Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

****This review has been cleared by the proprietary vendors used to conduct the consult. Therefore, information it contains can be shared with third parties outside of the agency.****

PID#: D040762

DATE: January 6, 2005

FROM: LT Kendra Worthy, USPHS, PharmD, Pharmacist / Drug Use Specialist
CAPT Andrea Feight, USPHS, DMD, MPH/Epidemiologist

THROUGH: Toni Piazza-Hepp, PharmD, Acting Director
Division of Surveillance, Research and Communication Support, HFD-410

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., Acting Deputy Director
Division of Pediatric Drug Development
Office of Counter-Terrorism and Pediatric Drug Development (OCTAP)

SUBJECT: One Year Post-Pediatric Exclusivity Post-marketing Adverse Event Review: Drug Use Data Sibutramine (Meridia®) Capsule: NDA 20-632

****This document contains proprietary drug use data which cannot be shared outside of FDA without clearance from the data vendors obtained through the Office of Drug Safety.****

EXECUTIVE SUMMARY

This consult examines drug utilization trends for sibutramine (Meridia®) in the pediatric population (ages 0-16 years). Sales and outpatient drug utilization data were examined for the three-year period from October 1, 2002 – September 30, 2005, with a primary focus on patterns 12 months before and 12 months following the granting of Pediatric Exclusivity for Meridia® on October 6, 2004. As comparators, the sales and outpatient drug use patterns of other commercially available anti-obesity products, such as orlistat and phentermine, were examined. Since over 96% of all sibutramine sales are into the retail channels, only outpatient drug utilization patterns will be addressed in this document.

The number of outpatient prescriptions of oral anti-obesity agents decreased by approximately 10% over the 3 years from October 2002 – September 2005. Compared to the other anti-obesity products, by the final year of this analysis (October 2004 - September 2005) sibutramine ranked third, accounting for 9% of prescriptions dispensed.

The top specialty prescribing sibutamine from October 2002 through September 2005 was the general practitioner[1], which accounted for 42% of dispensing both pre-exclusivity (October 2003 – September 2004) and post-exclusivity (October 2004 – September 2005); pediatricians were ranked 8th in each of these years. In general, prescribing patterns for sibutramine dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period.

The total number of sibutramine prescriptions dispensed to pediatric patients ages 0-16 years old decreased by an estimated 33% during the 3 years of this analysis, and during this time the yearly percentage of prescriptions attributable to pediatric patients ages 0-16 years was consistently less than 1%. Patients in the 12-16 year old subgroup accounted for at least 80% of the yearly total of sibutramine prescriptions dispensed to patients ages 0-16 years.

The two diagnoses associated with a mention of sibutramine for pediatric patients (ages 0-16 years) in office-based physician-patient encounters were "Polycystic Ovaries" (ICD-9 256.4) and "Obesity" (ICD-9 278.0) which together accounted for less than 1% of mentions in each of the 3 years from October 2002 – September 2005.

In summary, use of sibutramine in pediatric patients ages 0-16 years accounted for less than 1% of overall outpatient usage during both the pre-exclusivity period and the post-exclusivity period.

INTRODUCTION

On January 4, 2002, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of the BPCA requires the reporting of adverse events associated with the use of a drug in children during the one-year period following the date on which the drug received pediatric marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs.

Meridia® (sibutramine) NDA 20-632 is an oral systemic anti-obesity agent. Sibutramine was approved November 22, 1997 for use in the management of obesity, including weight loss and maintenance of weight loss in conjunction with a reduced calorie diet. It is available as 5mg, 10mg, and 15mg capsules for oral administration. On February 16, 2001, approval was given for maintenance of weight loss over an 18 month period, thus extending the use from 1 year to 2 years.

[1] The general practitioner category includes general practice, family practice, and osteopathic physicians.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for Meridia® on October 6, 2004, under efficacy supplement NDA 20-632/S-021.

This review describes outpatient drug usage of sibutramine (Meridia®) in the pediatric population as compared to the adult population several years before and one year after the granting of pediatric exclusivity. The utilization of Meridia® is provided in the context of other drug products routinely used in the management of obesity. These products include phentermine and orlistat, as well as other products in the anti-obesity class.

METHODS

Propietary drug use databases licensed by the Agency were used to conduct this analysis. The data sources for this analysis are described in detail in the Appendix.

Settings of Use

The IMS Health, IMS National Sales Perspectives was used to examine the sales and drug distribution channels of oral anti-obesity products from October 1, 2002 – September 30, 2005 (Table 1). Retail channels are the largest purchasers of sibutramine, representing at least 96% of the capsules sold in each of the three one-year periods of this analysis. Total sales of sibutramine capsules decreased by a third over the 3 years of this analysis, from 25.7 million capsules sold during October 2002 - September 2003 to 17.7 million sold during October 2004 - September 2005. Compared to the pre-exclusivity period (October 2003 - September 2004), total sales of sibutramine in the post exclusivity period (October 2004 - September 2005) represented 4.5% of the anti-obesity market, down from 6.0%.

Table 1. Total Number of Capsules and/or Tablets of Select Anti-Obesity Agents Sold into U.S. Distribution Channels During October 2002 – September 2005 (in thousands)

	Oct 2002 - Sept 2003		Oct 2003 – Sept 2004		Oct 2004 - Sept 2005	
	N (000)	%	N (000)	%	N (000)	%
Total Anti-Obesity Market	**450,759**	***100.0%***	**411,706**	***100.0%***	**391,378**	***100.0%***
Phentermine	**144,418**	***32.0%***	**172,951**	***42.0%***	**208,550**	***53.3%***
Orlistat	**107,838**	***23.9%***	**82,703**	***20.1%***	**58,728**	***15.0%***
Sibutramine	**25,744**	***5.7%***	**24,753**	***6.0%***	**17,686**	***4.5%***
Retail	*24,802*	*96.3%*	*23,856*	*96.4%*	*16,994*	*96.1%*
Non-Retail	*944*	*3.7%*	*899*	*3.5%*	*692*	*3.9%*
Herbal Products[§]	**51,471**	***11.4%***	**31,993**	***7.8%***	**23,369**	***6.0%***
Ephedrine	**8,418**	***1.9%***	**6,017**	***1.5%***	**3,258**	***0.8%***
Others (7)	**112,870**	***25.0%***	**93,290**	***22.6%***	**79,787**	***20.3%***

IMS Health, National Sales Perspectives™ Combined, October 2002 – September 2005, Data Extracted 11-2005 (File:051sibc.dvr)
*Retail includes chain, independent, mail order, food store pharmacies
** Non-retail includes Non-federal hospitals, federal facilities, long term care, clinics, HMOs, home health care, prisons, universities, and other
[†]Subtotals may not sum exactly due to rounding
[§] Herbal Products include: Metabolife 356, Metabolife Evening, Ultra Slim Down Kit, Diet, and Diet Suppl. Ephedra

RESULTS

Dispensed Prescriptions

Outpatient prescriptions for the selected oral anti-obesity agents decreased by approximately 10% over the 3 years from October 2002 – September 2005, falling from 5.9 million prescriptions dispensed in the 12-month period from October 2002 - September 2003 to 5.3 million prescriptions dispensed in October 2004 - September 2005 (Table 2). During October 2002 - September 2003, sibutramine accounted for 13% (765,000 prescriptions) of the oral anti-obesity prescriptions and orlistat accounted for 21% (1.2 million prescriptions). In the final year of this analysis (October 2004 – September 2005), sibutramine prescriptions accounted for 9% (486,000 prescriptions) of the market and orlistat accounted for 12.5% (661,000 prescriptions). Throughout the 3-year period examined, phentermine accounted for the majority of prescriptions for anti-obesity products with 65% of the market (3.4 million prescriptions).

Prescriptions for sibutramine decreased by 36% over the three 1-year periods of this analysis from 764,000 prescriptions dispensed during October 2002 - September 2003, 620,000 prescriptions dispensed during the pre-exclusivity year (October 2003 - September 2004), to 486,000 prescriptions dispensed during the post-exclusivity year (October 2004 - September 2005).

Table 2: Total Number of Prescriptions[†] Dispensed in Retail Pharmacies Nationwide for Anti-Obesity Products During October 2002 – September 2005

	Oct 2002 - Sept 2003	Oct 2003 - Sept 2004	Oct 2004 - Sept 2005

	N	%	N	%	N	%
Anti-Obesity Market	**5,854,778**	***100.0%***	**5,337,507**	***100.0%***	**5,269,674**	***100.0%***
Phentermine	3,119,560	*53.3%*	3,124,734	*58.5%*	3,419,478	*64.9%*
Orlistat	1,218,174	*20.8%*	899,511	*16.9%*	660,449	*12.5%*
Sibutramine	**764,449**	***13.1%***	**619,944**	***11.6%***	**486,109**	***9.2%***
Phendimetrazine	316,114	*5.4%*	299,434	*5.6%*	303,235	*5.8%*
Diethylpropion tartrate	309,875	*5.3%*	283,238	*5.3%*	297,206	*5.6%*
Benzphetamine	126,606	*2.2%*	110,646	*2.1%*	103,197	*2.0%*

Verispan, LLC, October 2002 – September 2005, Data Extracted 12-2005 (File: VONA D040762 12-02-05 sibutramine bpca class.qry)
† Totals and subtotals may not sum exactly due to rounding

Prescriber Specialty

The top prescriber specialty prescribing sibutramine from October 2002 through September 2005 was the general practitioner[2], which accounted for approximately 42% of dispensing during each of the three one-year periods of this analysis (Table 3). Of all specialties, pediatricians were ranked 8th in prescribing sibutramine during both the pre-exclusivity and post-exclusivity years with just over 1% of dispensed prescriptions of sibutramine. Prescribing patterns for orlistat were similar to those of sibutramine, with pediatricians ranked 8th in prescribing. In general, prescribing patterns for sibutramine dispensed in outpatient retail pharmacy settings showed no substantial change across provider specialties during the 36-month study period.

Table 3: Total Number of Prescriptions† Dispensed for Sibutramine and Orlistat Nationwide by Physician Specialty During October 2002 – September 2005

	October 2002 - September 2003		October 2003 - September 2004		October 2004 - September 2005	
	N	%	N	%	N	%
Sibutramine	**764,439**	***100.0%***	**619,944**	***100.0%***	**486,112**	***100.0%***
GP, FM, & DO* (1st)	323,641	*42.3%*	265,455	*42.8%*	204,316	*42.0%*
Internal Medicine (2nd)	239, 075	*31.3%*	191,948	*31.0%*	151,560	*31.2%*
Pediatricians (8th)	9,199	*1.2%*	8,155	*1.3%*	7,428	*1.5%*
All Others	192,524	*25.2%*	154,396	*24.9%*	122,808	*25.3%*
Orlistat	**1,218,175**	***100.0%***	**899,510**	***100.0%***	**660,460**	***100.0%***
GP, FM, & DO* (1st)	456,610	*37.5%*	335,903	*37.3%*	244,440	*37.0%*
Internal Medicine (2nd)	377,657	*31.0%*	276,366	*30.7%*	206,429	*31.3%*
Pediatricians (8th)	15,198	*1.2%*	12,746	*1.4%*	9,232	*1.4%*
All Others	368,710	*30.3%*	274,495	*30.5%*	200,359	*30.3%*

Verispan, LLC, October 2002 – September 2005, Data Extracted 12-2005 (File: VONA D040762 12-05-05 sibutramine detail MD.qry)
* General Practice, Family Medicine & Osteopathic physicians
† Totals and subtotals may not sum exactly due to rounding

Patient Demographics

The total number of sibutramine prescriptions dispensed to pediatric patients ages 0-16 years old decreased 33%, from approximately 4,505 to approximately 3,006, during the 3 years of this analysis. During the same period, the overall percentage of prescriptions dispensed to pediatric

[2] The general practitioner category includes general practice, family practice, and osteopathic physicians.

patients age 0-16 years remained steady at less than 1% of total sibutamine prescriptions dispensed (Table 4). Patients in the 12-16 year old subgroup accounted for over 80% of prescriptions dispensed to pediatric patients.

Table 4. Number and Percentage of Sibutramine Prescriptions† Dispensed to Adult and Pediatric Patients by Retail Pharmacies During October 2002 – September 2005.

	Oct 2002 - Sept 2003		Oct 2003 - Sept 2004		Oct 2004 - Sept 2005	
	N	%	N	%	N	%
Sibutramine	**764,561**	***100.0%***	**619,902**	***100.0%***	**486,112**	***100.0%***
Age 0-16	**4,505**	***0.6%***	**3,848**	***0.6%***	**3,006**	***0.6%***
0-1	90	*2.0%*	83	*2.1%*	38	*1.3%*
2-11	654	*14.5%*	441	*11.5%*	368	*12.2%*
12-16	3,761	*83.5%*	3,324	*86.4%*	2,600	*86.5%*
Age 17+	**758,584**	***99.2%***	**613,363**	***98.9%***	**481,993**	***99.2%***
Age Unspecified	2,472	*0.2%*	2,691	*0.4%*	1,113	*0.2%*

Verispan, LLC, VONA Vector One October 2002 – September 2005, Data Extracted 12-2005 (File: D040762 12-05-05 antiobesity Ag.qry)
†Totals and subtotals may not sum exactly due to rounding

According to data from Verispan's Total Patient Tracker, over the 3 years of this analysis, the estimated number of patients receiving a sibutramine prescription has decreased approximately 35% (Table 5). The number of pediatric patients ages 0-17 years that received a sibutramine prescription has continued to represent an estimated 1% of all patients receiving sibutramine prescriptions over the three-year period.

Table 5. The Estimated Number of Unique Patients Receiving a Prescription for Sibutramine From Retail Pharmacies During October 2002 – September 2005

	Oct 2002 - Sept 2003		Oct 2003 - Sept 2004		Oct 2004 – Sept 2005	
	Projected Patient Count	%	Projected Patient Count	%	Projected Patient Count	%
Sibutramine	315,072		252,402		203,516	
Age 0-17	3,070	.98%	2,541	1.01%	1,751	.86%
Age 17+	321,510	102.04%	257,095	101.87%	207,631	102.03%

Verispan, LLC, Total Patient Tracker, October 2002 – September 2005, Data Extracted 12-2005 (File: TPT D040762 Sibutramine 12.9.05.xls)
†Subtotals may not sum exactly due to rounding error and patients aging in the course of the study period.

The two diagnoses mentioned for pediatric patients ages 0-16 years associated with a mention of sibutramine in office-based physician-patient encounters were "Polycystic Ovaries" (ICD-9 256.4) and "Obesity" (ICD-9 278.0) which together accounted for less than 1% of all mentions during both the pre-exclusivity (October 2003 - September 2004) and post-exclusivity (October 2004 - September 2005) periods (Table 6). The most common diagnosis for adult patients ages

17 years and older was "Obesity" (ICD-9 278.0), which accounted for 79% of mentions during the pre-exclusivity period and 84% of mentions during the post-exclusivity period.

Table 6. Top Diagnoses Associated with Mentions of Sibutramine in visits to Office-Based Physicians (in thousands) During October 2002 - September 2005

	October 2002 - September 2003		October 2003 - September 2004		October 2004 - September 2005	
IMS Reported ICD-9 Code	**N (000)**		**N (000)**		**N (000)**	
Total All Patients	357	100.%	336	100.%	289	100.%
Age 0 - 16	**1**	**0.3%**	**1**	**0.3%**	**1**	**0.3%**
2564 Polycystic Ovaries	---	---	---	---	1	0.3%
2780 Obesity	1	0.3%	1	0.3%	---	---
Age 17 +	**330**	**92.4%**	**296**	**88.1%**	**270**	**93.4%**
2780 Obesity	304	85.2%	266	79.1%	243	84.0%
7831 Abnormal Weight Gain	20	5.6%	20	6.0%	15	5.2%
3075 Eating Disorder Other, Unspec.	---	---	5	1.5%	5	1.7%
Total Others (8)	6	1.7%	6	1.8%	8	2.8%
Age Unspecified	26	7.3%	39	11.6%	18	6.2%

IMS National Disease and Therapeutic Index™, MAT6yr Oct 2002 -Sep 2005. Data extracted 12-2005
(File: NDTI D040762 12-08-05 0512sibutraminediag.xls)
†Subtotals may not sum exactly due to rounding error

LIMITATIONS

Sales data

The IMS Health, National Sales Perspectives™ does not provide a direct estimate of use but does provide a national estimate of units sold from the manufacturer to various channels of distribution. It does not include demographic information for the patients receiving these products, such as age and gender. The amount of products purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

Outpatient use data

Sales and prescription data of the competing anti-obesity agents are included as comparators for sibutramine. Xenical® (orlistat) is approved for obesity management including weight loss and weight maintenance when used in conjunction with a reduced calorie diet. Phentermine is used as a short-term adjunct in a regimen of weight reduction based on exercise, behavioral modification, and caloric reduction in the management of obesity.

While we conducted a comprehensive analysis of the use of this product in the outpatient settings, in which the majority of use occurred, use outside of the retail pharmacy settings was not captured in our analysis.

Throughout our analysis, we used the agency's cut-off age definition of a pediatric patient (age 0-16 years), except when we use Verispan's Total Patient Tracker tool for providing estimates of the total number of unique patients receiving prescriptions for sibutramine. Age bands available through this data resource with an age break at age 17 years are fixed and cannot yet be customized to reflect the agency's definition. In addition, using this tool does not allow summary of age bands in each time period, due to patient aging in the course of the study period.

NDTI™ data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly when use is not common in the pediatric population, as in the case of sibutramine. Therefore, the data provided that relate to indication for use of sibutramine in pediatric patients should be interpreted with caution.

Prescription totals in tables 2, 3, and 4 do not match exactly due to rounding within the particular version of Verispan used to retrieve the data.

CONCLUSION

For all age groups, prescriptions for sibutramine decreased by 36% over the three 1-year periods of this analysis. The use of sibutramine is concentrated in adult patients, with 0-16 year olds accounting for less than 1% of overall outpatient usage during the 36-month study period. Patients in the 12-16 year old subgroup accounted for the majority of prescriptions dispensed to pediatrics, with at least 80% of the yearly sibutramine prescriptions dispensed to this group of pediatric patients.

APPENDIX

IMS Health, National Sales Perspectives™

IMS Health National Sales Perspectives™ measures the volume of drug products (both prescription and over-the-counter) and selected diagnostic products moving from manufacturers into retail and non-retail markets. The volume of drug products transferred to these markets is expressed in terms of sales dollars, vials, and market share. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings. These data are based on national projections.

For this analysis, the sales trend of oral anti-obesity agents was examined from October 1, 2002 – September 30, 2005 inclusive.

Verispan, LLC; Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions.

Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.8 billion prescription claims, representing over 160 million patients tracked across time.

The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC; Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 1.8 billion prescription claims per year, which represents over 160 million patients tracked across time.

Data for this analysis included all sibutramine prescriptions dispensed to patients from October 1, 2002 – September 30, 2005 inclusive.

IMS Health, National Disease And Therapeutic Index™ (NDTI™)

The National Disease and Therapeutic Index™ (NDTI™) is an ongoing survey designed and conducted by IMS Health to provide descriptive information on the patterns and treatment of disease encountered in office-based practices in the continental U.S. The data are collected from a panel of approximately 3,000 office-based physicians who complete and submit a survey of their practice patterns to IMS Health for two consecutive days per quarter. These data may include profiles and trends of diagnoses, patients, drug products mentioned, and treatment patterns. These data are projected nationally to reflect national prescribing patterns.

NDTI™ uses the term drug uses for mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a drug use does not necessarily result in the generation of a prescription. Rather, the term indicates that a given drug was mentioned during an office visit.

For this analysis, we examined annual mentions of sibutramine during office-based physician visits during the time period from October 1, 2002 – September 301, 2005 inclusive.

LT Kendra Worthy, USPHS, Pharm.D.
Pharmacist/Drug Utilization Data Specialist
Division of Surveillance, Research, and
Communication Support (DSRCS)

CAPT Andrea Feight, DMD, MPH
Epidemiologist
Division of Surveillance, Research, and
Communication Support (DSRCS)

Laura Governale, Pharm D., MBA.
Team Leader
Division of Surveillance, Research, and
Communication Support (DSRCS)

Judy A. Staffa, Ph.D., R.Ph.
Epidemiology Team Leader
Division of Surveillance, Research, and
Communication Support (DSRCS)

Toni Piazza-Hepp, Pharm.D.
Acting Division Director
Division of Surveillance, Research, and
Communication Support (DSRCS)

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/s/

Kendra Worthy
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Toni Piazza Hepp
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