**Clinical Pharmacology and Biopharmaceutics Review**
**BPCA Summary Review**

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| Product (Generic Name): | Mixed salts of a single entity amphetamine product |
| Product (Brand Name): | Adderall XR |
| Dosage Form: | Extended release capsules |
| Dosage Strength: | 5, 10, 15, 20, 25, 30 mg |
| NDA: | 21-303 (SE5-009) |
| NDA Type: | Supplement for ADHD in adolescents in response to FDA Pediatric Written Request Letter |
| Submission Date: | 9/17/04 |
| Sponsor: | Shire |
| OND Division: | HFD-120 |

**Executive Summary**

Adderall XR capsules have been approved for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children (6- 12 years) and adults. This sNDA provides support to change the current Adderall XR prescription labeling to include an indication for treatment in adolescents age 13 – 17 years, to include once daily dosage of up to 20 mg/day.

The sNDA included a single dose pharmacokinetic study in adolescents with doses up to 40 mg in adolescents ≤ 75 kg/165 lbs or up to 60 mg in adolescents > 75 kg/165 lbs, one randomized, double blind, placebo controlled study to assess the safety and efficacy in doses up to 60 mg/day for adolescents with ADHD and one long term safety extension study.

The pharmacokinetic study (Study SLI381.110) was an open label, single dose, 3-treatment, 3-period, randomized, crossover, trial. The primary cohort included 17 adolescents (12 males and 5 females) with ADHD, weighing less than or equal to 75 kg/165 lbs. Each of the groups in the cohort received a single oral dose of 10, 20 or 40 mg Adderall XR after an overnight fast in period 1. Then, they were crossed over to the alternate treatment after a 7-day washout period. Six adolescents with ADHD weighing > 75 kg/165 lbs enrolled in a secondary cohort. Each of the groups in the 2$^{nd}$ cohort received single oral dose of 20, 40 or 60 mg Adderall XR after an overnight fast in period 1. Then, they were crossed over to the alternate treatment after 7-day washout period.

The overall conclusions from the pharmacokinetic study in adolescents were:

1) The pharmacokinetics of d- and l-amphetamine after administration of Adderall XR to adolescents (13 – 17 years) weighing ≤ 75 kg/165 lbs were linear between 10 to 40 mg

2) The pharmacokinetics of d- and l-amphetamine after administration of Adderall XR to adolescents (13 – 17 years) weighing > 75 kg/165 lbs were linear between 20 to 60 mg

3) The pharmacokinetics of d- and l- amphetamine after administration of Adderall XR were similar in males and females

4) Differences in pharmacokinetics were observed between pediatric patients (6- 12 years) and adolescents (13 – 17 years), pediatric patients and adults. There were no significant differences in the pharmacokinetics between adolescents and adults.

5) Covariate analysis using data from children, adolescents and adults indicated that body weight primarily accounted for apparent differences in pharmacokinetics. Exposure (AUC and Cmax) decreased with increases in body weight.

**Recommendation**

From a Clinical Pharmacology and Biopharmaceutics perspective, this sNDA is acceptable with the labeling recommendations suggested by the reviewer.

The sponsor's proposed dosing recommendations for the adolescent population are acceptable from a pharmacokinetics perspective provided the medical reviewer from a clinical perspective agrees that it is a safe and effective dose.

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