Clinical Pharmacology and Biopharmaceutics Summary

NDAs: 20-548 Serial # SE8-018	
Sponsor:	GlaxoSmithKline.
Type of Submission:	Pediatric Exclusivity/ Labeling
Indications:	Asthma/Allergic Rhinitis
Reviewer:	Sayed (Sam) Al Habet, R.Ph., Ph.D.
Pharmacometrics	He Sun, Ph.D., CBS
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Date of Submission:	December 13, 2002

1. Executive Summary

The active component of FLOVENT Inhalation Aerosol is fluticasone propionate (FP), a glucocorticoid that is approved for the maintenance treatment of asthma as prophylactic therapy. It is also indicated for patients requiring oral corticosteroid therapy for asthma. FLOVENT inhalation aerosol is pressurized, metered-dose aerosol unit intended for oral inhalation only.

This submission is part of the Agency's Written Request dated June 25, 1999 requesting submission of pediatric information for Flovent Inhalation Aerosol. A population pharmacokinetic (pop PK) approach was used to determine the PK of FP in pediatric population. The safety of Flovent Inhalation Aerosol delivered through either Optichamber® or Aerochamber® with a face mask to children was studied in 2 double-blind, parallel-group, placebo-controlled, 12-week clinical trials. The first study was in children of 24-47 months of ages (Study FMS30058) and the second study was in children with age group ranging from 6 months to 23 months (Study FMS30059). A single blood sample was withdrawn from each subject at a randomized sampling time point ranging from 0 to 11 hours post inhalation of morning doses of either 44 mcg or 88 mcg of Flovent Inhalation Aerosol.

FP was detected in 13 subjects who were treated with placebo. The FP plasma concentration in these thirteen placebo treated subjects ranged from 11.2 to 135 pg/ml with a mean concentration of 40.5 pg/ml. These concentrations are within the range observed in FP treated group. The sponsor did not provide an adequate explanation for this observation thus making the reliability of the PK data questionable.

FP plasma concentrations were below the detectable levels in 49% and 31% of samples collected after oral inhalation of 44 mcg and 88 mcg doses, respectively. Overall, FP concentrations following 88 mcg dose were higher than 44 mcg dose. Concentrations were highest at 2.5 hours post dose. There was a high variability in FP plasma concentration which ranged from approximately 10 pg/ml to 450 pg/ml following 44 mcg and 88 mcg doses. For comparison, according to the current Flovent label the FP plasma concentration in adult subjects following 880 mcg inhaled dose ranges from 100 pg/ml to 1000 pg/ml. Considering the differences in study design, doses, and methodology the concentration of FP in children is not greater than in adult.

The relationship between FP systemic exposure and FP pharmacodynamics (PD) in terms of FP efficacy (change in morning and evening asthma scores, use of albuterol, symptoms free days) and safety (growth as in change in height, urinary cortisol) was explored but no relationship was found. The main reason for lack of PK/PD relationship is that inhaled FP formulations deliver the drug directly to the site of action (lungs) where it exerts its local effect. While FP systemic exposure was found to increase with height, other measures of growth did not affect this exposure. Ethnicity was also found to be a covariate, but interpretation was limited due to the small number of individuals. Therefore, the inclusion of this information in the label is not recommended

The collection of a single blood sample from each subject was not an optimal approach for Pop PK analysis. This approach did not allow for adequate determination of individual subject's PK parameters and subsequently for PK/PD analysis.

RECOMMENDATION:
The clinical pharmacology section of the submission is unacceptable to the Office of Clinical Pharmacology and Biopharmaceutics because of the major Data Quality and Integrity issues observed in the study reports.

Reviewer
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