

Clinical Pharmacology/Biopharmaceutics Review

BPCA Summary Review

PRODUCT (Generic Name):	Methylphenidate HCl
PRODUCT (Brand Name):	CONCERTA
DOSAGE FORM:	Extended Release Tablets
DOSAGE STRENGTHS:	18, 27, 36 and 54 mg
NDA:	21,121 (SE1-008)
NDA TYPE:	Supplement for ADHD in adolescents in response to FDA Pediatric Written Request Letter
SUBMISSION DATE:	9/5/03, 9/15/03, 10/13/03
SPONSOR:	McNeil
OND DIVISION:	HFD 120

EXECUTIVE SUMMARY

CONCERTA is currently indicated in the United States for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) with a maximum daily dose of 54 mg in children ages 6-12 years. This sNDA provides support to change the current CONCERTA prescription labeling information to include an indication for treatment in adolescents age 13-17 years, to include once-daily dosage of up to 72 mg/day for adolescents, and to update various sections of the labeling with data included in this submission.

This sNDA includes a multiple dose pharmacokinetic study in adolescents with doses up to 72 mg, one randomized controlled clinical study of CONCERTA to assess safety and efficacy in doses up to 72mg/day in adolescents with ADHD and two long term safety studies at doses up to 54 mg.

The multiple dose pharmacokinetic study (Study 12-001) of a 6 day duration was conducted in 26 healthy adolescents with ADHD (ages 13-17), consisting of 19 males

and 7 females. The number of subjects enrolled at the 18, 27, 36, 54 and 72 mg doses were 1, 1, 10, 8 and 6 respectively. Doses were chosen based on the dose prescribed by the subject's personal physician.

The overall conclusions from the pharmacokinetic study in adolescents were:

- The plasma concentration-time profiles of d- and total methylphenidate in adolescents were similar to the unique ascending profiles observed in previous studies with CONCERTA® in adults and children. These profiles showed the rapid increase in concentrations over the first hour due to the immediate-release overcoat followed by gradual ascending concentrations over the next six hours due to the OROS® osmotic core.
- The pharmacokinetics of methylphenidate in adolescents were linear with dose up to 72 mg.
- In cross study comparisons the CL/F of total methylphenidate in children, adolescents and adults were 243, 384 and 497 L/h respectively, showing an increase of 58% in adolescents and 104% in adults compared to children. The weight normalized CL/F in these populations were 6.58, 6.60 and 7.31 L/h/kg respectively.
- In the covariate analyses using pooled data from children, adolescents, and adults (historical studies), there were some statistically significant findings. Body weight had a significant effect on CL/F and Vz/F for both d- and total methylphenidate. A 10 kg increase in weight resulted in a 66.9 L/h increase in CL/F for total methylphenidate and a 22.4 L/h increase in CL/F for d-methylphenidate. A 10 kg increase in weight resulted in a 441 L increase in Vz/F for total methylphenidate and a 104 L increase in Vz/F for d-methylphenidate.
- The effect of age using pooled data from children, adolescents, and adults was investigated on weight-normalized CL/F and Vz/F so as not to confound the effect of age with differences in body size. There was a statistically significant age effect on these weight-normalized CL/F and Vz/F and T_{1/2} for total methylphenidate, which included data for children, adolescents, and adults. However, there was no significant age effect on any parameter for d-methylphenidate, which included data for only adolescents and adults. This analysis showed that the weight-normalized CL/F for total methylphenidate increased slightly with age. A 10-year increase in age resulted in a 0.6 L/h/kg increase in weight-normalized CL/F for total methylphenidate. A 10-year increase in age resulted in a 5.7 L/kg increase in weight-normalized Vz/F for total methylphenidate.

RECOMMENDATION

From a Clinical Pharmacology/Biopharmaceutics perspective this sNDA is acceptable with the labeling changes suggested by the reviewer.

The sponsor's proposed dosing recommendations for the adolescent population are acceptable from a pharmacokinetics perspective provided the 72 mg dose is evaluated to

be safe by the Medical Reviewer from a clinical perspective in an adequate number of subjects.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Ramana S. Uppoor
2/13/04 11:25:15 AM
BPCA Clin. Pharm. Summary