CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Paxil ® (Paroxetine) **PRIMARY REVIEWER**: Andre Jackson
NDA: 20-031 SE5-037 **TYPE:** Pediatric supplement (7-17 years)
FORMULATION: Tablet **STRENGTH:** 10, 20, 30 mg
APPLICANT: Glaxo SmithKline **SUBMISSION DATES:** 4-11-02
7-3-02
8-8-02
INDICATION: Obsessive Compulsive Disorder(OCD) or Depression
Generic Name: Paroxetine

1.**EXECUTIVE SUMMARY**

The sponsor has conducted two clinical studies (one each in OCD and depressed pediatric patients). A pharmacokinetic study was done with Paxil in 62 pediatric depressed or OCD patients (27 children and 35 adolescents) aged 7-11 years and 12-17 years respectively (Study no. 715). Paxil is metabolized by CYP2D6 and has phenotypically extensive metabolizers (EM) and poor metabolizers (PM) within the population. The current study population was found to consist mainly of EM subjects. The study was conducted as a dose-rising study involving 10 mg/day, 20 mg/day and 30 mg/day dosing for 14 days with steady-state samples taken on day 14 from 0-24 hrs for each dose.

This Clinical Pharmacology/Biopharmaceutics review will evaluate whether the applicant has adequately described the pharmacokinetics of Paxil in the pediatric population and if the pharmacokinetics of Paxil are similar in the pediatric population and in adults.

Adult steady-state data obtained from the original NDA were compared to the current pediatric data. Adult subjects ranged in age from 19-56 yr. Children and adolescents received doses of 10 mg/day, 20 mg/day and 30 mg/day while adult doses were 20 mg/day and 30 mg/day.

Children had a larger Cmax (34-51%) and AUC(0-24)(23-40%) at each dose compared to adolescents. CL/F was also lower in children compared to adolescents. Children's Cmax values at 20 mg were 52% higher than adults while children's AUC(0-24) values were 44% higher than adults. The only significant gender difference was for weight corrected clearance in children (1.6 times higher in males than females) at the 20 mg/day dose [i.e., 0.49 (L/hr)/kg for females and 0.81 (L/hr)/kg for males].

Based upon these findings the sponsor recommends that the starting dose in children should be one-half of the 20 mg initial dose in adults.

There were larger differences in Cmax, AUC(0-24), Cl/Fand CL/F_w between male children and male adults than between female children and female adults. AUC(0-24) and Cmax at the 20 mg dose were 57% and 66% higher for male children than male adults. However, female children's AUC(0-24) and Cmax were only 19% and 23% greater, respectively than those for adult females.

The sponsor's proposed label changes of the currently approved label relate to inclusion of information related to special populations. The Office of Clinical Pharmacology and Biopharmaceutics (OCPB) recommends some revisions of the proposed text.

1.1 Recommendation: The pharmacokinetic studies provided in this pediatric supplement for Paxil submitted to the Division of Neuropharmacological Drug Products to fulfil the pediatric written request provide an understanding of the pharmacokinetics of Paxil in pediatric patients between the ages of 7 and 17 years, inclusive. This submission is acceptable from the OCPB perspective.