CLINICAL PHARMACOLOGY EXECUTIVE SUMMARY

NDA: 20-632 SE5 021	Submission Date(s): 21 June 2004 and November 4, 2004
Brand Name	Meridia®
Generic Name	Sibutramine hydrocholoride monohydrate capsules
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Abbott Laboratories
Relevant IND(s)	27,624 (obesity); 59,162 (Binge-Eating Disorder), 57,236 (Aid to Smoking Cessation)
Submission Type	Prior Approval Supplement: Pediatric Exclusivity and Labeling
Formulation; Strength(s)	Capsule; 5, 10, and 15 mg
Indication	Obesity

The studies performed have met the Written Request and pediatric exclusivity is granted.

In Written Request Amendment #2 dated Dec. 17, 2003, the study design was stated as "A pharmacokinetic study at doses of 10 mg and 15 mg should be conducted in 12 to 16 year old obese adolescents. This study can be conducted as an appropriate subset of the clinical study using sparse sampling, or as a conventional single-dose pharmacokinetic study supplemented with additional data (trough plasma concentrations at steady-state) in a large group of subjects within a clinical efficacy study." Under study evaluations, it was indicated that "Relevant pharmacokinetic parameters for sibutramine and its active metabolites should be calculated. Tanner stages for the patients in the pharmacokinetic study must be recorded and provided in the study report".

The sponsor conducted a conventional single dose (15 mg) pharmacokinetic study in 12 to 16 year old obese adolescents (Study SB240) and provided trough plasma concentrations at steady-state in a subset of 91 patients within a clinical efficacy trial (Study SB238). The sponsor calculated pharmacokinetic parameters for sibutramine and its active metabolites M1 and M2. Tanner states for the patients in the PK study was recorded and provided in the submission.

Following the oral administration of a single dose of 15 mg sibutramine in obese adolescents, sibutramine was rapidly absorbed with Tmax of 1.3 hours and underwent extensive first-pass metabolism with CL/F of 2071 L/h. Sibutramine was rapidly eliminated with a half-life of 1.6 hours. The active metabolites M1 and M2 were formed rapidly with Tmax of approximately 3 hours. The harmonic mean half-lives of M1 and M2 were 5.2 and 13.4 hours, respectively. The geometric means for Cmax and AUC_{0-t} of M1 in obese adolescents were 3.22 ng/mL and 22.1 ng.h/mL, respectively. The geometric means for Cmax and AUC_{0-inf} of M2 in obese adolescents were 6.19 ng/mL and 90.5 ng.h/mL, respectively. The geometric means for Cmax and AUC_{0-t} of M1 in obese adults obtained from previous study SB3813 were 3.68 ng/mL and 21.2 ng.h/mL, respectively. The geometric means for Cmax and AUC_{0-inf} of M2 in obese adults were 6.12 ng/mL and 89.4 ng.h/mL, respectively. Crossover study comparison (SB240 in adolescents and SB3813 in adults) suggested that the exposure of active metabolites M1 and M2 were similar between obese adolescents and obese adults.

For the 10 mg dose, trough concentrations of sibutramine, M1 and M2 were 0.083 ± 0.287, 0.749 ± 0.896, and 1.95 ± 0.876 ng/mL, respectively (Study SB238). The trough concentrations of M1 and M2 obtained from a previous study in adults (Study BPI852) were 0.343 ± 0.584 and 1.560 ± 1.043 ng/mL, respectively. For the 15 mg dose, trough concentrations of sibutramine, M1 and M2 in obese adolscents were 0.118 ± 0.263, 0.918 ± 0.790, and 2.534 ± 1.521 ng/mL, respectively. Trough concentrations of M1 and M2 in obese adults were 1.086 ± 1.233 and 3.167 ± 2.069 ng/mL, respectively. Sibutramine trough concentrations in adults were not determined. Statistically analysis suggested that M1 and M2 trough concentrations were not different between obese adolescents and adults. The results were consistent with the comparison of single dose pharmacokinetics.

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/s/

Hae-Young Ahn

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