MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 06, 2006

FROM: Joslyn Swann, Pharm.D., Postmarketing Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

THROUGH: Rosemary Johann-Liang, M.D., Deputy Director
For
Mark Avigan, M.D., Director
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TO: M. Dianne Murphy, M.D., Director
Office of Pediatric Therapeutics (OPT), OIASI
Office of the Commissioner
And
Solomon Iyasu, M.D., M.P.H., Team Leader
Division of Pediatric Drug Development, HFD-960
Office of Counter-Terrorism and Pediatric Drug Development, HFD-950

SUBJECT: One Year Post-Pediatric Exclusivity Postmarketing Adverse Event Review
PID #: D040762
Drug: Sibutramine (Meridia®, Abbott Laboratories)
NDA#: 20-632
Pediatric Exclusivity Approval Date: 10/06/2004

Executive Summary

The Office of Counter-Terrorism and Pediatric Drug Development asked the Office of Drug Safety to identify and review reports of adverse events associated with the use of sibutramine during the 12-month period starting from 10/06/2004, the date that pediatric exclusivity was granted.

To analyze the adverse events, two searches were performed in the Adverse Event Reporting System database (AERS): a) 11/22/1997 (U.S. approval date) through 10/06/2005, and b) 10/06/2004 through 10/06/2005 (referred to hereafter as the *pediatric exclusivity period*). We used an AERS "cut-off" date of 11/06/2005 to allow time for all reports received by 10/06/2005 to be entered into AERS.

For the pediatric exclusivity period, our AERS search determined that a total of 154 reports (raw count) were received; this count includes adults, pediatrics, and null age reports. Of this total number, there was one pediatric case. Because of the low yield, we will continue to monitor adverse events for a second year for possibly a more meaningful analysis.

AERS Search Results: Sibutramine

AERS searches include all sources - U.S. & foreign

A. From U.S. marketing approval date (11/22/1997) through AERS data cut-off date (11/06/2005).

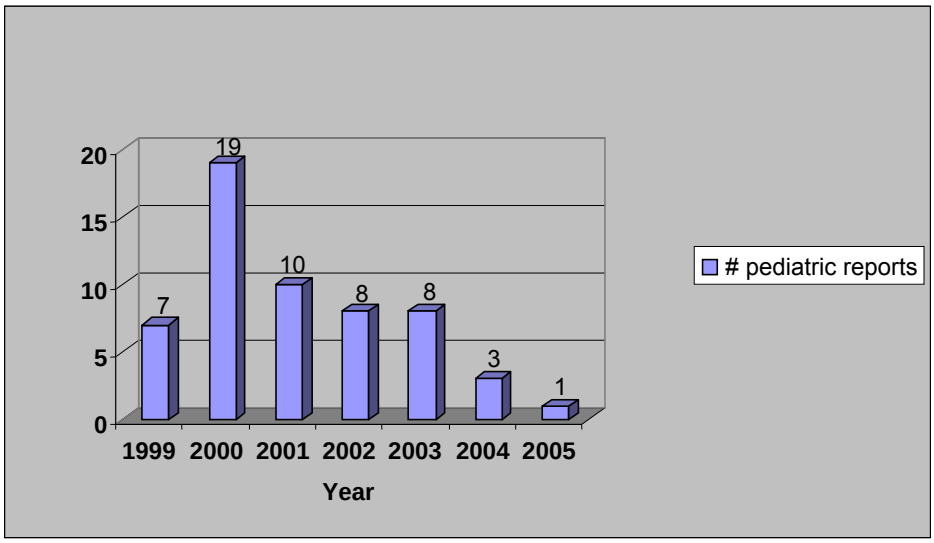
1. Raw counts of reports: see Table 1.

Table 1: Raw counts of reports from U.S. marketing approval date through AERS data cut-off date

	All Reports (US)	Serious (US)	Death (US)
All Ages ±	5788 (5071)	1032 (544)	118 (58)
Adults (≥17)	4969 (4374)	848 (446)	75 (38)
Pediatrics (0-16)	56 (45)	31 (22)	5 (0)

± includes null ages

Figure 1: Reporting trend for pediatric reports from approval (11/22/1997)



2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups including identifying events not previously described in the label. An adverse event term that is **underlined and bold-italics,** signifies the event is not included in the current labeling. See Table 2.

Table 2: Counts of Top 20 Reported Events by Preferred Terms from Approval Date †

Ages	Reported Preferred Term	Count of Term	% of Total
All Ages ±	Headache	639	11.04
	Insomnia	595	10.28
	Dry Mouth	429	7.41
	Drug Ineffective	416	7.19
	Increased Appetite	392	6.77
	Blood Pressure Increased	375	6.48
	Decreased Appetite	372	6.43
	Constipation	371	6.41
	Dizziness	340	5.87
	Nausea	299	5.17
	Condition Aggravated	297	5.13
	Therapeutic Response Unexpected	257	4.44
	Fatigue	230	3.97
	Weight Increased	221	3.82
	Palpitations	214	3.70
	Central Nervous System Stimulation	201	3.47
	Hyperhidrosis	196	3.39
	Sedation	189	3.27
	Dyspnoea	188	3.25
	Depression	172	2.97
Adults (≥17 years)	Headache	584	11.75
	Insomnia	550	11.07
	Dry Mouth	396	7.97
	Drug Ineffective	377	7.59
	Increased Appetite	348	7.00
	Decreased Appetite	341	6.86
	Constipation	333	6.70
	Blood Pressure Increased	329	6.62
	Dizziness	316	6.36
	Condition Aggravated	277	5.57
	Nausea	271	5.45
	Therapeutic Response Unexpected	228	4.59
	Fatigue	212	4.27
	Weight Increased	199	4.00
	Palpitations	197	3.96
	Central Nervous System Stimulation	186	3.74
	Hyperhidrosis	186	3.74
	Sedation	177	3.56
	Dyspnoea	171	3.44
	Heart Rate Increased	156	3.14

Continued

Table 2: Counts of Top 20 Reported Events by Preferred Terms from Approval Date †			
Ages	**Reported Preferred Term**	**Count of Term**	**% of Total**
Pediatrics (0-16 years)	***Maternal Drugs Affecting Foetus***	11	19.64
	Medication Error	9	16.07
	Accidental Exposure	6	10.71
	Accidental Overdose	6	10.71
	Depression	5	8.93
	Neonatal Disorder	5	8.93
	Intentional Overdose	4	7.14
	Pregnancy	4	7.14
	Premature Baby	4	7.14
	Tachycardia	4	7.14
	Complications Of Maternal Exposure To Therapeutic Drugs	3	5.36
	Electrocardiogram Qt Prolonged [1, *]	3	5.36
	Aspiration	2	3.57
	Condition Aggravated	2	3.57
	Congenital Anomaly	2	3.57
	Dermatitis	2	3.57
	Haemoglobin Decreased	2	3.57
	Menstruation Irregular	2	3.57
	Mydriasis	2	3.57
	Suicidal Ideation	2	3.57

† raw counts: includes terms from duplicate reports
± includes null ages
* A hands-on review of these three reports determined that there was one case and two duplicate reports.

B. From Pediatric Exclusivity approval date (10/06/2004) through AERS data cut-off date (11/06/2005):

1. Raw counts of reports: see Table 3.

Table 3: Raw counts of reports from marketing approval date through AERS data cut-off date			
	All Reports (US)	Serious (US)	Death (US)
All Ages ±	154 (33)	140 (25)	18 (2)
Adults (≥17)	102 (14)	96 (12)	4 (0)
Pediatrics (0-16)	1 (1)	1 (1)	0 (0)

± includes null ages

[1] Swann J. CDER/ODS Postmarketing Review: NDA 020-632, Sibutramine (Meridia®) and Prolongation of QT Interval. Dated: December 7, 2005. Available on DFS or at the following link: 

2. Counts of top 20 reported event preferred terms for all ages, adults, and pediatric age groups including identifying events not previously described in the label. An adverse event term that is **underlined and bold-italics,** signifies the event is not included in the current labeling. See Table 4.

Table 4: Counts of Top 20 Reported Events by Preferred Terms from Pediatric Exclusivity Date †

Ages	Reported Preferred Term	Count of Term	% of Total
All Ages ±	Cardiovascular Disorder	9	5.84
	Headache	9	5.84
	Dyspnoea	8	5.19
	Abortion Induced	7	4.55
	Drug Exposure During Pregnancy	7	4.55
	Drug Interaction	7	4.55
	Nausea	6	3.90
	Blood Pressure Increased	5	3.25
	Confusional State	5	3.25
	Hypertension	5	3.25
	Irritability	5	3.25
	Myocardial Infarction	5	3.25
	Pulmonary Hypertension	5	3.25
	Arrhythmia	4	2.60
	Asthenia	4	2.60
	Cardiac Failure	4	2.60
	Chest Pain	4	2.60
	Constipation	4	2.60
	Dizziness	4	2.60
	Fatigue	4	2.60
Adults (≥17 years)	Drug Interaction	7	6.86
	Dyspnoea	7	6.86
	Headache	5	4.90
	Irritability	5	4.90
	Nausea	5	4.90
	Pulmonary Hypertension	5	4.90
	Asthenia	4	3.92
	Cardiac Failure	4	3.92
	Confusional State	4	3.92
	Constipation	4	3.92
	Hypersensitivity	4	3.92
	Hypertension	4	3.92
	Insomnia	4	3.92
	Laryngeal Oedema	4	3.92
	Muscular Weakness	4	3.92
	Abdominal Pain Upper	3	2.94
	Abortion Induced	3	2.94
	Blood Pressure Increased	3	2.94
	Depression	3	2.94
	Dizziness	3	2.94

Continued

Table 4: Counts of Top 20 Reported Events by Preferred Terms from Pediatric Exclusivity Date †			
Ages	**Reported Preferred Term**	**Count of Term**	**% of Total**
Pediatrics (0-16 years)	***Electrocardiogram QT Prolonged*** [1]	1	100.00
† raw counts: includes terms from duplicate reports ± includes null ages			

Postmarketing hands-on review of all pediatrics adverse event reports from all sources received during the 12-month after a drug receives pediatric market exclusivity.

A. Description of the pediatric case.

Case Narrative (ISR #: 4211426-3):
A 14-year old male, weighing 88.3 kgs or 194.3 lbs, who was part of a phase III study to assess the safety and efficacy of Meridia® in obese adolescents, was initiated in the study with sibutramine 10 mg per day on November 11, 2000. On November 3, 2000, the patient had a baseline screening ECG which showed a sinus rhythm with non-specific intraventricular conduction delay (QTc was 436 msec). Upon completion of the study one year later, on November 3, 2001, the patient had another ECG which showed a sinus rhythm with sinus arrhythmia, a non-specific intraventricular conduction delay and a new development of prolonged QT interval (QTc was 465). On December 3, 2001, the patient underwent another ECG which showed prolonged QT interval persistence (QT values not reported). This case was reported as having a 'medically important' outcome by the reporter.

B. Similarities between the top 20 pediatric adverse events and the adult adverse event profile.

Only one pediatric case was identified during the *pediatric exclusivity period*. The adverse event reported for that one pediatric case was 'QT prolongation'. Our AERS search identified various cardiovascular events reported for the adult reports (ages ≥17 years), but QT prolongation was not identified in the adult group. While various cardiovascular disorders are currently identified in the **ADVERSE REACTIONS** section of the product label, QT prolongation was not one of these labeled events.

For the time period of 11/22/1997 through 10/06/2005, our AERS search identified of three pediatric reports coded for QT prolongation. Once a hands-on review was completed for the three reports, it was determined that the reports were duplicates and that there was actually only one pediatric case.[1]

C. Comment and recommended action for any pediatric events not labeled for adult population.

AERS identified one pediatric case that resulted in QT prolongation; this adverse event is not a labeled event in the adult population. While this case was identified, it was confounded case. Not only is obesity a risk factor for the development of cardiovascular disease[2], this patient also had a pre-existing sinus rhythm with non-specific intraventricular conduction delay (QTc was 436 msec) prior to initiation in the study. Therefore, these confounders make it difficult to determine the role sibutramine may have played in the reported adverse event.[1]

There are no recommendations at this time.

D. Comment on any labeled events are uniquely reported in pediatrics but are not reported in adult population.

Only one pediatric case identified and this case resulted in QT prolongation, which is not a labeled event. No trend or action was identified at this time.

E. Comment any increased frequency reporting of any expected events.

With only once case identified, there is no trend at this time. No action is recommended at this time.

F. Summary of all reports of pediatric death.

There were no pediatric deaths identified in this consult.

G. Summarize of the pediatric adverse event profile.

Given that only one pediatric case was identified, an adverse event risk profile can not be determined at this time.

Summary

Our AERS search yielded only one pediatric report for the 12-month time period after pediatric exclusivity was granted. We will continue to monitor adverse events for a second year for possibly a more meaningful analysis.

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Joslyn Swann, Pharm.D.

[2] Flier JS, Maratos-Flier E. Part Four – Nutrition, Chapter 64 Obesity. In: Harrison's Principles of Internal Medicine, 16th Ed. 2005, Online. Available at: http://online.statref.com/Document.aspx?DocId=464&FxId=55&SessionId=5954F5RGXZFZSXBN&Scroll=1&Index=0. Accessed: November 2005.

Concur:

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Lanh Green, Pharm.D., MPH

Limitations of the Adverse Event Reporting System (AERS)

The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting. For any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s). The main utility of a spontaneous reporting system, such as AERS, is to provide signals of potential drug safety issues. Therefore, counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing drug risk between drugs.

Attachment 1

Standard AERS Printouts
Distributed by Age Category

AGE CATEGORY	AERS PRINTOUT	PDF FILE
Adults (17 yrs and above)	All PT in cases	 Adult PT count
	All PT in cases with serious outcomes	 Adult serious PT count
	All PT in cases with death as an outcome	 Adult death PT count
	Cases by gender and ages	 Adult age and gender
Pediatrics (0 to 16 yrs only)	All PT in cases	 Peds PT count
	All PT in cases with serious outcomes	 Peds serious PT count
	All PT in cases with death as an outcome	*There were no cases of pediatric death during the pediatric exclusivity period.*
	Cases by gender and ages	 Peds age and gender

Appendix 1

Drug Product Information

Sibutramine hydrochloride monohydrate is available as Meridia® in 5 mg, 10 mg, or 15 mg capsules. This product was approved in the United States in November 22, 1997; its sponsor is Abbott Laboratories.

The Meridia® labeling contains information regarding pediatric use in the following sections:

> **CLINICAL PHARMACOLOGY**
> **Special Populations:**
> ***Pediatric:*** The safety and effectiveness of MERIDIA in pediatric patients under 16 years old have not been established.
>
> **PRECAUTIONS**
> **Pediatric Use**
> The safety and effectiveness of MERIDIA in pediatric patients under 16 years of age have not been established.

Additionally, the **PRECAUTION** section gives information regarding use of Meridia® during pregnancy and when nursing.

> **Pregnancy**
> ***Teratogenic Effects-Pregnancy Category C***
> Radiolabeled studies in animals indicated that tissue distribution was unaffected by pregnancy, with relatively low transfer to the fetus. In rats, there was no evidence of teratogenicity at doses of 1, 3, or 10 mg/kg/day generating combined plasma AUC's of the two major active metabolites up to approximately 32 times those following the human dose of 15 mg. In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the human dose of 15 mg caused maternal toxicity. At markedly toxic doses, Dutch Belted rabbits had a slightly higher than control incidence of pups with a broad short snout, short rounded pinnae, short tail and, in some, shorter thickened long bones in the limbs; at comparably high doses in New Zealand White rabbits, one study showed a slightly higher than control incidence of pups with cardiovascular anomalies while a second study showed a lower incidence than in the control group.
>
> No adequate and well controlled studies with MERIDIA have been conducted in pregnant women. The use of MERIDIA during pregnancy is not recommended. Women of childbearing potential should employ adequate contraception while taking MERIDIA. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.
>
> **Nursing Mothers**
> It is not known whether sibutramine or its metabolites are excreted in human milk. MERIDIA is not recommended for use in nursing mothers. Patients should be advised to notify their physician if they are breast-feeding.

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/s/

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1/11/2006 04:17:16 PM
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