OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

BPCA SUMMARY REVIEW

NDA:	21-078/SE8-006
Submission date:	May 30, 2003
Drug Substance:	250 mg atovaquone/100 mg proguanil (adult) 62.5 mg atavoquone/25 mg proguanil (pediatric)
Brand name:	MALARONE® Tablets
Applicant:	GlaxoSmithKline
Type of submission:	Pediatric Supplemental NDA

1. EXECUTIVE SUMMARY

1.1 Recommendation

The office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation III (OCPB/DPE III) has reviewed the NDA 21-078, Supplement 006 for the use of MALARONE® Tablets for treatment of acute malaria for pediatric patients. The population pharmacokinetic (PPK) analysis performed in this sNDA is acceptable for pediatric patients with body weight >10 kg. However, the PPK information for pediatric patients with body weight ≤10 kg is inadequate and should not be included in the label.

1.2 Phase IV Commitments

No Phase IV studies are requested.

2. SUMMARY OF CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS FINDINGS

MALARONE® is currently approved for the prevention of malaria in adults and pediatric patients and for the treatment of acute malaria in adults. In adults, one MALARONE® tablet (250 mg atovaquone/100 mg proguanil hydrochloride) per day is recommended for prevention of malaria and 4 malarone tablets as a single dose daily for 3 days is recommended for treatment of acute malaria. A pediatric tablet formulation containing a fixed dose of atovaquone and proguanil (62.5 mg atovaquone/25 mg proguanil hydrochloride) was developed for administration to pediatric subjects.

This current submission is a supplement to the MALARONE® NDA for use in pediatric patients for the treatment of acute malaria. The proposed doses in pediatric patients for the new indication of treatment of acute malaria as well as for the approved indication for prevention of malaria are shown in the following table:

Bodyweight	Treatment	Prevention
5-8 kg	125 mg/50 mg QD x 3 Days (2 Pediatric Strength Tablets)	No Dosage Recommendation
9-10 kg	187.5 mg/75 mg QD x 3 Days (3 Pediatric Strength Tablets)	No Dosage Recommendation
11-20 kg	250 mg/100 mg QD x 3 Days (1 Adult Strength Tablet)	62.5 mg/25 mg Single Daily Dose
21-30 kg	500 mg/200 mg QD x 3 Days (2 Adult Strength Tablets)	125 mg/50 mg Single Daily Dose
31-40 kg	750 mg/300 mg QD x 3 Days (3 Adult Strength Tablets)	187.5 mg/75 mg Single Daily Dose
>40 kg	1000 mg/250 mg QD x 3 Days (4 Adult Strength Tablets)	250 mg/100 mg Single Daily Dose

The sponsor conducted a population pharmacokinetic (PPK) analysis by pooling data from 9 clinical studies that included 4 studies in adults and 5 studies in pediatric patients. The objectives of the PPK analysis were as follows:

- describe the pharmacokinetics of atovaquone and proguanil in children and adult subjects with either acute *P. falciparum* malaria or at risk of developing P. *falciparum* infection;
- assess the effect of covariates (e.g., weight, age, race and gender) and concomitant therapy with other anti-malarial agents (for atovaquone only) on the pharmacokinetics of atovaquone and proguanil;
- assess the magnitude of inter-subject and residual variability on the pharmacokinetics of atovaquone and proguanil.

The PPK analysis was performed using atovaquone and proguanil concentration - time data from 783 and 673 subjects, respectively. A one-compartment model was selected for both atovaquone and proguanil and was supported by previous data. Estimates of atovaquone and proguanil apparent clearance (CL/F), apparent volume of distribution (V/F), and half-life ($T_{1/2}$) were determined from the PPK analysis. However, no post-hoc estimates of systemic exposure (i.e., AUC; Cmax) to either atovaquone or proguanil were determined.

The pertinent findings obtained from the analysis are described below.

Atovaquone:

- The apparent clearance of atovaquone (CL/F) was affected by the patients' body weight, race, gender and co-administration with tetracycline.
  - A power relationship between CL/F and body weight was demonstrated
    Africans: CL (L/hr) = $0.135 \cdot WT^{0.783}$
    Oriental/Malaysians: CL/F (L/hr) = $0.350 \cdot WT^{0.783}$
  - CL/F in African patients was significantly lower as compared to Oriental/Malaysian patients (i.e., reduction of approximately 60%; p

<0.005). For patients with the same body weight, the CL/F in Oriental/Malaysians is 2.6-times the CL/F in Africans
  - CL/F in females was 12.9% lower as compared to males
  - CL/F in patients receiving atovaquone concomitantly with tetracycline was 52.9% higher as compared with patients who did not receive tetracycline

- The apparent volume of distribution for atovaquone (V/F) increased linearly as a function of body weight across all patient groups: V/F=(8.83 L/kg • WT).

- The changes in CL/F and V/F for these patients resulted in an overall incremental increase in the half-life ($T_{1/2}$) of atovaquone with the increase in body weight from 10 to 80 kg. The $T_{1/2}$ estimates in the Oriental/Malaysian patients ranged from approximately 30 to 45 hr (~1 to 2 days). However, the $T_{1/2}$ estimates in the African patients were substantially prolonged as compared to the Oriental/Malaysian patients and ranged from approximately 74 to 116 hr (~3 to 5 days).

- Based on these differences in CL/F and $T_{1/2}$ estimates between the African and Oriental/Malaysian patients in this PPK analysis, although the sponsor did not determine post-hoc estimates of systemic exposure (i.e., AUC), it is expected that the systemic exposure to atovaquone would be higher in African patients given the same body weight-based dose.

Proguanil:

- The apparent clearance (CL/F) for proguanil was affected by body weight and race
  - A power relationship between CL/F and body weight was demonstrated, i.e., Africans: CL (L/h) = $3.43 \cdot WT^{0.743}$.
  - Compared to African patients, the CL/F values were 19.5% higher in Orientals and 23.2% lower and Malaysians, respectively.

- Significantly lower estimates of apparent volume of distribution (V/F) in patients aged ≤15 years was demonstrated, as compared to those >15 years of age
  - age ≤15 years old: V/F=339 (L)+11.2 (L/kg)·WT
  - age >15 years old: V/F=1270 (L)+11.2 (L/kg)·WT

3. OVERALL CONCLUSIONS

- The pharmacokinetics of MALARONE® in pediatric patients with body weight ≤10kg could not be adequately defined from this population pharmacokinetic analysis for the following reasons:
  (a) Only one study (Study 30013) enrolled pediatric patients with bodyweight ≤10 kg (age range from 3 months to 43 months). In addition, only one blood sample was collected from each subject in this study. Thus, the PK parameter estimates (i.e., CL/F; V/F) for these patients are uncertain

because one sample/patient would not allow a separate estimation of inter-subject and residual variability.

(b) Because of (a), it appeared that the patients with body weight ≤10 kg provided limited information on covariate model building. Specifically, the body weight effect on CL/F appears to be actually driven by the data from patients whose body weights were >10 kg.

- The population pharmacokinetic analysis suggested that for pediatric patients with body weight above 10 kg, the reduction in CL/F for Africans might result in an expected increase in the atovaquone systemic exposure in Africans as compared to Oriental/Malaysian patients. However, the systemic exposure to proguanil between African and Oriental/Malaysian patients would be expected to be similar. Even though systemic exposure to atovaquone and proguanil would be expected to be different between African and Oriental/Malaysian patients, no dose adjustment is recommended for African patients or other ethnic groups. However, the efficacy and safety observed in African patients can not be extrapolated to Oriental/Malaysian patients or vice-versa, since it would be expected that the systemic exposure to MALARONE® between African and Oriental/Malaysian patients would be different.

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