CLINICAL REVIEW FOR NDA 20-632, SE5-021

1 BPCA EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Approve for labeling change. Not Approvable for pediatric indication.

1.2 Recommendation on Postmarketing Actions

I recommend against marketing of sibutramine for use in children with obesity because the clinical trial data are of poor quality and do not permit conclusions regarding safety and efficacy in this population. Therefore, no recommendations for postmarketing actions are made. Any pediatric studies conducted in the future will need to address theoretical psychiatric risks (i.e., depression, impaired cognitive function) of sibutramine.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Sibutramine hydrochloride monohydrate, chemical class tertiary amine, trade name Meridia, is a serotonin and norepinephrine re-uptake inhibitor that was originally studied as a treatment for depression; however phase 3 trials did not provide evidence of the drug's efficacy and this development program was terminated. Sibutramine was approved for the long-term management of obesity in November 1997, for adult patients with an initial body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

The efficacy and safety of sibutramine in pediatric patients was assessed in a single study as outlined in the Agency's 12 July 2000 Written Request. The study was a 12-month, randomized (3:1), double-blind, placebo-controlled, non-forced dose-escalation trial of 498 obese adolescents (BMI > 2 units above the 95^{th} percentile).

1.3.2 Efficacy

The primary endpoint of the study was the absolute change in body mass index, (BMI) expressed as weight in kg divided by height in m^2. Although change in weight is the typical endpoint used in the evaluation of weight-loss drugs in adults, in children, both increased adiposity and normal growth contribute to weight gain. Calculation of BMI based on measurement of height and weight is therefore the best measure of efficacy of a drug intended to induce weight loss in growing children.

Abbott reported a statistically significant difference in decrease in BMI between sibutramine (-3.0 ± 2.9) and placebo (-0.4 ± 2.1) treated subjects over the course of one year. However, detailed review of serial height measurements for each subject over the course of the study raised concerns regarding the reliability or accuracy of the data from more than 30% of the study participants. For example, 12% of the subjects followed for the entire year reportedly lost height over the course of the study, a biological impossibility. Because a sizable portion of the subjects had questionable height data and height is a critical component of BMI, this reviewer does not believe that valid conclusions regarding the efficacy of sibutramine in obese children can be made from this trial.

1.3.3 Safety

Cardiovascular:
Ambulatory Blood Pressure Monitoring (ABPM) and 'Cuff' Blood Pressure: ABPM was performed in the seventh month of exposure to study drug. Standard 'cuff' measurements were made at several time points throughout the study. A review of ABPM curves suggests an increase from baseline in DBP (about 1-3 mm Hg) and SBP (about 3-5 mm Hg) in sibutramine-treated subjects. There is a small but consistent increase in DBP outliers in sibutramine-treated subjects compared to placebo (see table below for definition of outliers). In addition, there was an increase in treatment-emergent hypertension in sibutramine-treated subjects compared to placebo (11% vs. 8%, respectively). The evidence suggests that sibutramine may increase BP in susceptible adolescents. The results of 'cuff' blood pressure monitoring did not show a statistically significant difference between sibutramine and placebo treated subjects. However, the interpretation of these data is perhaps limited in that subjects were prohibited from taking study medication the morning of the days they were scheduled to have blood pressure measurements.

Pulse measurements: The results of pulse monitoring did not show a statistically significant difference between sibutramine and placebo treated subjects. However, as with the blood pressure measurements, the interpretation of these data are potentially limited in that subjects were prohibited from taking study medication the mornings of the days they were scheduled to have pulse measurements.

Shortcomings in data gathering aside, the incidence of outliers for blood pressure and/or pulse was significantly greater in sibutramine-treated subjects (32%) compared to placebo-treated subjects (16%).

The criteria for evaluating outliers are outlined in the following table:

Variable	Single Visit		Three Consecutive Visits	
	Absolute Threshold	Change from Baseline	Absolute Threshold	Change from Baseline
SBP (mmHg)	> 150	> 20	NA	> 15 but ≤ 20
DBP (mmHg)	> 95	> 15	NA	> 10 but ≤ 15
Pulse Rate (bpm)	> 110	> 20	> 105 but ≤ 110	> 15 but ≤ 20

Echocardiography: Echocardiographic evaluations in 105 sibutramine and 34 placebo[1] patients did not reveal any abnormalities in valvular structure or function, nor did it detect evidence of sibutramine-induced left ventricular hypertrophy. However, as pointed out by the consulting reviewer from the Division of CardioRenal Drug Products, interpretation of the echocardiographic findings is limited due to missing data and the small size of the subset of patients studied.

Psychiatric:
Two suicide attempts were reported, 1 in the sibutramine-treatment group (0.3%) and 1 in the placebo-treatment group (1%). Suicidal ideation was reported in 2 sibutramine-treated subjects. These subjects were prematurely discontinued from the study. Depression or depressed state was reported in 3 sibutramine-treated subjects. Accidental injury was reported in a greater number of sibutramine treated subjects (41; 11%) compared to placebo-treated subjects (8; 6%).

The increased incidence of CNS and other psychiatric adverse events raises concerns that sibutramine, a drug initially developed as an antidepressant, may increase the risk of depression or other mood disturbances. The increased incidence of 'accidental injury' in the sibutramine group compared to placebo may also reflect outcomes due to depression or mood disturbances. The company was requested to provide full narratives of the 'accidental injuries' to further investigate the nature of these occurrences. However, Abbott responded that they were unable to provide these records because the source information had not been compiled. At the request of the Agency (letter date June 22, 2005), Abbott is performing an analysis for suicidality. All narratives related to accidental injuries will be evaluated during this assessment. Until completion of that assessment, the absence of complete narratives makes it impossible to further elucidate the contribution, if any, sibutramine may have made in the imbalance of 'accidental injuries'.

This study was not designed to assess the neuropsychiatric effects of sibutramine .

Given the recent concern that some antidepressants may increase the risk for suicidality in adolescents with psychiatric disorders together with the fact sibutramine's mechanism of action to inhibit the re-uptake of serotonin and norepinephrine is similar to some antidepressants, it would be prudent to include precautionary language, shown below, in the drug's labeling.

Pediatric Use

The efficacy of sibutramine in adolescents who are obese has not been adequately studied.

Sibutramine's mechanism of action inhibiting the reuptake of serotonin and norepinephrine is similar to the mechanism of action of some antidepressants. Pooled analyses of short-term

1 This is consistent with the 3:1 randomization of the subjects.

placebo-controlled trials of antidepressants in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), and other psychiatric disorders have revealed a greater risk of adverse events representing suicidal behavior or thinking during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.

No placebo-controlled trials of sibutramine have been conducted in children or adolescents with MDD, OCD, or other psychiatric disorders. In a study of adolescents with obesity in which 368 patients were treated with sibutramine and 120 patients with placebo, one patient in the sibutramine group and one patient in the placebo group attempted suicide. Suicidal ideation was reported by 2 sibutramine-treated patients and none of the placebo patients. It is unknown if sibutramine increases the risk of suicidal behavior or thinking in pediatric patients.

The data are inadequate to recommend the use of sibutramine for the treatment of obesity in pediatric patients.

1.3.4 Dosing Regimen and Administration

Abbott proposes inclusion of 15 mg dosing in the pediatric section of the label, with dose escalation from 10 mg to 15 mg after 4 weeks if there is inadequate weight loss. This dose regime is not supported by the data or the study. As per protocol, patients who did not have a decrease in BMI of > 10% from baseline at month 6 had the dose increased from 10 mg to 15 mg.

The results from the one-year time point show that patients who did not loss > 10% of the baseline BMI and had their dose of sibutramine increased from 10 mg to 15 mg at six months, did not experience improved weight loss despite the higher dose (Table below).

Mean Absolute Change in BMI by Final Dose	**Full Analysis Set**			**Completers Set**		
Final Dose	**N**	**Mean BL kg/m^2 (SE)**	**Mean Change kg/m^2 (SE)**	**N**	**Mean BL kg/m^2 (SE)**	**Mean Change kg/m^2 (SE)**
Sibutramine 10 mg	189	35.4 (0.3)	-3.9 (0.2)	130	34.8 (0.3)	-5.1 (0.2)
Sibutramine 15 mg	174	36.9 (0.3)	-1.8 (0.2)	151	36.8 (0.3)	-1.9 (0.2)
Placebo	127	35.9 (0.3)	-0.3 (0.2)	79	35.9 (0.4)	-0.4 (0.3)

From Table 18

1.3.5 Drug-Drug Interactions

No new drug-drug interaction data were provided in this submission.

1.3.6 Special Populations

This was a pediatric study conducted in response to a Pediatric Written Request. The Written Request specified that the study population should be composed of 50-75% females. Efforts should be directed to obtain a study population comprising approximately 30% African-American. The study enrolled 322 females (64.7%) and 105 African-Americans (21.1%). The enrollment of these subjects satisfied this component of the Written Request.

With the exception of obesity, all subjects enrolled in the trial were otherwise healthy. Subjects were excluded if they had psychiatric or medical disorders.

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/s/

David Orloff

11/2/2005 09:40:10 AM