4.1.1.3. Body Length

The protocol for body length measurement is in Vol. 003/pg 065. ✓

[Large section of text is redacted with multiple horizontal lines.]

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Mean body length increased across visits in all 3 treatment groups, although mean body length in the BIS 1.0 mg group increased less from Week 8 to Week 12 compared with the other treatment groups. The mean changes in body length for the ITT group are in the table below. [vol.001/pg 216][Vol.002/pg. 231-232]

| Study SD-004-0732: Summary of Mean Body Length Increase Over 12-week study in ITT Group | | | |
|---|--------------------|--------------------|-----------------|
| | BIS 1.0 mg N=43 | BIS 0.5 mg N=47 | Placebo N=47 |
| Mean Baseline (cm) | 71.0 | 70.2 | 70.9 |
| Mean Last Visit (cm) | 74.1 | 73.5 | 74.4 |
| Mean Change (cm) | 3.1 | 3.3 | 3.5 |

Review Comment: The sponsor's value for Mean body length increase are 3.1, 3.5 and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. Although we have not reproduced the same numbers, the trend is the same and reveals dose ordering.

This table may not be an accurate reflection of growth changes due to drop-outs. The biostatistics reviewer, Dr. Jim Gebert developed an "evaluable group" of subjects that completed the study and had complete data. This table is below.

| Study SD-004-0732: Summary of Mean Body Length Increase Over 12-week study in Evaluable Group | | | |
|---|--------------------|--------------------|-----------------|
| | BIS 1.0 mg N=35 | BIS 0.5 mg N=39 | Placebo N=42 |
| Mean Baseline (cm) | 70.8 | 70.9 | 70.6 |
| Mean Last Visit (cm) | 74.1 | 74.4 | 74.3 |
| Mean Change (cm) | 3.3 | 3.5 | 3.7 |

By this analysis we again have dose ordering in reduction of growth velocity. It may be instructive to review growth per visit in the evaluable group presented in the table below.

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| Study SD-004-0732: Mean Body Length Change per Visit (Evaluable Group) | | | | | | |
|--|-------------------------|--|-------------------------|--|----------------------|---------------------------------------|
| | BIS 1.0 mg (cm) N=41 | Δ BIS 1.0 mg from previous Visit (cm) | BIS 0.5 mg (cm) N=43 | Δ BIS 0.5 mg from previous Visit (cm) | Placebo (cm) N=38 | Δ Placebo from previous Visit (cm) |
| Visit 3 (2 wks) Δ from baseline | 0.63 | | 0.44 | | 0.61 | |
| Visit 4 – Visit 3 | | 0.80 | | 0.61 | | 0.60 |
| Visit 4 (4 wks) Δ from baseline | 1.43 | | 1.05 | | 1.21 | |
| Visit 5 – visit 4 | | 1.09 | | 1.11 | | 1.14 |
| Visit 5 (8 wks) Δ from baseline | 2.52 | | 2.16 | | 2.35 | |
| Visit 6 – Visit 5 | | 0.7 | | 1.30 | | 1.31 |
| Visit 6 (12 wks) Δ from baseline | 3.22 | | 3.46 | | 3.66 | |

As the Sponsor has noted, the BIS 1.0 mg group had less of an increase from Visit 5 to Visit 6 compared to the other groups. However, there is again dose ordering and as the dose of BIS increases total growth over the 12 week study decreases. While this is not statistically significant (p=0.2861 BIS 1.0 mg vs. placebo on change from baseline) this study was not powered with any pre-specified criteria and this trend does seem to indicate that increasing the dose will decrease growth velocity. This should not be surprising, as this is an effect that is expected from corticosteroids. The overall difference in total growth between the placebo and BIS 1.0 group is **0.44 cm**.

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| Study SD-004-0732: Mean Body Length Change per Visit for subjects 6mo to <9mo (Evaluable Group) | | | | | | |
|---|-------------------------|--|-------------------------|--|----------------------|---------------------------------------|
| | BIS 1.0 mg (cm) N=21 | Δ BIS 1.0 mg from previous Visit (cm) | BIS 0.5 mg (cm) N=21 | Δ BIS 0.5 mg from previous Visit (cm) | Placebo (cm) N=21 | Δ Placebo from previous Visit (cm) |
| Visit 3 (2 wks) Δ from baseline | 0.50 | | 0.45 | | 0.85 | |
| Visit 4 – Visit 3 | | 1.00 | | 0.58 | | 0.55 |
| Visit 4 (4 wks) Δ from baseline | 1.50 | | 1.03 | | 1.40 | |
| Visit 5 – visit 4 | | 0.90 | | 1.08 | | 1.23 |
| Visit 5 (8 wks) Δ from baseline | 2.40 | | 2.11 | | 2.63 | |
| Visit 6 – Visit 5 | | 1.23 | | 1.23 | | 1.29 |
| Visit 6 (12 wks) Δ from baseline | 3.18 | | 3.34 | | 3.92 | |

From the above results, it appears that decrease in growth velocity occurs in a dose related fashion. The magnitude of difference between placebo and BIS 1.0 is greater in this age group than for the data regarding all combined age groups. This might be expected as the greatest amount of growth velocity in 6mo to 12 mo old infants would occur in the 6 to < 9 mo old subgroup compared to the 9 to 12 mo group. The overall difference in growth between the placebo and BIS 1.0 mg group is **0.74 cm**.

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| Study SD-004-0732: Mean Body Length Change per Visit for subjects 9mo to 12mo (Evaluable Group) | | | | | | |
|---|-------------------------|--|-------------------------|--|----------------------|---------------------------------------|
| | BIS 1.0 mg (cm) N=21 | Δ BIS 1.0 mg from previous Visit (cm) | BIS 0.5 mg (cm) N=21 | Δ BIS 0.5 mg from previous Visit (cm) | Placebo (cm) N=21 | Δ Placebo from previous Visit (cm) |
| Visit 3 (2 wks) Δ from baseline | 0.81 | | 0.43 | | 0.37 | |
| Visit 4 – Visit 3 | | 0.50 | | 0.65 | | 0.65 |
| Visit 4 (4 wks) Δ from baseline | 1.31 | | 1.08 | | 1.02 | |
| Visit 5 – visit 4 | | 1.38 | | 1.13 | | 1.04 |
| Visit 5 (8 wks) Δ from baseline | 2.69 | | 2.21 | | 2.06 | |
| Visit 6 – Visit 5 | | 0.60 | | 1.40 | | 1.35 |
| Visit 6 (12 wks) Δ from baseline | 3.29 | | 3.61 | | 3.41 | |

This stratified age group does not have a clear dose related suppression of growth velocity. However, this age grouping would have less total growth compared to the 6 mo to < 9 mo age group and therefore would not be as sensitive to possible corticosteroid suppressing effects. The difference between the placebo and BIS 1.0 mg group is **0.12 cm**.

mostly in the first two years (Wohl and Majzoub). Therefore, the long-term consequence of steroid use in this age population on subsequent lung/organ development is unknown and it would probably benefit society and public health if studies are designed and conducted to answer this question.

8. DOSING, REGIMEN, AND ADMINISTRATION ISSUES

The dosages used in the active treatment arms of this study were BIS 0.5 mg and BIS 1.0 mg once a day. Pulmicort Respules are presently approved at a starting dose of 0.25 mg once daily and total daily doses of 0.5 or 1 mg depending on the patient population.

9. USE IN SPECIAL POPULATIONS

9.1. Evaluation of Applicant's Gender, Age, Race, or Ethnicity Efficacy and Safety Analyses and Adequacy of Investigation

The sponsor has done an adequate safety evaluation of Gender in this submission. The population studied for this submission was mainly Caucasian.

9.2. Pediatric Program

The sponsor has fulfilled the requirements of a pediatric program in patients aged 6 months to 8 years of age.

9.3. Comments on Data Available or Needed in Other Populations (Such as Renal or Hepatic Compromised Patients, Use in Pregnancy)

There is a great deal of information available in the literature regarding the use of budesonide in other populations.

Reviewer Comment: Decreased growth velocity in infants receiving corticosteroid agents is expected and consideration should be given to placing this information into the label, not as a criticism of the drug, but as a reminder to practitioners that they should always use the lowest effective dose and not be lulled into a false sense of security that because they are giving a corticosteroid by inhalation there will not be systemic consequences. If the present rate of growth differential would be sustained the BIS 1.0 mg group would have approximately 1.8 cm less growth over a year which is consistent with the literature on reduced growth velocity and gives more credibility to these results.

7.5. Miscellaneous Studies

Not applicable

7.6. Literature Review of Safety

See heading 7.3.

7.7. Postmarketing Surveillance – If Applicable

Not Applicable

7.8. Safety Update – If Available

Not Applicable

7.9. Drug Withdrawal, Abuse, and Overdose Experience

None

7.10. Adequacy of Safety Testing

The safety study gives data pertinent to the short-term adverse effects of use of inhaled corticosteroids. This study does not give any information on the possible long-term effects of corticosteroid use, particularly on organ (lung) maturation and function. It would be useful if studies could be performed on long-term effects of inhaled steroids use in infants on lung functions and development, particularly in this age group where alveoli development is possibly vulnerable. However, for purposes of the Written Request, the sponsor has performed the negotiated study.

7.11. Labeling, Safety Issues, and Postmarketing Commitments

Please refer to section 10.3 for safety labeling issues. Again, it should be noted that there are animal studies demonstrating that the administration of corticosteroids during a period of alveolar development results in decrease lung-cell mass and the presence of too few abnormally large alveoli (Muglia, Bae, Brown)(Carson, Tausch and Avery)(Massaro and Massaro). It is also known that in babies alveoli increase by a factor of six after birth,

Use in Special Populations

10. CONCLUSIONS AND RECOMMENDATIONS

10.1. Conclusions Regarding Safety and Efficacy

The results of this study do not indicate a population mean suppressive effect on adrenal function in subjects aged 6 to 12 months with once-daily dosages of 0.5 or 1.0 mg BIS, however, there may be individual subjects with increased sensitivity and possible adrenal suppression. The safety profile of BIS was generally comparable to the safety profile in the approved label except for higher percentages of Tooth disorder, Nervousness, Pneumonia and Urticaria in the BIS group compared to placebo. A dose -dependent decrease in growth velocity was seen in the BIS groups compared to placebo. Efficacy was a secondary objective of this study and was assessed by comparing differences between treatment groups in the following variables: nighttime asthma symptom scores, daytime asthma symptom scores, use of breakthrough medication, percentage of symptom-free days, number of treatment failures, number of subject discontinuations, and investigator's global assessment of each subject's asthma status at the end of the study. The BIS treatment groups demonstrated trends of greater mean reduction in subjective parameters, with no clear advantage in the objective parameters, and not to the extent that any efficacy conclusions could be made.

10.2. Recommendations on Approvability

The sponsor is not seeking new indications in the label. This submission has fulfilled the requirements of the Written Request and is approvable with need for label revisions to gain full approval.

10.3. Labeling

Under heading "PRECAUTIONS", subheading Pediatric Use, Also the labeling should reflect that, while there was no difference in mean cosyntropin stimulation values, 6 subjects in the treatment group and one in the placebo group had abnormal (low cortisol secretion) cosyntropin responses at the end of the 12 week study. This section should also reflect that there might be dose-ordered growth velocity suppression

Under the heading "CLINICAL PHARMACOLOGY", subheading Pharmacodynamics, the double-lined addition beginning "12-week study...." Should be amended to reflect the number of patients who actually had an evaluation of serum cortisol levels post-ACTH stimulation at baseline and Week 12 and the finding that 6 subjects in the Pulmicort Respules group and one subject in the placebo group had a subnormal (<500 nmol/L) response.

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Conclusions and Recommendations

APPENDIX

11. DETAILED STUDY REVIEWS

11.1. Study #SD-004-0732: "A Safety and Efficacy Study of Two Dosage Levels of Pulmicort® Respules™ (budesonide inhalation suspension, 0.5 or 1.0 mg/day) versus Placebo in Infants Between the Ages of Six and Twelve Months with Mild to Moderate Asthma"

11.1.1. Protocol

11.1.1.1. Investigators and Centers

This was a multicenter clinical study employing 55 centers in the United States. One hundred and forty one subjects were randomized into this study.

11.1.1.2. Objective/Rationale

The primary objective of this study was to evaluate the safety of once-daily administration of Pulmicort Respules (0.5 and 1.0 mg) compared with placebo for the treatment of mild to moderate asthma or recurrent or persistent wheezing in infants between the ages of 6 and 12 months. The primary safety variable was assessment of adrenal function as assessed as the mean change from baseline at Week 12 in basal and 1-hour post adrenocorticotrophic hormone (ACTH) stimulated cortisol levels or changes in urinary cortical excretion. Secondary objectives included evaluating the efficacy of Pulmicort Respules and placebo by comparing nighttime and daytime asthma symptom scores, use of breakthrough medication, number of treatment failures, and subject discontinuations, and physician's global assessment of each subject's asthma status.

11.1.1.3. Overall Design

A 12-week, multicenter, randomized, double-blind, placebo-controlled study of 2 doses of Pulmicort Respules (Budesonide Inhalation Suspension referred to further as BIS) (0.5 mg and 1.0 mg) and placebo. It was planned that 144 subjects would be randomized throughout approximately 50 clinical sites to obtain 90 subjects completing the study.

11.1.1.4. Study Population

Male and female patients between the ages of 6 and 12 months who had not reached their first birthday and who were diagnosed with asthma or have demonstrated, historically, signs and symptoms of asthma defined as at least 2 episodes of persistent/recurrent wheezing, who may have benefited from inhaled anti-inflammatory therapy.

11.1.1.5. Inclusion Criteria

1. Male or Female between the ages of 6 and 12 months.
2. Diagnosed with asthma by historical signs and symptoms (consisting of at least 2 episodes of persistent or recurrent wheezing).

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3. Agree to basal cortisol specimens drawn in the morning at Visits 2 and 6 and post-ACTH specimens
4. Normal baseline electrocardiogram (ECG) on file if being treated with propulsid (cisapride) for gastroesophageal reflux disease.
5. Asthma symptoms scores (nighttime or daytime; score of 1, 2, 3) on 3 or more of the last 7 days prior to Visit 2. Asthma scale:
 - 0= None; no symptoms
 - 1= Mild symptoms; awareness of asthma symptoms and/or signs that are easily tolerated
 - 2= Moderate symptoms; asthma symptoms and/or signs with some discomfort, causing some interference of daily activities (daytime) or sleep (nighttime)
 - 3= Severe symptoms; incapacitating asthma symptoms and/or signs, with inability to perform daily activities (daytime) or sleep (nighttime)

Reviewer note: These symptoms scores seemed more geared toward self reporting which is not possible in this population. Therefore limited conclusions may be made based on this system.

11.1.1.6. Exclusion Criteria

1. Diagnosed with severe asthma
2. History of assisted ventilation
3. Having a functioning tracheostomy
4. Require chronic or intermittent oxygen therapy
5. Severe GERD
6. Severe chronic lung disease which may lead to hypoxia (Note: subjects with mild cystic fibrosis or bronchopulmonary dysplasia who were normoxic and demonstrated reversible airway disease could be considered for study entry)
7. Severe immunodeficiencies disease
8. HIV positive
9. Hospitalized for pulmonary disease or respiratory infection within the past 4 weeks
10. Born less than 32 weeks of gestation
11. Failure-to-thrive within past 2 months
12. Treatment with systemic steroids within past 4 weeks
13. Endocrine abnormality
14. Receiving treatment with any of the following medications: systemic steroids, inhaled steroids including intranasal steroids, slow-release oral beta2 agonists, long-acting

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| Study SD-004-0732: Study Summary/Flow Chart | | | | | | |
|--|----------|-------------------|---|---|---|----|
| | Baseline | Double-blind Week | | | | |
| Week Number | -2 ± 1 | 0 | 2 | 4 | 8 | 12 |
| Visit Number | 1 | 2 | 3 | 4 | 5 | 6 |
| Informed Consent | X | | | | | |
| Inclusion/Exclusion Criteria | X | X | | | | |
| Medical & Surgical Histories | X | | | | | |
| Complete Physical Examination | X | | | | | X |
| Brief Physical Examination | | X | X | X | X | |
| Vital Signs, including Length and Weight | X | X | X | X | X | X |
| Randomization | | X | | | | |
| Hematology, Blood Chemistry | | X | | | | X |
| Oropharyngeal & Nasal Fungal Cultures | | X | | | | X |
| Cortisol Specimens (blood) or (urine) | | X | | | | X |
| Dispense Study Drug & Instructions on dosing | | X | X | X | X | |
| Drug Accountability | | | X | X | X | X |
| Instruct Parent/Guardian in Diary Completion | X | X | X | X | X | |
| Collect and review Diary Entries | | X | X | X | X | X |
| Adverse Event Assessments | | X | X | X | X | X |
| Review Use of Concomitant Medications | X | X | X | X | X | X |
| Physician's Global Assessment | | | | | | X |

11.1.1.8. Efficacy Parameters

Efficacy was a secondary objective of this study and was assessed by comparing differences between treatment groups in the following variables: nighttime asthma symptom scores, daytime asthma symptom scores, use of breakthrough medication, percentage of symptom-free days (see scale under inclusion criteria), number of treatment failures, number of subject discontinuations, and investigator's global assessment of each subject's asthma status at the end of the study.

Investigator Global Assessment:

- 1 = a great deal better
- 2 = somewhat better

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- 3 = unchanged
4 = somewhat worse
5 = a great deal worse

11.1.1.9. Safety Evaluations

The primary safety variable was adrenal function as determined by plasma cortisol levels (pre- and 1-hour post- ACTH) and overnight urinary free cortisol levels at Visits 2 and 6. Subnormal adrenal function by plasma cortisol levels was defined as a post-ACTH plasma cortisol value less than 500 nmol/L at either Visit 2 or Visit 6. Urinary cortisol excretion was measured as the _____ and also as total free cortisol levels from overnight timed urine samples. Subjects who did not undergo the cosyntropin stimulation test were to provide timed urine samples. Other secondary safety variables included the incidence and severity of adverse events, changes from baseline in hematology and chemistry laboratory, body length/height and body weight and oropharyngeal and nasal fungal cultures.

Body length was measured with the subject on _____

11.1.1.10. Statistical Plan

The sponsor's state that this study was designed to address whether BIS is safe compared to placebo and differs from placebo in terms of improvement of asthma/wheezing. All statistical comparisons were carried out as two-sided tests. The Intent-to-treat (ITT) population was all subjects who were randomized and received at least one dose of study medication and had one observation taken. The "Evaluable" population is all subjects with at least a pre- and post-cosyntropin stimulation sample obtained before and at the end of treatment or urine samples obtained before and at the end of treatment.

The last observed value carried forward (LOCF) was used for analysis and summary of plasma and urinary cortisol and for the investigator's global assessment of asthma status. Only observed data were summarized for the remaining efficacy safety analyses.

The primary variable was analyzed using an analysis of covariance (ANCOVA) model with treatment as the main effect and baseline as the covariate. The p-value from the Wilcoxon Rank Sum test is also provided for this analysis.

For efficacy variables, the change from baseline in nighttime and daytime symptom scores were analyzed using an ANCOVA with treatment as the main effect and baseline as the covariate. Investigator's global assessment were analyzed using Mantel-Haenszel test.

The sponsor states that sample size calculations were not based upon strict statistical criteria but rather on pediatric exclusivity guidance from the FDA that approximately half of the subjects were to be between the 6 and 9 months of age and the other half were to be between

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9 and 12 months of age with at least 90 completing subjects, at least 60 of whom had to be in the active treatment groups.

11.1.2. Results

11.1.2.1. Subject Disposition

A total of 216 subjects were screened. There were 75 screening failures. A total of 141 pediatric patients were randomized into the study to receive Pulmicort Respules (48 to BIS 0.5 mg, 44 to BIS 1.0 mg and 49 to placebo).

| Study SD-004-0732: Summary of Subject Disposition | | | | |
|--|-------------------|--------------------|-----------------|----------------|
| Parameter | BID 0.5mg N=48 | BIS 1.0 mg N=44 | Placebo N=49 | Total N=141 |
| Total Randomized | 48 | 44 | 49 | 141 |
| Age strata | | | | |
| 6 to < 9 months | 26 | 25 | 25 | |
| 9 to <12 months | 22 | 19 | 24 | |
| Completed Study | 40 (83.3%) | 35 (79.5%) | 42 (85.7%) | 117 (83.0%) |
| Discontinued Study | 8 (16.7%) | 9 (20.5%) | 7 (14.3%) | 24 (17.0%) |
| Reason for Discontinuation ^a | | | | |
| Lost to follow-up | 4 (50.0%) | 2 (22.2%) | 2 (28.6%) | 8 (33.3%) |
| Other ^b | 3 (37.5%) | 2 (22.2%) | 3 (42.9%) | 8 (33.3%) |
| Consent withdrawn | 0 | 3 (33.3%) | 2 (28.6%) | 5 (20.8%) |
| Adverse event | 1 (12.5%) | 2 (22.2%) | 0 | 3 (12.5%) |
| Treatment failure | 0 | 0 | 0 | 0 |
| ^a Percentages based on number discontinuing in each treatment group | | | | |
| ^b Other included noncompliance, doctor's choice, moving | | | | |

Reviewer Comment: It is interesting to note that a higher percentage of subjects in the placebo group completed the study than in either active treatment group. Adverse events as a reason for stopping the study were limited to the active treatment groups and appeared dose related.

The sponsor's state that only a total of 82 pediatric subjects (33 in the BIS 0.5 mg group, 17 in the BIS 1.0 mg group and 32 in the placebo group) were considered evaluable for the

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analyses of adrenal function due to inability to obtain plasma cortisol levels as the result of unsuccessful blood draws [Vol. 001/Pg 086].

11.1.2.2. Demographics

Overall, most subjects were Caucasian (99, 70%) and male (87, 62%). With the exception of a higher proportion of males vs. females among subjects aged 9 to < 12 months compared with younger subjects in the BIS 0.5 mg group (82% vs. 18%), demographic characteristics were comparable across treatment groups and age strata [Vol.001/pg. 088].

11.1.2.3. Efficacy Endpoint Outcomes

Efficacy was evaluated by examination of asthma symptom scores (AM and PM), physician's global assessments, withdrawal/treatment failure, and the use of breakthrough medication.

Reviewer comment: Symptom scores and global assessments are "soft" endpoints and should only be used to look for signals of concern. Withdrawal rates and use of breakthrough medication may give a better indication of effectiveness.

These results are presented in the following tables.

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| Study SD-004-0732: Summary of Mean Change from Baseline in AM and PM Asthma Symptom Scores (ITT Population) | | | | | | | | | |
|---|-----------------|----|---------------|---------------------|---|---|------------|----------------|------------------|
| Parameter | Treatment Group | N | Baseline Mean | Week 1-12 Mean (SE) | Baseline change Adjusted Mean (SE) ^a | Difference from Placebo (SE) ^a | 95% CI | ANCOVA P-Value | Wilcoxon P-Value |
| Daytime Score (Week 1-12) | Placebo | 46 | 1.20 | 0.8 (0.1) | 0.4 (0.1) | | | | |
| | BIS 0.5 mg | 45 | 1.28 | 0.6 (0.1) | 0.6 (0.1) | -0.2 (0.1) | -0.4, 0.0 | 0.060 | 0.040 |
| | BIS 1.0 mg | 43 | 1.10 | 0.7 (0.1) | 0.4 (0.1) | -0.0 (0.1) | -0.2, 0.1 | 0.634 | 0.853 |
| Nighttime Score (Week 1-12) | Placebo | 46 | 1.21 | 0.8 (0.1) | 0.4 (0.1) | | | | |
| | BIS .5 mg | 45 | 1.24 | 0.6 (0.1) | 0.6 (0.1) | -0.2 (0.1) | -0.4, -0.0 | 0.047 | 0.173 |
| | BIS 1.0 mg | 43 | 1.08 | 0.7 (0.1) | 0.5 (0.1) | -0.1 (0.1) | -0.3, 0.1 | 0.447 | 0.944 |

^a Mean adjusted for baseline

The BIS 0.5 mg group had a greater change from baseline compared to the placebo group, but the 95% CI included 0. It would appear that the BIS 0.1 mg group was less symptomatic than the placebo group at baseline so it is not unexpected that there would less opportunity for an effect size difference to be realized.

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| Study SD-004-0732: Summary of Percentage of Symptom-Free Days (ITT Population) | | | | | | | |
|--|----|------------|--------------------|------------------------------|------------|---------------|------------------|
| Treatment Group | N | Mean (SE) | Adjusted Mean (SE) | Placebo Difference Mean (SE) | 95% CI | ANOVA P-Value | Wilcoxon P-Value |
| Placebo | 47 | 37.5 (4.4) | 37.5 (4.8) | | | | |
| BIS 0.5 mg | 46 | 48.9 (4.9) | 48.8 (4.9) | 11.3 (6.8) | -2.3, 24.8 | 0.102 | 0.081 |
| BIS 1.0 mg | 43 | 43.4 (5.5) | 43.4 (5.0) | 5.8 (7.0) | -7.9, 19.6 | 0.403 | 0.372 |

Both active treatment groups experienced a greater mean number of symptom free days compared to placebo.

For the ITT population, physician global assessments rated asthma symptomatology as a "Great Deal Better" or "Somewhat Better" for 90% and 85% of subjects in the BIS 0.5 mg and BIS 1.0 mg groups, respectively, compared with 67% of placebo-treated subjects.

There were no significant differences in withdrawal rates of the ITT population between groups during the double-blind period with 7 (14.6%), 8 (18.2%) and 7 (14.3%) of subjects withdrawing from the BIS 0.5 mg, BIS 1.0 mg and Placebo groups respectively.

Treatment failure was defined as the use of an additional asthma/breakthrough maintenance therapy for uncontrolled asthma symptoms or the use of prednisone for an asthma exacerbation. Treatment failure occurred for 7 (14.6%), 8 (18.2%) and 11 (22.4%) of subjects in the BIS 0.5 mg, BIS 1.0 mg and placebo groups respectively. It is interesting to note that under the summary of prior medication use [Vol. 001/Pg 224], total glucocorticoid use was 29.2%, 15.9% and 14.3% for the BIS 0.5 mg, BIS 1.0mg and placebo groups respectively indicating that almost twice as many subjects with prior corticosteroid use were randomized into the BIS 0.5 mg group.

The percentage of total days on study treatment without use of breakthrough medication was not statistically significant for either of the BIS dosage groups compared with placebo (72.8, 76.6 and 72.3 days for placebo, 0.5 mg, and 1.0 mg groups respectively).

11.1.2.4. Safety Outcomes

11.1.2.4.1. ACTH-stimulated plasma cortisol

A total of 101 subjects had basal and ACTH-stimulated plasma cortisol values at baseline (33, 29, and 39 in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups respectively). The mean basal and ACTH-stimulated plasma cortisol values at baseline averaged 244.7 nmol/L and 631.4 nmol/L across all treatment groups, respectively. The mean change from baseline to

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Visit 6 in ACTH-stimulated minus basal plasma cortisol levels did not indicate apparent suppression as monitored by mean values. [vol. 001/Pg. 093]

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Study SD-004-0732: Summary of change from Baseline in Mean Plasma Cortisol Values (nmol/L) at Week 12 (Evaluable Population^a)

| Parameter | Treatment Group | N | Baseline Mean | Visit 6 Mean (SE) | Change from Baseline Mean (SE) | Change from Baseline Adjusted Mean (SE) ^b | Adjusted Mean Difference from Placebo (SE) ^b | 95% CI | ANCOVA P-Value | Wilcoxon P-Value |
|--|-----------------|----|---------------|-------------------|--------------------------------|--|---|--------------|----------------|------------------|
| Plasma Cortisol (Pre-Stimulation) | Placebo | 31 | 268 | 234 (24.5) | -33.3 (26.4) | -17.8 (22.0) | | | | |
| | BIS 0.5 mg | 28 | 233 | 231 (25.8) | -2.3 (20.8) | -6.3 (23.0) | 11.6 (31.8) | -51.9, 75.0 | 0.718 | 0.671 |
| | BIS 1.0 mg | 17 | 202 | 244 (32.1) | 42.2 (44.8) | 20.4 (29.7) | 38.3 (37.2) | -36.0, 112.5 | 0.307 | 0.168 |
| Plasma Cortisol (Post-Stimulation) | Placebo | 31 | 647 | 650 (31.6) | 2.8 (32.0) | 5.6 (30.4) | | | | |
| | BIS 0.5 mg | 28 | 646 | 674 (40.0) | 27.9 (41.0) | 30.0 (31.9) | 24.4 (44.1) | -63.5, 112.2 | 0.582 | 0.891 |
| | BIS 1.0 mg | 17 | 627 | 661 (33.4) | 33.5 (46.7) | 24.8 (41.0) | 19.2 (51.1) | -82.6, 121.0 | 0.708 | 0.940 |
| Plasma cortisol (Post-Minus Pre-Stimulation) | Placebo | 31 | 379 | 415 (38.4) | 36.1 (48.9) | 19.8 (36.1) | | | | |
| | BIS 0.5 mg | 28 | 412 | 443 (43.7) | 30.2 (44.3) | 37.9 (38.0) | 18.0 (52.5) | -86.6, 122.7 | 0.732 | 0.832 |
| | BIS 1.0 mg | 17 | 426 | 417 (37.0) | -8.7 (62.6) | 8.4 (48.8) | -11.4 (60.8) | -133, 109.8 | 0.852 | 0.140 |

^a Included subjects with a baseline plasma cortisol value ≥ 500 nmol/L and who did not receive a steroid within the 4 weeks prior to final cortisol testing

^b Mean adjusted for baseline

Reviewer Comment: Noted that the BIS 1.0 mg group only contained 17 subjects which could introduce a considerable bias if the excluded subjects did not reflect the mean report.

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Few subjects had shifts from a baseline post-ACTH-stimulation plasma cortisol value ≥ 500 nmol/L to a Week 12 post-ACTH plasma cortisol value of < 500 nmol/L (4 (14%), 2 (12%), and 1 (3%) in the BIS 0.5 mg, BIS 1.0 mg, and placebo groups respectively. For 5 of the 7 subjects with a subnormal ACTH-stimulated plasma cortisol value at Week 12 the end-of-treatment post-ACTH-stimulated plasma cortisol value was near the cut-off value of 500 nmol/L (18 $\mu\text{g/dL}$) (values of \sim all exposed to BIS 0.5mg and \sim both exposed to BIS 1.0mg). For the remaining 2 subjects (BIS 0.5 and Placebo) the post-stimulation value was low, 155nmol/L and 109 nmol/L (pre-stimulation values were \sim nmol/L \sim nmol/L). The sponsor speculates that the discrepancy may be due to sampling or labeling errors.

Reviewer Comment: The mean values of the three different group did not indicate any difference in adrenal responsiveness of the populations while there were 5 individuals (maybe 6 depending on labeling errors), all exposed to BIS, that did not have an adequate response to cosyntropin. This may indicate that, while populations may expect no adrenal suppression, there are individuals that may have increased sensitive to exogenous corticosteroid suppression and must be kept in mind by practicing physicians when approaching individual patients.

11.1.2.4.2. Urinary Cortisol

A total of 6 subjects (5 in the BIS 0.5 mg group and 1 in the placebo group) had urinary cortisol testing at Visits 2 and 6. The mean change from baseline at Week 12 was 52.2 ug/g \sim among subjects in the BIS 0.5 mg group compared to a -44.8 mean change for the placebo subject. See table below. [Vol. 001/Pg. 102]

| Study SD-004-0732: Urinary Cortisol Data (Evaluable Population) | | | | |
|---|---------|-----------|-------------------------------|---------|
| Treatment Group | Sex/Age | Race | Urinary Cortisol Value (ug/g) | |
| | | | Visit 2 | Visit 6 |
| BIS 0.5 mg | F/6 | Caucasian | 13.7 | 10.0 |
| BIS 0.5 mg | M/11 | Caucasian | 21.0 | 34.8 |
| BIS 0.5 mg | M/9 | Black | 5.9 | 181.6 |
| BIS 0.5 mg | F/7 | Caucasian | 12.9 | 8.1 |
| BIS 0.5 mg | M/8 | Caucasian | 28.1 | 108.0 |
| Placebo | F/6 | Black | 62.6 | 17.8 |

Review Comment: The data from this aspect of adrenal evaluation has a great deal of variability as demonstrated by the Placebo group's minus mean change which would fulfill the criteria for abnormal response. Therefore since there is not a placebo control and because of wide range of variability (perhaps reflecting the difficulty collecting proper urine samples in this age group) this data should not be used to make any HPA function conclusions for labeling purposes.

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Frequency of Adverse Events with discrepancies between active arms and placebo are listed in the table below. [vol. 001/pgs 112-114]

| Study SD-004-0732: Frequency of Adverse Events with discrepancy reporting of BIS compared to placebo | | | |
|--|----------------------|----------------------|-------------------|
| | BIS 0.5 mg (N=48) | BIS 1.0 mg (N=44) | Placebo (N=49) |
| Otitis Media | 23 (47.9%) | 12 (27.3%) | 20 (40.8%) |
| Fever | 12 (25.0%) | 10 (22.7%) | 17 (34.7%) |
| Asthma Aggravated | 4 (8.3%) | 4 (9.1%) | 8 (16.3%) |
| Tooth Disorder | 6 (12.5%) | 7 (15.9%) | 2 (4.1%) |
| Coughing | 4 (8.3%) | 2 (4.5%) | 6 (12.2%) |
| Conjunctivitis | 7 (14.6%) | 0 (0.0%) | 4 (8.2%) |
| Pharyngitis | 7 (14.6%) | 0 (0.0%) | 2 (4.1%) |
| Rhonchi | 1 (2.1%) | 1 (2.3%) | 6 (12.2%) |
| Dermatitis Fungal | 2 (4.2%) | 2 (4.5%) | 4 (8.2%) |
| Nervousness | 3 (6.3%) | 1 (2.3%) | 0 (0.0%) |
| Pneumonia | 2 (4.2%) | 1 (2.3%) | 0 (0.0%) |
| Urticaria | 1 (2.1%) | 1 (2.3%) | 0 (0.0%) |
| Lymphadenopathy | 0 (0.0%) | 0 (0.0%) | 2 (4.1%) |
| Dysphonia | 1 (2.1%) | 0 (0.0%) | 0 (0.0%) |

Three subjects (2 in the BIS 1.0 mg for asthma and pneumonia and 1 in the BIS 0.5 mg group for rash) had treatment discontinued prematurely as the result of an adverse event.

Reviewer Comment: Tooth disorder, Pharyngitis, Nervousness, Pneumonia and Urticaria are not presently in the Label and ~~it is noted~~ is the favorable effect of active treatment with regard to Asthma aggravation, rhonchi, dermatitis fungal and lymphadenopathy.

11.1.2.4.3. Body Length

The protocol for body length measurement is in Vol. 003/pg 065. //

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Mean body length increased across visits in all 3 treatment groups, although mean body length in the BIS 1.0 mg group increased less from Week 8 to Week 12 compared with the other treatment groups. The mean changes in body length for the ITT group are in the table below. [vol.001/pg 216][Vol.002/pg. 231-232]

| Study SD-004-0732: Summary of Mean Body Length Increase Over 12-week study in ITT Group | | | |
|---|--------------------|--------------------|-----------------|
| | BIS 1.0 mg N=43 | BIS 0.5 mg N=47 | Placebo N=47 |
| Mean Baseline (cm) | 71.0 | 70.2 | 70.9 |
| Mean Last Visit (cm) | 74.1 | 73.5 | 74.4 |
| Mean Change (cm) | 3.1 | 3.3 | 3.5 |

Review Comment: The sponsor's value for Mean body length increase are 3.1, 3.5 and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. Although we have not reproduced the same numbers, the trend is the same and reveals dose ordering.

This table may not be an accurate reflection of growth changes due to drop-outs. Dr. Gebert has developed an evaluable group of subjects that completed the study and had complete data. This table is below.

| Study SD-004-0732: Summary of Mean Body Length Increase Over 12-week study in Evaluable Group | | | |
|---|--------------------|--------------------|-----------------|
| | BIS 1.0 mg N=35 | BIS 0.5 mg N=39 | Placebo N=42 |
| Mean Baseline (cm) | 70.8 | 70.9 | 70.6 |
| Mean Last Visit (cm) | 74.1 | 74.4 | 74.3 |
| Mean Change (cm) | 3.3 | 3.5 | 3.7 |

By this analysis we again have dose ordering in reduction of growth velocity. It may be instructive to review growth per visit in the evaluable group presented in the table below.

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NDA #20-929, Pulmicort Respules

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| Study SD-004-0732: Mean Body Length Change per Visit (Evaluable Group) | | | | | | |
|--|-------------------------|--|-------------------------|--|----------------------|---------------------------------------|
| | BIS 1.0 mg (cm) N=41 | Δ BIS 1.0 mg from previous Visit (cm) | BIS 0.5 mg (cm) N=43 | Δ BIS 0.5 mg from previous Visit (cm) | Placebo (cm) N=38 | Δ Placebo from previous Visit (cm) |
| Visit 3 (2 wks) Δ from baseline | 0.63 | | 0.44 | | 0.61 | |
| Visit 4 – Visit 3 | | 0.80 | | 0.61 | | 0.60 |
| Visit 4 (4 wks) Δ from baseline | 1.43 | | 1.05 | | 1.21 | |
| Visit 5 – visit 4 | | 1.09 | | 1.11 | | 1.14 |
| Visit 5 (8 wks) Δ from baseline | 2.52 | | 2.16 | | 2.35 | |
| Visit 6 – Visit 5 | | 0.7 | | 1.30 | | 1.31 |
| Visit 6 (12 wks) Δ from baseline | 3.22 | | 3.46 | | 3.66 | |

As the Sponsor has noted, the BIS 1.0 mg group had less of an increase from Visit 5 to Visit 6 compared to the other groups. However, there is again dose ordering and as the dose of BIS increases total growth over the 12 week study decreases. While this is not statistically significant (p=0.2861 BIS 1.0 mg vs. placebo on change from baseline) this study was not powered with any pre-specified criteria and this trend does seem to indicate that increasing the dose will decrease growth velocity. This should not be surprising, as this is an effect that is expected from corticosteroids. The overall difference in total growth between the placebo and BIS 1.0 group is **0.44 cm**.

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| Study SD-004-0732: Mean Body Length Change per Visit 6mo to <9mo (Evaluable Group) | | | | | | |
|--|-------------------------|--|-------------------------|--|----------------------|---------------------------------------|
| | BIS 1.0 mg (cm) N=21 | Δ BIS 1.0 mg from previous Visit (cm) | BIS 0.5 mg (cm) N=21 | Δ BIS 0.5 mg from previous Visit (cm) | Placebo (cm) N=21 | Δ Placebo from previous Visit (cm) |
| Visit 3 (2 wks) Δ from baseline | 0.50 | | 0.45 | | 0.85 | |
| Visit 4 – Visit 3 | | 1.00 | | 0.58 | | 0.55 |
| Visit 4 (4 wks) Δ from baseline | 1.50 | | 1.03 | | 1.40 | |
| Visit 5 – visit 4 | | 0.90 | | 1.08 | | 1.23 |
| Visit 5 (8 wks) Δ from baseline | 2.40 | | 2.11 | | 2.63 | |
| Visit 6 – Visit 5 | | 1.23 | | 1.23 | | 1.29 |
| Visit 6 (12 wks) Δ from baseline | 3.18 | | 3.34 | | 3.92 | |

From the above results, it appears that decrease in growth velocity occurs in a dose related fashion. The magnitude of difference between placebo and BIS 1.0 is greater in this age group than in the over study results presented in the table above. This might be expected as the greatest amount of growth velocity in 6mo to 12 mo old infants would occur in the 6 to < 9 mo old subgroup compared to the 9 to 12 mo group. The overall difference in growth between the placebo and BIS 1.0 mg group is 0.74 cm.

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| Study SD-004-0732: Mean Body Length Change per Visit 9mo to 12mo (Evaluable Group) | | | | | | |
|--|-------------------------|--|-------------------------|--|----------------------|---------------------------------------|
| | BIS 1.0 mg (cm) N=21 | Δ BIS 1.0 mg from previous Visit (cm) | BIS 0.5 mg (cm) N=21 | Δ BIS 0.5 mg from previous Visit (cm) | Placebo (cm) N=21 | Δ Placebo from previous Visit (cm) |
| Visit 3 (2 wks) Δ from baseline | 0.81 | | 0.43 | | 0.37 | |
| Visit 4 – Visit 3 | | 0.50 | | 0.65 | | 0.65 |
| Visit 4 (4 wks) Δ from baseline | 1.31 | | 1.08 | | 1.02 | |
| Visit 5 – visit 4 | | 1.38 | | 1.13 | | 1.04 |
| Visit 5 (8 wks) Δ from baseline | 2.69 | | 2.21 | | 2.06 | |
| Visit 6 – Visit 5 | | 0.60 | | 1.40 | | 1.35 |
| Visit 6 (12 wks) Δ from baseline | 3.29 | | 3.61 | | 3.41 | |

This stratified age group does not have a clear dose related suppression of growth velocity. However, this age grouping would have less total growth compared to the 6 mo to < 9 mo age group and therefore would not be as sensitive to possible corticosteroid suppressing effects. The difference between the placebo and BIS 1.0 mg group is **0.12 cm**.

Reviewer Comment: This effect is expected and consideration should be given to placing this information into the label, not as a criticism of the drug, but as a reminder to practitioners that they should always use the lowest effective dose and not be lulled into an erroneous false sense of security that because they are giving a corticosteroid by inhalation there will not be systemic consequences. If the present rate of growth differential would be sustained the BIS 1.0 mg group would have approximately 1.8 cm less growth over a year which is consistent with the literature on reduced growth velocity and gives more credibility to these results.

11.1.3. Discussion and Conclusions

The primary purpose of this study was to evaluate the effects of BIS 0.5 mg and 1.0 mg on adrenal function in a 6 to 12 month of age population with wheezing. Adrenal function was assessed before and at the end of the 12-week treatment period by measuring changes in plasma cortisol levels in response to the 1-hour cosyntropin (ACTH) stimulation test or by changes in urinary free cortisol excretion obtained from overnight timed urine samples. The mean values of the three different group did not indicate any difference in adrenal responsiveness of the populations to the ACTH stimulation test. However, there were 5 individuals (maybe 6 depending on labeling errors), all exposed to BIS, that did not have an adequate response (as pre-defined as a post-ACTH infusion level >500 nmol/L) to cosyntropin. This may indicate that, while populations may expect no adrenal suppression, there are individuals within those populations that may have increased sensitive to exogenous corticosteroid than the group mean and this sensitivity must be kept in mind by practicing physicians when approaching therapy for the individual patient. It is also important to note that the BIS 1.0 mg group only contained 17 subjects (compared to 28 for the BIS 0.5mg and 31 for the placebo groups) which could introduce a considerable bias if the excluded subjects did not reflect the group mean.

A total of 6 subjects (5 in the BIS 0.5 mg group and 1 in the placebo group) had urinary cortisol testing at Visits 2 and 6. The data from this aspect of adrenal evaluation has a great deal of variability and questionable validity of the single placebo comparator and as such should not be used to make any HPA function conclusions for labeling purposes.

Regarding adverse events, three subjects (2 in the BIS 1.0 mg for asthma and pneumonia and 1 in the BIS 0.5 mg group for rash) had treatment discontinued prematurely as the result of an adverse event. Tooth disorder, Nervousness, Pneumonia and Urticaria occurred in higher percentages in the active treatment group compared to placebo and are not presently contained in the Label for the Respules.

While there did not seem to group mean differences in adrenal suppression, the same cannot be said of Body Length changes. While mean body length increased across visits in all 3 treatment groups in the ITT group, the BIS 1.0 mg group increased less from Week 8 to Week 12 compared with the other treatment groups. Overall Mean body length increases were 3.1, 3.5 and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. There appears to be dose ordering growth suppression. In order to see if there was a possible drop-out bias, Dr. Gebert investigated growth for an "evaluable group" consisting of subjects that

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had all data points and completed the study. However, this group demonstrated the same trend with mean changes of 3.3 cm, 3.5 cm and 3.7 cm for the BIS 1.0, BIS 0.5 and placebo groups respectively. While this is not statistically significant ($p=0.2861$ BIS 1.0 mg vs. placebo on change from baseline) this study was not powered with any pre-specified criteria and this trend does seem to indicate that increasing the dose will decrease growth velocity. This should not be surprising, as this is an expected effect of corticosteroids. This effect should be placed in the label, not as a criticism of the drug, but as a reminder to practitioners that they should always use the lowest effective dose and not be lulled into an erroneous false sense of security that because they are giving a corticosteroid by inhalation there will not be systemic consequences.

I agree with the sponsor's that assessing efficacy in this population is difficult, since there are no standard methods for measurement of lung function and few objective parameters. The sponsor is not making any label claims of efficacy based on this study. Efficacy was a secondary objective of this study and was assessed by comparing differences between treatment groups in the following variables: nighttime asthma symptom scores, daytime asthma symptom scores, use of breakthrough medication, percentage of symptom-free days (see scale under inclusion criteria), number of treatment failures, number of subject discontinuations, and investigator's global assessment of each subject's asthma status at the end of the study. The BIS treatment groups demonstrated trends of greater mean reductions in subjective parameters, less so in objective parameters, such that no efficacy conclusions could be made.

In conclusion, the results of this study do not indicate a population mean suppressive effect on adrenal function in subjects aged 6 to 12 months with once-daily dosages of 0.5 or 1.0 mg BIS, although there may be individual subjects with increased sensitivity and possible adrenal suppression. The safety profile of BIS was comparable to that of placebo or is already existing in labeling except for higher percentages of Tooth disorder, Nervousness, Pneumonia and Urticaria in the BIS group compared to placebo. Dose proportional growth velocity retardation was seen in the BIS groups compared to placebo. The clinical relevance of this is unknown.

12. DETAILED LABELING CHANGES OR REVISED DRUG LABEL

Under heading "PRECAUTIONS", subheading Pediatric Use, Also the labeling should reflect that, while there was no difference in mean cosyntropin stimulation values, 6 subjects in the treatment group and one in the placebo group had abnormal (low cortisol secretion) cosyntropin responses at the end of the 12 week study. This section should also reflect that there might be dose-ordered growth velocity suppression

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Under the heading "CLINICAL PHARMACOLOGY", subheading Pharmacodynamics, the double-lined addition beginning "12-week study...." Should be amended to reflect the number of patients who actually had an evaluation of serum cortisol levels post-ACTH stimulation at baseline and Week 12 and the finding that 6 subjects in the Pulmicort Respules group and one subject in the placebo group had a subnormal (<500 nmol/L) response.

Citations

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/s/

Lydia McClain
2/14/03 01:43:58 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-929/S-013

MEDICAL REVIEW(s)

DIVISION DIRECTOR'S MEMORANDUM

Date: February 26, 2003

To: NDA 20-929

From: Badrul A. Chowdhury, MD, PhD
Acting Director, Division of Pulmonary and Allergy Drug products

Product: Pulmicort Respules (budesonide inhalation suspension)

Applicant: AstraZeneca LP

Administrative and Introduction

AstraZeneca submitted supplement to Pulmicort Respules NDA 20-929 (SE 8-013) on August 30, 2002, to fulfill the requirements of the Written request issued by the Agency on December 14, 1998, for pediatric studies for budesonide. The Written Request asked for two studies - a safety study with Pulmicort Respules (budesonide inhalation suspension) in subjects 6 to 11 months of age, and a safety study with Rhinocort Aqua (budesonide) Nasal Spray in subjects 2 to 6 years of age. With this submission the applicant has completed the requirement of the Written Request and pediatric exclusivity for budesonide was granted on November 14, 2002.

Pulmicort Respules is currently the only corticosteroid formulation approved in the United States for use in nebulizer. Pulmicort Respules also has the lowest age of indication for any corticosteroid for asthma. Pulmicort Respules was approved on August 8, 2000, for use in patients 12 months to 8 years of age with asthma. The Written Request was issued by the Agency approximately two years before the drug was approved. At that time it was realized that safety data in the very young subjects was lacking for Pulmicort Respules. Therefore, the Written Request asked for safety data in the very young children. In this submission the applicant has submitted safety information on Pulmicort Respules in subjects 6 to 11 months of age. AstraZeneca is proposing to add new information to the Pharmacodynamics sub section under Clinical Pharmacology section, and Pediatric Use sub section under Precautions section of the label. AstraZeneca is not seeking changes in the Indications section of the label.

Chemistry, Manufacturing, and Controls, and Establishment Evaluation

Pulmicort Respules is a marketed product. No new chemistry or manufacturing data is submitted with this application. All manufacturing facilities related to this application have an acceptable EER status.

Clinical and Statistical

The supplemental NDA contain results from one study (No. SD-004-0732). The study is reviewed in detail in Dr. Rosebraugh's excellent medical review. Brief comments on the study are made below.

The study was a 12-week, multi-center, randomized, double-blind, placebo-controlled study that evaluated the safety of two doses of Pulmicort Respules (0.5 mg and 1.0 mg once daily) in children between the ages of 6 and 11 months with mild-to-moderate asthma or persistent wheezing. The study was not powered for efficacy assessment. A total of 141 subjects were randomized and 117 completed the study. There were 40 subjects in the Pulmicort Respules 0.5 mg arm, 35 subjects in the Pulmicort Respules 1 mg arm, and 42 subjects in the placebo arm. There total number of study subjects was reasonable, and also there were reasonable distribution of subjects between the ages of 6 to 8 months and 9 to 11 months.

The primary safety variable of the study was assessment of adrenal function by plasma cortisol levels pre- and 1-hour-post ACTH stimulation or by overnight free cortisol levels at week 12 compared to randomization. Subnormal adrenal function was defined as post-ACTH plasma cortisol value less than 500 nmol/L. Growth velocity of the subjects was measured by recording of body lengths. Growth velocity is a useful marker of systemic corticosteroid effect. Other safety assessments included recording of adverse events, blood count and chemistry, and oropharyngeal and nasal fungal cultures. Overall safety profiles of the study subjects were generally similar to those seen in older children, but the results of the ACTH stimulation test and the growth velocity are worth noting. The mean ACTH stimulation test results between the three groups did not differ, but there were six subjects in the Pulmicort Respules groups and one subject in the placebo group that had post-ACTH stimulation cortisol value below the cut off value of 500 nmol/L. There was a dose-dependent decrease in the mean growth velocity over the 12 weeks of treatment. The mean growth velocity was 3.7 cm in the placebo arm, 3.5 cm in the Pulmicort Respules 0.5 mg arm, and 3.1 cm in the Pulmicort Respules 1 mg arm. Urinary cortisol assessments did not give any information as the assessment could only be completed for 6 subjects and in these subjects there was a wide variability of results. These results suggest that there was possibly a subtle systemic effect of budesonide in this study.

Efficacy in this young patient population is difficult to assess for several reasons, such as the difficulty in making a diagnosis of asthma in the very young, and the challenge to obtain objective measures of efficacy since lung function cannot be measured in the very young age group. Nevertheless, the applicant made a reasonable assessment of efficacy by measures such as nighttime and daytime asthma symptom scores, percentage of symptom free days, investigator global assessment of asthma, treatment failures, study withdrawals, and rescue medication use. In general Pulmicort Respules treatment groups demonstrated trends in greater improvement in subjective parameters (asthma symptom scores, symptom free days, investigator global assessment), but not in the objective parameters (study withdrawals, rescue medication use) with the exception of treatment failures that occurred less frequently in the active treatment groups compared to the

placebo group. Definitive efficacy conclusion cannot be drawn from the study. The applicant is also not making any specific efficacy claim in children between the ages of 6 and 11 months based on this study. The efficacy data does not raise any safety concern on the use of Pulmicort Respules in this patient population.

Pharmacology and Toxicology

There are no outstanding preclinical issues. No preclinical pharmacology or toxicology studies were conducted for Pulmicort Respules in support of this application.

Clinical Pharmacology and Biopharmaceutics

There are no outstanding clinical pharmacology and biopharmaceutics issues. No specific clinical pharmacology studies were conducted for Pulmicort Respules in support of this application.

Data Quality, Integrity, and Financial Disclosure

No DSI audit of clinical study sites was requested or conducted for this supplement. Budesonide is not a new molecular entity, and during the review process of this application no irregularities that would raise question on the data integrity were found. No ethical issues are present. All studies were conducted in accordance with accepted ethical standards. No financial disclosure issues are present. The applicant submitted an acceptable financial disclosure statement and statements of good clinical practice.

Pediatric Consideration

Pulmicort Respules is currently indicated down to the age of 12 months in subjects with asthma, and with this submission the applicant has proposed to update the label to incorporate data on the safety and use of Pulmicort Respules down to the age of 6 months. The applicant has not specifically asked that the indication be lowered. The Division agrees with this position, because asthma is very difficult to diagnose in the very young children and possibly overlaps with other diseases of infancy that manifests as wheezing. Furthermore, efficacy is difficult to establish in the very young children. With this application the pediatric development program for Pulmicort Respules is considered to be complete.

Product Name

The proprietary name of Pulmicort Respules is approved and used by AstraZeneca for this product.

Labeling

AstraZeneca is proposing to add new information to the Pharmacodynamics sub section under Clinical Pharmacology section, and Pediatric Use sub section under Precautions

section of the label. AstraZeneca is not seeking changes in the Indications section of the label. These changes and additions were reviewed by the clinical and statistical review disciplines, and the Division and AstraZeneca have agreed on the final version of the label. The final version of the label describes the effect of Pulmicort Respules on post-ACTH plasma cortisol and on growth velocity, and other relevant findings of the study. The adverse reaction section contains relevant safety findings from the clinical study.

Recommendation and Action

The applicant has submitted results from one study in subjects between the ages of 6 and 11 months on the safety of Pulmicort Respules, and has proposed changes in various sections of the label to incorporate the results of the study. The applicant is not seeking to lower the age of indication. The Division and AstraZeneca have agreed on the labeling changes. The action on this application is therefore an APPROVAL.

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/s/

Badrul Chowdhury
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MEDICAL OFFICER
Div Dir Memo

Clinical Team Leader Review Memorandum

Memorandum to: sNDA 20-929 SE8-013 file
Product: Pulmicort® Respules™ (Budesonide Inhalation Suspension)
Memo Date: February 12, 2003
Memo From: Lydia I. Gilbert-McClain, MD, Clinical Team Leader (Actg)

This memorandum is to document the secondary review of Dr. Curtis Rosebraugh's, Primary Medical Review of the sNDA 20-929 SE8-013 for Pulmicort® Respules™. The study report in this application was submitted in fulfillment of the requirements of the Written Request for pediatric studies for budesonide issued December 14, 1998. The submission is a labeling supplement with proposed changes to the CLINICAL PHARMACOLOGY, Pharmacodynamics and PRECUATIONS, Pediatric Use sections of the label.

OVERVIEW

The NDA for Budesonide Inhalation Suspension (BIS), PULMICORT® Respules™ was originally submitted on November 18, 1997. The proposed labeling indicated the product for use in children with persistent asthma between the ages of 6 months and 8 years. The application was initially given an APPROVABLE action (mainly because of CMC issues) and was later approved on August 8, 2000 for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age. There were very limited safety and efficacy data and very few patients studied between the ages of 6 and 11 months and an indication was not given for patients below 1 year of age.

A Written Request for pediatric studies with budesonide was issued on December 14, 1998, nearly 2 years before the final approval for Pulmicort® Respules™. The Written Request required 2 studies – one with Pulmicort® Respules™ in subjects 6 months to ≤ 1 year and the other with budesonide nasal spray (Rhinocort®). The Sponsor's submission of the study report for Pulmicort® Respules™ completed the requirements of the Written Request for pediatric exclusivity determination and pediatric exclusivity for budesonide was granted on November 12, 2002.

The sponsor submitted proposed labeling changes to the CLINICAL PHARMACOLOGY, Pharmacodynamics, and PRECUATIONS, Pediatric Use sections of the label and is not seeking changes to the INDICATIONS section of the label.

The submission is comprised of one study report No. SD-004-0732 and proposed labeling. The primary objective of the study as set forth in the Written Request was to evaluate the safety of Budesonide Inhalation Suspension (BIS) 0.5 mg and 1.0 mg once daily compared with placebo for the treatment of mild to moderate asthma, or recurrent or persistent wheezing in infants between the ages of 6 and 12 months. The study was not required to be, nor was it powered for efficacy.

A total of 141 pediatric subjects were randomized into the study to receive either BIS 0.5 mg, BIS 1.0 mg, or placebo once daily for 12 weeks. The distribution of subjects in the treatment groups was fairly equal. A total of 117 subjects completed the study. The safety findings will be discussed briefly followed by a brief discussion of efficacy. Please see Dr. Curtis Rosebraugh's primary review for more details if desired. Since the sponsor used the approved marketed product in this study there are no CMC, biopharm, or pharm/tox issues with this application.

Safety

The primary safety variable was adrenal function which was determined by either plasma cortisol levels pre and post-ACTH stimulation, or overnight urinary free cortisol levels. Additional safety assessments included body length (crown – heel length) measured at each study visit, incidence of adverse events, changes in hematology and chemistry laboratory, and oropharyngeal and nasal fungal cultures. Although the overall safety profile of the population was generally similar to what is reported for the pediatric population > 12 months of age, there are a few findings that need to be noted that should be reflected in the label.

Of the 141 subjects randomized, 76 had a basal and post-ACTH stimulation cortisol measurement both at baseline and at Week 12. While the mean values of the three treatment groups did not indicate any difference in adrenal responsiveness, there were 6 subjects in the BIS group and one subject in the placebo group with a post-ACTH plasma cortisol value below the <500 nmol/L cutoff value for normal. Four of the 7 subjects, all in the BIS group had plasma cortisol values near the cutoff value of < 500 nmol/L and two subjects, one in the placebo group and one in the BIS 0.5 mg group had a very low value (109 nmol/L, and 155 nmol/L respectively).

Urinary cortisol assessments were done for only 6 subjects and the wide variability in the results renders those data unsuitable for making assessments about adrenal function.

Also observed in the study, was a dose-dependent decrease in growth velocity as seen by a mean growth velocity of 3.7 cm, 3.5 cm, and 3.1 cm in the placebo, BIS 0.5 mg and BIS 1.0 mg treatment group respectively. A similar result was seen even when the "evaluable population" consisting of only subjects who completed the study to correct for potential "drop out bias" was analyzed. It is important to note that this study was not primarily a growth study and the measurements (crown-heel length) are not gold standard measurements [such as stadiometry] for growth. Therefore, this observation is all the more noteworthy in view of these drawbacks. The finding is not surprising however, since there is a significant body of evidence to support that inhaled corticosteroids can suppress growth. While, the sponsor has language in the label that addresses the effect of inhaled corticosteroids on growth as part of the class labeling for inhaled corticosteroids, the specific findings for this product in this younger population (≤ 12 months of age) need to be reflected in the label.

There were a few adverse events that were reported more frequently in the BIS group compared to placebo: tooth disorder, pharyngitis, nervousness, pneumonia, and urticaria.

Of these events, pharyngitis is currently noted in the label and of the other adverse events, pneumonia (n = 3 in the BIS group) versus 0 in the placebo group is worth noting in the label, in view of the possible association of inhaled corticosteroids with a slightly higher incidence of respiratory infections. Other adverse events in the study were reported with a similar frequency to the placebo group or is currently reflected in the label.

Efficacy

Efficacy was not a primary objective of this study and efficacy in this age group is difficult to establish for several reasons one of which is the difficulty in making a diagnosis of asthma in patients this young, and secondly, the ongoing challenge to obtain objective measures of efficacy since measurements of lung function cannot be done in this age group. The sponsor looked at asthma symptom scores, and Investigator global assessments of asthma, treatment failures, study withdrawals and medication use. There were trends in asthma symptom scores, symptom-free days, and Investigator global assessments that favored the BIS treatment group compared with placebo. The more objective parameters such as withdrawals, and breakthrough medication use, did not show a similar trend although there were less treatment failures in the BIS groups compared to placebo. Firm conclusions on efficacy cannot be made based on these data and they will not be reflected in the label.

Conclusions

This proposed label submitted with this sNDA needs to be revised to reflect the following findings:

1. The abnormal post-ACTH plasma cortisol response seen in 7 subjects inspite of the normal population mean plasma cortisol results. This finding suggests that there are individual subjects within a population that might be more sensitive to exogenous corticosteroid exposure.
2. The dose-dependent decrease in growth velocity should be stated as these data suggest that Pulmicort® Respules™ at these doses can have systemic effects. This is not a criticism of the drug but yet more evidence indicating that inhaled corticosteroids can cause systemic effects and therefore practitioners should always use the lowest effective dose.
3. The number of pneumonias (n = 3) reported for Pulmicort ® Respules™ compared to placebo (n =0) should be stated as this finding is not in the current label.

With these changes the label will more accurately reflect the safety findings seen in the 6-month to 12-month-old patients in this study than what is currently proposed by the sponsor.

Recommendations

I recommend that the application be APPROVED, once all the above labeling changes have been made.

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/s/

Lydia McClain
2/28/03 02:17:02 PM

Badrul Chowdhury
2/28/03 02:50:54 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 20-929/S-013

ADMINISTRATIVE DOCUMENTS
AND
CORRESPONDENCE



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: April 8, 2003

| | |
|-----------------------------------|--|
| To: Chris Blango | From: Colette Jackson |
| Company: AstraZeneca | Division of Pulmonary and Allergy Drug Products |
| Fax number: 302-886-4684 | Fax number: 301-827-5586 |
| Phone number: 302-885-1809 | Phone number: 301-827-5584 |

Subject: NDA 20-929 February 20, 2003, teleconference

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MEMORANDUM OF TELECONFERENCE

DATE: February 20, 2003

APPLICATION: NDA 20-929/ Pulmicort Respules/AstraZeneca

FDA ATTENDEES, DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

Lydia Gilbert-McClain, MD, Acting Clinical Team Leader
Colette Jackson, Project Manager

ASTRAZENECA ATTENDEES AND TITLES:

Christopher Blango, Director, Regulatory Affairs
Liza O'Dowd, MD, Director, Clinical Research
Mike Young, MPH, Regulatory Project Manager

BACKGROUND: The purpose of this meeting is to discuss minor labeling changes in the pediatric submission.

DISCUSSION:

Dr. Gilbert-McClain informed the sponsor that the Agency has reviewed the February 12, 2003, revised pediatric labeling submission and the Agency is in agreement with the changes

Pneumonia was reported in 3 subjects on Pulmicort and 0 in placebo and is not currently listed among the adverse events in the current label. The sponsor questioned if "n" could be included, separating by doses. Dr. Gilbert-McClain indicated this approach seems reasonable. The sponsor stated they will make the suggested changes and fax them in as soon as possible.

Colette Jackson, Minutes Preparer

cc: Original

HFD570/Div. Files

HFD-570/Meeting Minutes files

HFD-570/Jackson

HFD-570/Gilbert-McClain

Drafted by: CCJ/MARCH 20, 2003

Initialed by: Gilbert-McClain/March 20, 2003

final: CCJ/MARCH 27, 2003

MEETING MINUTES

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Colette Jackson
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

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DATE: April 8, 2003

| | |
|---|--|
| To: Chris Blango | From: Colette Jackson |
| Company: AstraZeneca | Division of Pulmonary and Allergy Drug Products |
| Fax number: 302-886-4684 | Fax number: 301-827-5586 |
| Phone number: 302-885-1809 | Phone number: 301-827-5584 |
| Subject: NDA 20-929 February 5, 2003, teleconference | |

Total no. of pages including cover:

Comments:

Document to be mailed: YES XNO

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MEMORANDUM OF TELECONFERENCE

DATE: February 5, 2003

APPLICATION: NDA 20-929/ Pulmicort Respules/AstraZeneca

FDA ATTENDEES, DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS

Badrul A. Chowdhury, M.D., Ph.D., Acting Division Director
Marianne Mann, M.D., Deputy Director
Lydia Gilbert-McClain, MD, Acting Clinical Team Leader
Emmanuel Fadiran, Ph.D., Clinical Pharmacology/Biopharmaceutics Team Leader
James Gebert, Ph.D., Statistical Reviewer
Colette Jackson, Project Manager

ASTRAZENECA ATTENDEES AND TITLES:

Barry Sickles, Executive Director, Regulatory Affairs
Christopher Blango, Director, Regulatory Affairs
Liza O'Dowd, MD, Director, Clinical Research
Michael Young, MPH, Regulatory Project Manager
Mitchell Goldman, Director, Clinical Research
Christopher Miller, MStat, Associate Director, Biostatistics Project Team

BACKGROUND: The purpose of this meeting is to discuss the labeling for the pediatric exclusivity submission.

DISCUSSION:

Dr. Gilbert-McClain referred to [redacted] the February 4, 2003, facsimile sent by the sponsor which included the sponsor's proposed labeling for their pediatric exclusivity submission.

[redacted] The Agency agrees with the use of the wording "7 patients". [redacted]

[redacted]

[redacted] The sponsor indicated that they could omit this, and revise the wording.

[redacted] The Agency would like to see the information in the label. [redacted]

[redacted]

[redacted]

~~_____~~ Also, the wording
~~_____~~ must be omitted. The sponsor questioned if mean
estimates can be added to further explain the findings. The Agency is willing to review the
language used by the sponsor.

Dr. Gilbert-McClain referred t ~~_____~~
~~_____~~ Pneumonia and
pharyngitis have previously occurred in studies with inhaled corticosteroids in the pediatric
population and should be added to the label. The sponsor indicated that pharyngitis was already
in the label, and the Division concurred. The sponsor agreed to add pneumonia.

The sponsor indicated they would respond to the Agency's suggestions as soon as possible with
newly proposed labeling.

Colette Jackson, Minutes Preparer

cc: Original

HFD570/Div. Files
HFD-570/Meeting Minutes files
HFD-570/Jackson
HFD-570/Mann
HDD-570/Chowdhury
HFD-570/Gilbert-McClain
HFD-570/Fadiran
HFD-570/Gebert

Drafted by: CCJ/MARCH 20, 2003

Initialed by: Gilbert-McClain/March 20, 2003

Mann/March 24, 2003

Chowdhury/April 3, 2003

final: CCJ/APRIL 8, 2003

MEETING MINUTES

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

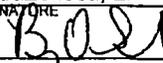
Colette Jackson
4/8/03 11:04:13 AM
CSO

74 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

 X § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

| | | | |
|---|--|--|--|
| Department of Health and Human Services Public Health Service Food and Drug Administration DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS | | Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02 | |
| TO BE COMPLETED BY APPLICANT | | | |
| <p>The following information concerning _____, who participated as <small>Name of clinical investigator</small> a clinical investigator in the submitted study <u>Pulmicort Respule</u> is submitted <small>Name of clinical study</small> in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:</p> | | | |
| <div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;"> <i>Please mark the applicable checkboxes.</i> </div> | | | |
| <p><input type="checkbox"/> any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;</p> <p><input checked="" type="checkbox"/> any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;</p> <p><input type="checkbox"/> any proprietary interest in the product tested in the covered study held by the clinical investigator;</p> <p><input type="checkbox"/> any significant equity interest in the sponsor of the covered study held by the clinical investigator in the sponsor of the covered study.</p> | | | |
| <p>Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.</p> | | | |
| NAME | | TITLE | |
| Barry D. Sickels | | Executive Director Regulatory Affairs | |
| FIRM/ORGANIZATION | | | |
| AstraZeneca, LP | | | |
| SIGNATURE | | DATE | |
|  | | 1/20/02 | |
| Paperwork Reduction Act Statement | | | |
| <p>An agency may not conduct or sponsor, and a person is not required to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection information to:</p> | | | |
| <p>Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857</p> | | | |



MEMO

Internal Memorandum

Clinical Trial Management
Respiratory Therapeutic Area
DCC1-E2342
Telephone 302-885-4121
Facsimile 302-886-5213

DATE: June 24, 2002
TO: Lee Berry, Financial Disclosure Coordinator
FROM: Jillian Crilly, Clinical Research Scientist
SUBJECT: Financial Disclosure – Pulmicort Respules™

_____ responded positively to receiving significant payments from AstraZeneca LP.

_____ was listed as the primary investigator for Pulmicort Respules™ _____ Center _____ and this center enrolled _____ patients into the trial. This trial was a multicenter study, double-blind, placebo-controlled, randomized study; this in combination with the low number of patients recruited by _____ should prevent any bias that possibly could have affected the outcome of the trial.

| | |
|---|--|
| <p>Department of Health and Human Services Public Health Service Food and Drug Administration</p> <p>DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS</p> | <p>Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02</p> |
| TO BE COMPLETED BY APPLICANT | |
| <p>The following information concerning _____, who participated <small>Name of clinical investigator</small></p> <p>as a clinical investigator in the submitted study <u>Pulmicort Respules</u> _____ is <small>Name of clinical study</small></p> <p>submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:</p> <div style="border: 1px solid black; padding: 5px; margin: 10px auto; width: fit-content;"> <p><i>Please mark the applicable checkboxes.</i></p> </div> <p><input type="checkbox"/> any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;</p> <p><input type="checkbox"/> any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;</p> <p><input type="checkbox"/> any proprietary interest in the product tested in the covered study held by the clinical investigator;</p> <p><input checked="" type="checkbox"/> any significant equity interest in the sponsor of the covered study held by the clinical investigator in the sponsor of the covered study.</p> <p>Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.</p> | |
| <p>NAME Barry D. Sickels</p> | <p>TITLE Executive Director Regulatory Affairs</p> |
| <p>FIRM/ORGANIZATION AstraZeneca, LP</p> | |
| <p>SIGNATURE </p> | <p>DATE 1/20/03</p> |
| <p style="text-align: center;">Paperwork Reduction Act Statement</p> <p>An agency may not conduct or sponsor, and a person is not required to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection information to:</p> <p>Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857</p> | |



MEMO

Internal Memorandum

Clinical Trial Management
Respiratory Therapeutic Area
DCC1-E2342
Telephone 302-885-4121
Facsimile 302-886-5213

DATE: June 24, 2002
TO: Lee Berry, Financial Disclosure Coordinator
FROM: Jillian Crilly, Clinical Research Scientist
SUBJECT: Financial Disclosure – Pulmicort Respules™

_____ responded positively to having Significant Equity Interests in AstraZeneca LP.

_____ was listed as the primary investigator for Pulmicort Respules™ _____ Center
_____ and this center enrolled _____ patients into the trial. This trial was a multicenter study,
double-blind, placebo-controlled, randomized study; this in combination with the low number of
patients recruited by _____ should prevent any bias that possibly could have affected the
outcome of the trial.

| | |
|---|--|
| <p style="text-align: center;">Department of Health and Human Services Public Health Service Food and Drug Administration</p> <p style="text-align: center;">DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS</p> | <p>Form Approved: OMB No. 0910-0396 Expiration Date: 3/31/02</p> |
| TO BE COMPLETED BY APPLICANT | |
| <p>The following information concerning _____, who participated as a clinical investigator in the submitted study _____ is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:</p> <p style="text-align: center;"><i>Name of clinical investigator</i></p> <p style="text-align: center;"><i>Name of clinical study</i></p> | |
| <div style="border: 1px solid black; padding: 5px; width: fit-content; margin: 0 auto;"> <p><i>Please mark the applicable checkboxes.</i></p> </div> | |
| <p><input type="checkbox"/> any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;</p> <p><input checked="" type="checkbox"/> any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;</p> <p><input type="checkbox"/> any proprietary interest in the product tested in the covered study held by the clinical investigator;</p> <p><input type="checkbox"/> any significant equity interest in the sponsor of the covered study held by the clinical investigator in the sponsor of the covered study.</p> | |
| <p>Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.</p> | |
| <p>NAME Barry D. Sickels</p> | <p>TITLE Executive Director Regulatory Affairs</p> |
| <p>FIRM/ORGANIZATION AstraZeneca, LP</p> | |
| <p>SIGNATURE </p> | <p>DATE 1/20/03</p> |
| <p style="text-align: center;">Paperwork Reduction Act Statement</p> <p>An agency may not conduct or sponsor, and a person is not required to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection information to:</p> <p style="text-align: center;">Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857</p> | |



MEMO

Internal Memorandum

Clinical Trial Management
 Respiratory Therapeutic Area
 DCC1-E2342
 Telephone 302-885-4121
 Facsimile 302-886-5213

DATE: June 24, 2002

TO: Lee Berry, Financial Disclosure Coordinator

FROM: Jillian Crilly, Clinical Research Scientist

SUBJECT: Financial Disclosure – Pulmicort Respules™
 _____ MD

_____ responded positively to receiving significant payments from AstraZeneca LP.

_____ was listed as the primary investigator for Pulmicort Respules™ _____ Center _____, and this center enrolled _____ patients into the trial. This trial was a multicenter study, double-blind, placebo-controlled, randomized study; this in combination with the low number of patients recruited by _____ should prevent any bias that possibly could have affected the outcome of the trial.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

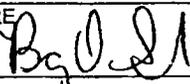
PULMICORT RESPULES

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

| | | |
|------------------------|------------------------|--|
| Clinical Investigators | SEE ATTACHED REPORT(S) | |
| | | |
| | | |

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

| | |
|--|--|
| NAME Barry D. Sickels | TITLE Executive Director Regulatory Affairs |
| FIRM/ORGANIZATION AstraZeneca, LP | |
| SIGNATURE  | DATE 1/20/03 |

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

15 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

 § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

Time Sensitive Patent Information

pursuant to 21 C.F.R. § 314.53

for

NDA 20-929

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

| | |
|-----------------------|-----------------------------------|
| Trade Name: | PULMICORT RESPULES™ |
| Active Ingredient(s): | Budesonide |
| Strength(s): | 0.25 mg/mL; 0.50 mg/mL; 1.0 mg/mL |
| Dosage Form: | Inhalation Suspension |

A. This section should be completed for each individual patent

U.S. Patent Number: 4,787,536

Expiration Date: February 27, 2006

Type of Patent—Indicate all that apply:

1. Drug Substance (Active Ingredient) Y N
2. Drug Product (Composition/Formulation) X Y N
3. Method of Use Y N

- a. If patent claims method(s) of use, please specify approved method(s) of use or method(s) of use for which approval is being sought that are covered by patent: _____

Name of Patent Owner: Aktiebolaget Draco

U.S. Agent (if patent owner or applicant does not reside or have place of business in the US): Astra USA, Inc.

B. The following declaration statement is required if any of the above listed patents have Composition/Formulation or Method of Use claims.

The undersigned declares that the above stated United States Patent Number 4,787,536 covers the formulation of PULMICORT RESPULES™. This product is:

currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

OR

the subject of this application for which approval is being sought.

Signed: 
Date: 11/17/87
Title: Vice President of Regulatory Affairs
Telephone Number: (508) 366-1100, ext. 4739

ITEM 16 DEBARMENT CERTIFICATION**RE: NDA 20-929****Pulmicort Respules® (budesonide inhalation suspension)****Submission of Pediatric Study Report – Pediatric Exclusivity Determination Requested****16.0 Certification Statement**

In response to the requirements of the Generic Drug Enforcement Act of 1992, I hereby certify on behalf of AstraZeneca LP, that we did not use and will not use in connection with this supplemental New Drug Application, the services of any person in any capacity debarred under section 306 (a) or (b).

Sincerely,



Anthony Rogers, Vice President
Regulatory Affairs
AstraZeneca

MEMORANDUM OF TELECON

DATE: November 12, 2002

APPLICATION NUMBER: NDA 20-746/Rhinocort Aqua (budesonide) Nasal Spray
NDA 20-929/Pulmicort Respules

BETWEEN:

Name: Mark DeSiato
Director, Regulatory Affairs, AstraZeneca Pharmaceuticals
Phone: 302-885-1386

AND

Name: Colette Jackson, Project Manager
Division of Pulmonary and Allergy Drug Products, HFD-570

SUBJECT: Pediatric Exclusivity for budesonide

Mark DeSiato was notified of the Pediatric Exclusivity Board's decision to grant pediatric exclusivity for budesonide for NDA 20-746 Rhinocort Aqua Nasal Spray and NDA 20-929 Pulmicort Respules. It was also conveyed that the information will be reflected on CDER's pediatric website and in the monthly update of the Electronic Orange Book.

Colette Jackson
Project Manager

cc:

HFD-570/Divfiles
HFD-570/Anthracite
HFD-570/Purucker
HFD-570/Mann
HFD-570/Chowdhury

Drafted: CCJ/November 13, 2002
Initialed: Barnes/December 12, 2002
Finalized: CCJ/December 12, 2002

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Colette Jackson
12/12/02 01:04:23 PM
CSO

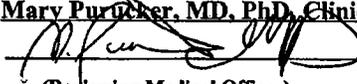
**PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST
PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.**

STUDY 1

Date of Written Request from FDA: 12/22/98. Application Written Request was made to: NDA#20-929
 Timeframe Noted in Written Request for Submission of Studies 09/03/02.
 NDA# 20-929, Supplement #SE8-013, Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
 Sponsor: AstraZeneca
 Generic Name: budesonide nebulizing suspension Trade Name: Pulmicort Respules
 Strength: 1.0 or 0.50 mg per 2mL unit Dosage Form/Route suspension for oral inhalation via jet nebulizer
 Date of Submission of Reports of Studies: 09/03/02.
 Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies): 11/14/02.

| | | |
|--|---|----------------------------|
| Was a formal Written Request made for the pediatric studies submitted? | Y <input checked="" type="checkbox"/> X | N <input type="checkbox"/> |
| Were the studies submitted after the Written Request? | Y <input checked="" type="checkbox"/> X | N <input type="checkbox"/> |
| Were the reports submitted as a supplement, amendment to an NDA, or NDA? | Y <input checked="" type="checkbox"/> X | N <input type="checkbox"/> |
| Was the timeframe noted in the Written Request for submission of studies met? | Y <input checked="" type="checkbox"/> X | N <input type="checkbox"/> |
| If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles? | Y <input checked="" type="checkbox"/> X | N <input type="checkbox"/> |
| Did the studies fairly respond to the Written Request? | Y <input checked="" type="checkbox"/> X | N <input type="checkbox"/> |

SIGNED: Mary Purdy, MD, PhD, Clinical Team Leader, DPADP DATE: 09/30/02


 (Reviewing Medical Officer) 11/12/02

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

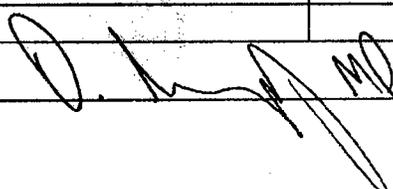
PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity **Granted** **Denied**

Existing Patent or Exclusivity Protection:

| NDA/Product # | Eligible Patents/Exclusivity | Current Expiration Date |
|---------------|------------------------------|-------------------------|
| <u>SEE</u> | <u>ATTACHMENT</u> | |
| | | |
| | | |
| | | |
| | | |

SIGNED



DATE Nov 12, 2002

IV. PEDIATRIC EXCLUSIVITY DETERMINATION CHECKLIST

PART I - TO BE COMPLETED BY THE REVIEWING DIVISION.

Date of Written Request from FDA 12/14/98. Application Written Request was made to: NDA/IND# 20,746.
 Timeframe Noted in Written Request for Submission of Studies 7/31/2002.
 NDA# 20,746 Supplement 009 Choose one: SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8 SLR
 Sponsor AstraZeneca.
 Generic Name budesonide. Trade Name Rhinocort Aqua™.
 Strength 32 mcg. Dosage Form/Route nasal inhaled micronized aqueous suspension.
 Date of Submission of Reports of Studies 9/3/2002.
 Pediatric Exclusivity Determination Due Date (60 or 90 days from date of submission of studies) 12/2/2002.

| | | |
|--|------------|--------------|
| Was a formal Written Request made for the pediatric studies submitted? | Y <u>X</u> | N <u> </u> |
| Were the studies submitted after the Written Request? | Y <u>X</u> | N <u> </u> |
| Were the reports submitted as a supplement, amendment to an NDA, or NDA? | Y <u>X</u> | N <u> </u> |
| Was the timeframe noted in the Written Request for submission of studies met? | Y <u>X</u> | N <u> </u> |
| If there was a written agreement, were the studies conducted according to the written agreement? OR If there was no written agreement, were the studies conducted in accord with good scientific principles? | Y <u>X</u> | N <u> </u> |
| Did the studies fairly respond to the Written Request? | Y <u>X</u> | N <u> </u> |

SIGNED [Signature], M.D.
 (Reviewing Medical Officer)

DATE Nov. 12, 2002

Do not enter in DFS - FORWARD TO PEDIATRIC EXCLUSIVITY BOARD, HFD-960.

PART II - TO BE COMPLETED BY THE PEDIATRIC EXCLUSIVITY BOARD

Pediatric Exclusivity

Granted

Denied

Existing Patent or Exclusivity Protection:

| NDA/Product # | Eligible Patents/Exclusivity | Current Expiration Date |
|---------------|------------------------------|-------------------------|
| <u>SEE</u> | <u>ATTACHMENT</u> | |
| | | |
| | | |
| | | |
| | | |

SIGNED

[Signature]

DATE Nov 12, 2002

Budesonide Patents and Exclusivity

NDA 20-441

| <i>Patents</i> | <i>Expiration Date</i> |
|----------------|------------------------|
| 4668218 | 4/11/06 |
| 4907583 | 3/13/07 |

NDA 20-746

| <i>Patents</i> | <i>Expiration Date</i> |
|----------------|------------------------|
| 6291445 | 4/29/17 |

| <i>Exclusivity</i> | <i>Expiration Date</i> |
|--------------------|------------------------|
| NDF | 10/1/02 |
| M-22 | 10/26/04 |

NDA 20-929

| <i>Patents</i> | <i>Expiration Date</i> |
|----------------|------------------------|
| 4787536 | 2/26/06 |

| <i>Exclusivity</i> | <i>Expiration Date</i> |
|--------------------|------------------------|
| NDF | 8/8/03 |

NDA 21-324

| <i>Patents</i> | <i>Expiration Date</i> |
|----------------|------------------------|
| 5643602 | 7/1/14 |

| <i>Exclusivity</i> | <i>Expiration Date</i> |
|--------------------|------------------------|
| NP | 10/2/04 |

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Grace Carmouze
11/12/02 02:43:55 PM