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 (≤ 12months 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
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Badrul Chowdhury
2/28/03 02:50:54 PM