MEDICAL TEAM LEADER MEMORANDUM

Date: May 30, 2003
To: NDA 20-548, (b)(4) 8-018
From: Eugene J. Sullivan, MD, FCCP
Acting Medical Team Leader
Division of Pulmonary and Allergy Drug Products (HFD-570)
Subject: Secondary medical review of NDA 20-548, (b)(4) 8-018 (GlaxoSmithKline)
(b)(4)

Administrative

This is a (b)(4) supplement for Flovent® (fluticasone propionate) Inhalation Aerosol. Flovent Inhalation Aerosol is currently approved for the maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. (b)(4)

These clinical studies were 12-week safety and efficacy studies of Flovent Inhalation Aerosol in children with asthma aged 24-47 months, and 6-23 months. The Applicant is not seeking to extend the indication to these younger age groups.

The two studies submitted in this Application were performed in partial response to a Written Request (WR) for pediatric studies, which the Agency issued on June 25, 1999, and amended on May 21, 2001, and October 25, 2001. The WR included a total of seven studies related to the fluticasone propionate moiety. In addition to the two studies submitted in this application, the WR included four studies of fluticasone propionate topical (Cutivate®), and one study of fluticasone propionate nasal spray (Flonase® Nasal Spray). Study reports from these additional five studies have previously been submitted to the Agency. On February 25, 2003, the Pediatric Exclusivity Board determined that the Applicant had fulfilled the requirements of the Written Request, and pediatric exclusivity was granted.

Chemistry, Manufacturing, and Controls

Flovent Inhalation Aerosol is a CFC-containing MDI that is currently approved for marketing. This Application did not contain or require new CMC information related to the drug product. However, the Written Request instructed the Applicant to "characterize the dose delivery from the inhaler with two different US-marketed spacers in *in vitro* studies." In response to this instruction, the Applicant performed a (b)(4) study of Flovent Inhalation Aerosol alone, and with three different spacer devices (Optichamber, Aerochamber, and Aerochamber Plus), with the facemasks removed. (b)(4)

Pharmacology, Toxicology and Biopharmaceutics

No new preclinical pharmacology or toxicology studies were conducted in support of this application.

Pharmacokinetic data from both clinical studies raised significant concern regarding the conduct of the studies and the integrity of the data. In each study, a single blood sample was taken from each patient on the last day of treatment. Samples were taken at one of four time intervals: pre-dose (-1 hour to 0 hrs), 0.25 to 2.5 hours post-dose, 3 to 8 hours post dose, and 9-11 hours post dose. Fluticasone propionate (FP) was detected in 13 of the 107 samples from patients randomized to placebo treatment. This included 10 patients from 10 study sites in Study FMS30058 and 3 patients from 2 study sites in Study FMS30059. The FP concentrations in the placebo patients were comparable to those in the patients randomized to active treatment. The Applicant was unable to explain this finding. One possible explanation, which cannot be excluded, is that some patients who were randomized to placebo treatment actually received active treatment. The observation that significant percentages of patients randomized to active treatment had undetectable FP concentrations (49% in the FP44 group, and 31% in the FP88 group) further complicates the picture. Given that patients treated with active drug may have undetectable FP concentrations, it is possible that the number of patients in the placebo group who may have received active drug might exceed the thirteen who were identified by pharmacokinetic sampling. Likewise, it is also possible that an unknown number of patients randomized to active treatment who had undetectable FP concentrations may

have received placebo rather than active treatment. The finding of FP concentrations in samples from placebo patients might possibly be explained by circumstances other than misallocation of study drug (e.g. mismanagement of blood samples, or failure of the assay methodology). Nonetheless, the results of the study must be interpreted in light of the very real possibility that an unknown number of subjects in each treatment group might have received incorrect treatment.

Clinical Studies

The two clinical studies (FMS30058 and FMS30059) were nearly identical, with the important exceptions of the ages of the populations studied, and the use of spacer devices. Both were randomized, double-blind, placebo-controlled, 12-week safety and efficacy studies in pediatric patients with asthma, using Flovent 44mcg Inhalation Aerosol, which delivers 44mcg of fluticasone propionate ex-actuator. In both studies, pharmacokinetic data were collected using a sparse sampling technique. Study FMS30058 enrolled patients aged 24 to 47 months of age, and Study FMS30059 enrolled patients aged 6 to 23 months of age. Study FMS30058 utilized two different spacer devices, the Aerochamber and the Optichamber. Study FMS30059 utilized only the Aerochamber spacer device.

Study FMS30058

This was a multicenter, randomized, double-blind, parallel group, placebo-controlled, 12 week study of Fluticasone Propionate 44mcg BID (FP44) and 88mcg BID (FP88) delivered via CFC MDI and a valved holding chamber with facemask in subjects with asthma aged 24 to 47 months. Two different holding chambers (spacers) were used, the Aerochamber and the Optichamber. Inclusion criteria included a documented history of symptomatic asthma, regular maintenance therapy other than systemic corticosteroids for the preceding 6 weeks (or use of short-acting beta-agonist at least twice per week over the preceding 3 weeks), and at least 2 episodes of increased symptoms requiring medical attention and pharmacotherapy within the preceding 12 months. At randomization, patients were also required to exhibit a specified degree of asthma symptoms and albuterol use during the screening period.

The primary efficacy endpoint was the change from baseline in daytime and nighttime (daily) asthma symptom scores to Endpoint, which was defined as the last two weeks of diary data prior to end of study, asthma exacerbation, or study withdrawal. The daily asthma symptom score was the average of daytime and nighttime asthma symptom scores using a 0-3 scale that described a composite of symptoms including wheeze, cough, and shortness of breath. Scores were determined by the parent/guardian. Secondary efficacy variables included symptom-free days, symptom-free and albuterol-free days, daytime and nighttime asthma symptom scores, time to treatment failure (asthma exacerbation), albuterol use, and diary recorded morning peak flow (AM PEF) measurements.

Efficacy findings must be interpreted in light of the possible misallocation of study drug described in the section above (Pharmacology, Toxicology, and Biopharmaceutics). Misallocation of study drug might be expected to diminish the apparent efficacy of a

study drug. In addition, statistical comparisons of each dose versus placebo were performed, without appropriate adjustment for multiplicity. In this study, FP88, but not FP44, was statistically superior to placebo on the primary endpoint, the change from baseline to Endpoint in the daily symptom score. Secondary efficacy endpoints were generally consistent with these results. In the FP44 group, the change from baseline in the daily symptom scores were numerically superior to placebo at most treatment weeks, but these differences reached statistical significance ($p<0.05$) at Weeks 5 and 6 only. In the FP88 group, the change from baseline in the daily symptom scores were numerically superior to placebo at all treatment weeks, but these differences reached statistical significance at Weeks 1, 2, and 6 only. The percentages of symptom-free days and symptom- and albuterol-free days was statistically higher in the FP88 group as compared to placebo, both at Endpoint and for the entire 12-week treatment period. The percentages of symptom-free days and symptom- and albuterol-free days were statistically higher in the FP44 group as compared to placebo, for the entire 12-week treatment period, but not at Endpoint. Asthma exacerbations were fewer in the FP88 (n=13) and the FP44 (n=14), as compared to placebo (n=24). Kaplan-Meier analyses of time to first asthma exacerbation indicated that FP88, but not FP44, was superior to placebo. Due to the young age of the patients, measurements of morning peak flow (AM PEF) was only possible in approximately 25% of patients. The AM PEF results showed numerical, but not statistical superiority of active treatment over placebo.

Safety assessments were adverse events, vital signs, physical examination (including oropharyngeal and nasal passage examinations), linear growth measurements, clinical laboratory tests, oropharyngeal and nasal passage cultures for Candida, and 12-hour overnight urine cortisol measurements.

Safety findings must be interpreted in light of the possible misallocation of study drug described in the section above (Pharmacology, Toxicology, and Biopharmaceutics). Misallocation of study drug might be expected to obscure potentially important differences between placebo and active study drug. Therefore, the absence of any particular safety signal must be interpreted with caution. However, safety signals that are identified would be relevant, although the magnitude of the apparent treatment effect might be diminished. In this study, the incidence of pharyngitis/throat infection was higher in the FP88 (3%) and FP44 (6%) groups than in placebo (0%). The incidences of candidiasis of the mouth/throat and nasal cavity were slightly higher in the FP88 group (5% and 2%, respectively) than in the placebo group (2% and 0%, respectively). Although no statistically significant effect was seen for growth velocity, there was a dose-related numerical reduction in growth velocity in the active treatment groups (1.7 mm/12 weeks in the FP44 group [p=0.246], and 2.4 mm/12 weeks in the FP88 group [p=0.095]).

Study FMS30059

This was a multicenter, randomized, double-blind, parallel group, placebo-controlled, 12 week study of Fluticasone Propionate 44mcg BID (FP44) and 88mcg BID (FP88) delivered via CFC MDI and a valved holding chamber with facemask in subjects with

asthma aged 6 to 23 months. The Aerochamber Plus holding chamber (spacer) was used. Safety and efficacy evaluations were identical to those used in Study FMS30058, with the exception that, due to the young age of the patients, PEF measurements were not obtained.

Efficacy findings must be interpreted in light of the possible misallocation of study drug described in the section above (Pharmacology, Toxicology, and Biopharmaceutics). Misallocation of study drug might be expected to diminish the apparent efficacy of a study drug. In addition, statistical comparisons of each dose versus placebo were performed, without appropriate adjustment for multiplicity. In this study, neither of the active treatment groups was statistically superior to placebo on the primary endpoint, the change from baseline to Endpoint in the daily symptom score. Numerically, the FP88 and placebo groups were comparable, and both were numerically superior to the FP44 group for this variable. Secondary efficacy endpoints were generally consistent with these results. The percentages of symptom-free days and symptom- and albuterol-free days were similar in all three groups. Asthma exacerbations were only slightly fewer in the FP88 (n=6) than in the FP44 (n=14) and placebo (n=10) groups. Kaplan-Meier analyses of time to first asthma exacerbation did not reveal statistically significant differences between groups.

Safety findings must be interpreted in light of the possible misallocation of study drug described in the section above (Pharmacology, Toxicology, and Biopharmaceutics). Misallocation of study drug might be expected to obscure potentially important differences between placebo and active study drug. Therefore, the absence of any particular safety signal must be interpreted with caution. However, safety signals that are identified would be relevant, although the magnitude of the apparent treatment effect might be diminished. In this study, the incidences of upper respiratory tract infection and ear, nose, and throat infection were actually higher in the FP44 group (37% and 41%, respectively) than in either the placebo group (30% and 26%), or the FP88 group (26% and 22%). There were no differences between groups in regard to the incidences of candidiasis of the mouth/throat. No treatment effect on growth velocity was evident.

Efficacy Assessment

Efficacy findings must be interpreted in light of the possible misallocation of study drug described in the section above (Pharmacology, Toxicology, and Biopharmaceutics). Specific efficacy findings from each study are discussed above. (b) (4)

Safety Assessment

Safety findings must be interpreted in light of the possible misallocation of study drug described in the section above (Pharmacology, Toxicology, and Biopharmaceutics). Specific safety findings from each study are discussed above. (b) (4)

Recommendation

(b) (4)

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/s/

Eugene Sullivan
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MEDICAL OFFICER