M E M O R A N D U M

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

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SUBJECT: Postmarketing Safety Review
Consult: Follow-up Pediatric Exclusivity Review
Drug: Xenical® (orlistat)
NDA#: 020-766
Event: Cholelithiasis and Acute Cholecystitis

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1.0 EXECUTIVE SUMMARY

This follow-up consult was requested by the Office of Pediatric Therapeutics (OPT). In the initial One-Year Post-Pediatric Exclusivity Postmarketing Review, dated November 4, 2004, only one pediatric case was identified.[1] The OPT requested a subsequent review for pediatric cases of cholelithiasis or other gall bladder issues in preparation for their Pediatric Advisory Committee (PAC) meeting scheduled for April 2007.

Xenical® was approved on Aril 23, 1999; sponsored by Hoffman La-Roche Inc. Xenical® (orlistat) is a reversible lipase inhibitor, indicated for obesity management. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with gastric and pancreatic lipases.

A Written Request to conduct pediatric studies using orlistat was made by the Food and Drug Administration on August 9, 2000.[6] Pediatric exclusivity was granted on September 13, 2003.[2] The indication for pediatric use was approved December 12, 2003. In pediatric populations, Xenical® is indicated for use in obese adolescent patients aged 12 to 16 years. The effective pediatric dose, determined during pediatric clinical studies, is 120 mg three times a day, is the same dose and regimen for the adult population.[7]

Searches in the MEDLINE and Scopus databases did not find any articles or case reports of children associated with orlistat and cholelithiasis or gallbladder disorders. There were several articles identified which described the effect of orlistat on the gallbladder in adults.[9, 10]

Regarding the product's use, for the time period 2002 through 2006, there was a 64% decrease in orlistat use in all patient ages. The majority of use was found in the age band 31 through 64; with females comprising 63% of this use. Overall, use in children, between the ages of 1 and 16 years, is approximately 0.35% of the total product use.[11]

A search of the Adverse Event Reporting System (AERS) resulted in 37 domestic cases of cholelithiasis (also known as gallstones) or acute cholecystitis associated with orlistat therapy in all patient ages. The AERS search time period was from April 23, 1999 (US approval date) through December 2006. Cases were further classified into three groups. The assigned class, definition, and identified numbers of cases are as follows: Class I or asymptomatic (seven cases), Class II or symptomatic (16 cases), and Class III or complicated (14 cases).

Within the series of 37 cases, 30 (81%) resulted a hospitalization, and 28 (76%) in a cholecystectomy. There were no fatalities and only **one pediatric case** in this series. Overall, 34 patients were females (92%), the average patient age was 45.5 years, and the average patient weight was 204.8 lbs (range 145.1 to 451.9lbs). See Table 4 below for the demographic characteristics and clinical data of the case series.

Obesity predisposes a person to many risk factors including cholelithiasis and acute cholecystitis. In addition, the mechanism by which orlistat acts on the body to encourage weight lost, inhibiting digestive lipases, could be the mechanism by which the risk for gallstone formation is increased in a patient.[9, 10] Further studies may be needed to determine the role of orlistat on the gallbladder.

Our case series resulted in one pediatric case; diagnosis was classified as acute cholecystitis with cholelithiasis. This case did not generate safety concerns about orlistat use and cholelithiasis that are specific to pediatrics patients. The clinical presentation of the pediatric case was similar to those observed in the adult population. On the other hand, when the entire case series is taken into account, some concerns are generated about the association of cholelithiasis and orlistat use in all populations, particularly as the drug is used in obese patients with co-morbidities. With the findings from our case series, and a possible contributory mechanism of action by orlistat, the Division of Drug Risk Evaluation (DDRE) will initiate further review on orlistat and cholelithiasis (with inclusion of postmarketing data for other anti-obesity drugs for perspective) to the Division of Metabolism and Endocrinology Products (DMEP). If warranted, we will make recommendations for changes to the orlistat product labeling in the future review.

2.0 INTRODUCTION

This follow-up consult was requested by OPT in preparation for their PAC meeting scheduled for April 2007. The initial One-Year Post-Pediatric Exclusivity Postmarketing Review, which was completed in November 4, 2004, identified only one pediatric case for the 12-month time period after pediatric exclusivity was granted (granted on September 12, 2003).[1, 2] As a result of this initial review, the PAC which convened on February 14, 2005, concluded that active monitoring of pediatric adverse events should continue for future review by the committee.[3] Subsequently, OPT requested a follow-up review of pediatric cases of cholelithiasis or other gall bladder-related adverse events.

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1 Swann J. Pediatric Exclusivity Review for Xenical® (orlistat), NDS 020-766, dated November 4, 2004. Available at: Division Files System.

2 Memo to File: Pediatric Exclusivity Granted for NDA 020-766, dated 9/26/03. Available at: Division System Files. Accessed: February 2007.

3 Transcript from the Pediatric Advisory Committee, Sixth Meeting, held February 14, 2005. Available at: http://www.fda.gov/ohrms/dockets/ac/oc05.html. Accessed: February 2007.

3.0 PRODUCT INFORMATION, PRODUCTS, INDICATIONS, PEDIATRIC LABELING, AND PEDIATRIC FILING HISTORY

3.1 Product Information[4]

Xenical® (orlistat) is a reversible lipase inhibitor, indicated for obesity management. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with gastric and pancreatic lipases. These inactivated enzymes are unavailable to hydrolyze dietary fat in the form of triglycerides, which then are not absorbed and this results in a reduction of available dietary calories which may have a positive effect on weight control.

3.1 Products[5]

Table 1: Orlistat Products

Drug Name	Active Ingredients	Strength	Dosage Form / Route	NDA Number	Sponsor	Approval Date
Xenical®	orlistat	120MG	capsule/ oral	020-766	Hoffmann-La Roche	April 23, 1999

3.2 Indications[4]

Xenical® is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. It is also indicated to reduce the risk for weight regain after prior weight loss. Xenical® is indicated for obese patients with an initial body mass index (BMI) =30 kg/m2 or =27 kg/m2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

3.3 Pediatric Labeling[4]

CLINICAL PHARMACOLOGY

Special Populations

Pediatrics

Plasma concentrations of orlistat and its metabolites M1 and M3 were similar to those found in adults at the same dose level. Daily fecal fat excretions were 27% and 7% of dietary intake in orlistat and placebo treatment groups, respectively.

Other Short-term Studies

Pediatrics

In a 3-week study of 32 obese adolescents aged 12 to 16 years, XENICAL (120 mg three times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, or copper. The iron balance was decreased by

4 Xenical® (orlistat), Labeling for NDA 020-766/S-022. Approved January 5, 2007. Available at: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory. Accessed: February 2007.

5 U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Drugs@FDA. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda. Accessed: February 2007.

64.7 µmole/24 hours and 40.4 µmole/24 hours in orlistat and placebo treatment groups, respectively.

CLINICAL STUDIES

Pediatric Clinical Studies

The effects of XENICAL on body mass index (BMI) and weight loss were assessed in a 54-week multicenter, double-blind, placebo-controlled study in 539 obese adolescents (357 receiving XENICAL 120 mg three times a day, 182 receiving placebo), aged 12 to 16 years. All study participants had a baseline BMI that was 2 units greater than the US weighted mean for the 95th percentile based on age and gender. Body mass index was the primary efficacy parameter because it takes into account changes in height and body weight, which occur in growing children.

During the study, all patients were instructed to take a multivitamin containing fat-soluble vitamins at least 2 hours before or after ingestion of XENICAL. Patients were also maintained on a well-balanced, reduced-calorie diet that was intended to provide 30% of calories from fat. In addition, all patients were placed on a behavior modification program and offered exercise counseling.

Approximately 65% of patients in each treatment group completed the study.

Following one year of treatment, BMI decreased by an average of 0.55 kg/m2 in the XENICAL-treated patients and increased by an average of 0.31 kg/m2 in the placebo-treated patients (p=0.001).
The percentages of patients achieving =5% and =10% reduction in BMI and body weight after 52 weeks of treatment for the intent-to-treat population are presented in Table 7.

Table 7 Percentages of Patients with >/=5% and >/=10% Decrease in Body Mass Index and Body Weight After 1-Year Treatment * (Protocol NM16189)

	Intent-to-Treat Population †							
	>/=5% Decrease				**>/=10% Decrease**			
	XENICAL	**n**	**Placebo**	**n**	**XENICAL**	**n**	**Placebo**	**n**
BMI	26.5%	347	15.7%	178	13.3%	347	4.5%	178
Body Weight	19.0%	348	11.7%	180	9.5%	348	3.3%	180

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
† Last observation carried forward

PRECAUTIONS

General

Table 10 illustrates the percentage of adolescent patients on XENICAL and placebo who developed a low vitamin level on two or more consecutive visits during the 1-year study.

Table 10 Incidence of Low Vitamin Values on Two or More Consecutive Visits (Pediatric Patients With Normal Baseline Values [*])

	Placebo [†]	XENICAL [†]
Vitamin A	0.0%	0.0%
Vitamin D	0.7%	1.4%
Vitamin E	0.0%	0.0%
Beta-carotene	0.8%	1.5%

* All patients were treated with vitamin supplementation throughout the course of the study

[†] Treatment designates placebo plus diet or XENICAL plus diet

Pediatric Use

The safety and efficacy of XENICAL have been evaluated in obese adolescent patients aged 12 to 16 years. Use of XENICAL in this age group is supported by evidence from adequate and well-controlled studies of XENICAL in adults with additional data from a 54-week efficacy and safety study and a 21-day mineral balance study in obese adolescent patients aged 12 to 16 years. Patients treated with XENICAL had a mean reduction in BMI of 0.55 kg/m2 compared with an average increase of 0.31 kg/m2 in placebo-treated patients (p=0.001). In both adolescent studies, adverse effects were generally similar to those described in adults and included fatty/oily stool, oily spotting, and oily evacuation. In a subgroup of 152 orlistat and 77 placebo patients from the 54-week study, changes in body composition measured by DEXA were similar in both treatment groups with the exception of fat mass, which was significantly reduced in patients treated with XENICAL compared to patients treated with placebo (-2.5 kg vs -0.6 kg, p=0.033). Because XENICAL can interfere with the absorption of fat-soluble vitamins, all patients should take a daily multivitamin that contains vitamins A, D, E, K, and beta-carotene. The supplement should be taken at least 2 hours before or after XENICAL (see CLINICAL PHARMACOLOGY: Other Short-term Studies; CLINICAL STUDIES: Pediatric Clinical Studies; ADVERSE REACTIONS: Pediatric Patients). XENICAL has not been studied in pediatric patients below the age of 12 years.

ADVERSE REACTIONS

Pediatric Patients

In clinical trials with XENICAL in adolescent patients ages 12 to 16 years, the profile of adverse reactions was generally similar to that observed in adults.

3.4 Pediatric Filing History[2, 6, 7]

Table 2: Relevant Pediatric Filing History	
Date	**Regulatory Activity**
8/9/2000	Written Request letter requested sponsor to conduct pediatric studies using orlistat. Two studies were requested: 1) A 52-week randomized, double-blind, placebo-controlled study in obese adolescents aged 12 to 16 years; and 2) A 3-week, randomized, double-blind, placebo-controlled mineral balance study in obese adolescents.
7/3/2002	Written Request reissued as a result of the Best Pharmaceuticals for Children Act, signed in 2002.
9/12/2003	Pediatric Exclusivity Granted
12/12/2003	Approval of supplemental NDA 20-755/S-018 for pediatric indication (obese adolescents aged 12 to 16 years)

4.0 LITERATURE SEARCH

Searches in the MEDLINE and Scopus databases were completed using the terms 'orlistat', 'Xenical', 'gallstones', 'cholelithiasis', and 'gallbladder'; and limited to English. No articles or case reports were identified for children using any of the search terms. While no case reports were identified for adults, several articles were identified which described the effect of orlistat on the gallbladder.

Some articles concluded that orlistat had no adverse effect of the gallbladder, other concluded that it did. Whether or not orlistat as a therapy was implicated in adversely affecting the gallbladder may be influenced by the sponsorship of a particular article. Guerciolini, who worked for Hoffman-La Roche at the time the article was published, concluded that orlistat did not "produce significant disturbances to GI physiological processes (gastric emptying and acidity, gallbladder motility, bile composition and lithogenicity)."[8] But the work of others found that orlistat significantly reduced gallbladder emptying via inhibition of cholecystokinin (CCK) release.[9, 10] And even with these finding, both articles state that long-term studies are needed to adequately evaluate the impact of orlistat on the gallbladder.[9, 10]

5.0 DRUG USAGE DATA

The following table summarizes the projected number of total prescriptions dispensed by retail pharmacies (chain, independents, food stores, and mass merchandisers; mail order

6 BPCA WR re-issued for NDA 020-766, dated 7/2/02. Available at: Division Files System. Accessed: February 2007.

7 Approval Letter for NDA 020-766, dated 12/12/03. Available at: Division System Files. Accessed: February 2007.

8 Guerciolini R. Mode of action of orlistat. Int J Obes Relat Metab Disord. 1997 Jun;21 Suppl 3:S12-23.

9 Ellrichmann M, Ritter PR, Otte JM, Schrader H, Banasch M, Brunke G, Herzig KH, Seebeck J, Schmidt WE, Schmitz F. Orlistat reduces gallbladder emptying by inhibition of CCK release in response to a test meal. Regul Pept. 2007 Mar 1;139(1-3):136-40.

10 Mathus-Vliegen EM, Van Ierland-Van Leeuwen ML, Terpstra A. Lipase inhibition by orlistat: effects on gall-bladder kinetics and cholecystokinin release in obesity. Aliment Pharmacol Ther. 2004 Mar 1;19(5):601-11.

facilities are excluded) in the U.S. for Xenical® (orlistat). The Table 3 is distributed by calendar years; 2002 through 2006.[11]

Table 3: Drug Utilization Data
Projected Number of Total Prescriptions Dispensed with Market Share
The values are absolute; do not add zeros

	2002 TRXs†	2003 TRXs	2004 TRXs	2005 TRXs	2006 TRXs	Total TRXs
Gender by Age Group	*Values are absolute. Do not add zeros.*					
Female	1,137,623	895,420	658,659	478,323	409,678	3,579,703
0-11	800	600	397	337	171	2,305
12-16	2,568	2,160	1,943	1,093	895	8,659
17-30	96,004	76,796	52,793	33,194	28,929	287,716
31-64	925,936	721,591	530,791	384,194	327,420	2,889,932
65+	107,964	90,781	70,232	58,314	51,604	378,895
Unspecified	4,351	3,492	2,503	1,191	659	12,196
Male	319,651	245,412	177,632	132,786	114,260	989,741
0-11	406	257	245	168	127	1,203
12-16	943	766	803	598	582	3,692
17-30	15,148	10,834	7,918	5,380	4,487	43,767
31-64	262,554	200,463	142,011	104,433	90,087	799,548
65+	39,291	32,088	25,904	21,679	18,672	137,634
Unspecified	1,309	1,004	751	528	305	3,897
Unspecified Age	1,790	2,084	3,772	2,027	1,503	11,176
0-11	5	9	9	--	1	24
12-16	2	6	4	--	4	16
17-30	50	75	118	95	66	404
31-64	749	1,040	1,593	1,280	556	5,218
65+	141	196	310	278	240	1,165
Unspecified	843	758	1,738	374	636	4,349
TOTAL USAGE	***1,459,064***	***1,142,916***	***840,063***	***613,136***	***525,441***	***4,580,620***

† TRXs (or Total Prescriptions) include New and Refill prescriptions.
Source Files: 2007-344 Swann 2-28-07 orlistatsibutramine TRx gender age 2002-2006 UNROUNDED.qry

11 Verispan Vector One™: National, Years 2002-2006, Data Extracted 2-13-07.

Because the AERS data were analyzed based on calendar year, the usage data provided are also distributed by calendar year. For the time period, 2002 through 2006, there was a 64% decrease in orlistat use in all patient ages. Regardless of gender, the majority of use was found in the age band 31 through 64; with females comprising 63% of this use.

Currently, the product is indicated for pediatric use in ages 12 to 16 years, but the data show some off-labeled use in ages 0 through 11. Overall, use in children of all ages is approximately 0.35% (15,899 TRXs) of the product's use; with use in children ages 0 through 11 totaling 3,532 prescriptions or 0.08%.

With respect to gender and age, pediatric females of all ages represented approximately 0.24% (10,964 TRXs) of the overall orlistat use, and pediatric males of all ages represented approximately 0.11% (4,895 TRXs). With both genders, use was largest in ages 12-16.

6.0 AERS SEARCH METHODS

6.1 AERS Search Criteria

Drug Name: Xenical® (orlistat)
Drug Role: Suspect
AERS Outcome: all domestic reports
MedDRA Terms: Higher Level Group Terms (HLGT)
a. Bile Duct Disorders
b. Gallbladder Disorder
Search Date: from April 23, 1999 (U.S. approval date) through December 2006

6.2 Case Selection Criteria

Case Inclusion Criteria

1. Clinical diagnosis of cholelithiasis, and/or cholecystitis OR
2. Event confirmed by diagnostic imaging or by surgery AND
3. Orlistat use preceded the diagnosis.

Case Exclusion Criteria

1. Cases with prior history of symptomatic gallstones, cholecystitis, or gallbladder or biliary disorders were excluded.

6.3 Case Classification

Gallbladder disease is a spectrum of disorders. The clinical stages of cholelithiasis are asymptomatic (the presence of gallstones without symptoms), symptomatic (the presence of gallstones with symptoms or biliary colic), and complicated (e.g., cholecystitis, choledocholithiasis, and cholangitis).[12,13] Since our AERS search did not identify any

12 eMedicine from WebMD, online. Cholelithiasis. Available at: http://www.medscape.com/files/emedicine/topic97.htm. Last Updated: June 12, 2006. Accessed: February 2007.

13 eMedicine from WebMD, online. Cholecystitis and Biliary Colic. Available at: http://www.emedicine.com/EMERG/topic98.htm. Last Updated: February 7, 2007. Accessed: February 2007.

cases of choledocholithiasis and cholangitis, only the event of acute cholecystitis will represent this class.

To aid in the analysis of this case series, each case was further evaluated and assigned to one of the following classes:

1. Class I - Asymptomatic Cholelithiasis[12]
   A. Clinical diagnosis OR
   B. Presence of gallstones confirmed by diagnostic imaging or by surgery, but no physical symptoms.

2. Class II - Symptomatic Cholelithiasis[13]
   A. Clinical diagnosis OR
   B. Presence of gallstones confirmed by diagnostic imaging or by surgery, and presence of physical symptoms which can include pain in epigastrium or upper right quadrant that may last from 1 to 5 hours, particularly after meals OR nausea, and vomiting, without fever.

3. Class III - Complicated or Acute Cholecystitis[13]
   A. Clinical diagnosis; OR
   B. Two or more elements from the signs and symptoms listed below:
      i. Nausea, vomiting, fever or increased white blood cell (WBC) count,
      ii. Abnormal liver tests: elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST);
      iii. Pain in epigastrium or upper right quadrant for more than 6 hours, particularly after meals; OR
      iv. Inflamed gallbladder.

7.0 AERS SEARCH RESULTS

7.1 Summary of Cases

The purpose of this consult was to search AERS for any new reports of cholelithiasis in the pediatric population (ages 0 to 16 years). The original consult, dated November 4, 2004, identified only one report of cholelithiasis in children and this report was received by the Agency outside of the Pediatric Exclusivity time period, which was September 12, 2003 through September 12, 2004, and therefore was not an area of focus until during the PAC of February 2005. Our current search of AERS did not identify any new reports.

To better understand the adverse event of interest and its association with orlistat therapy, we identified all cases of cholelithiasis for this series. A search of the AERS database resulted in 95 reports. After a hands-on review, three duplicates were identified and 55 cases excluded for the following reasons: insufficient data (29), not an event of interest (24), prior history of gallbladder-related disorders (2). The remaining 37 cases were further evaluated and assigned to one of three classes outlined above. This classification resulted in the following distribution: seven asymptomatic cases, 16 symptomatic case, and 14 complicated cases. See Table 4 below for the demographic characteristics and clinical data of the case series.

Within the series of 37 cases, 30 (81%) resulted a hospitalization, and 28 (76%) in a cholecystectomy. There were no fatalities in this series and **only one pediatric case** (see case narrative below). Overall, 34 patients were females (92%), the average patient age was 45.5 years, and the average patient weight was 204.8 lbs (range 145.1 to 451.9lbs). Thirty-three cases reported daily dose, and the average dose was 301.8 mg/day. Thirty-six cases (97%) reported at least one risk factor which could have contributed to the adverse event (see Appendixes 1 and 2 below). Two cases reported baseline ultrasounds negative for the presence of gallstones.

The distribution of cases by Classes is as follows: seven asymptomatic (19%), 16 symptomatic (43%), and 14 complicated (38%). With respect to the numbers of cholecystectomy (n=28) by diagnoses (% of total surgeries), the distribution is the following: five for asymptomatic (18%), 10 for symptomatic (36%), and 13 for complicated (46%). See Table 4 for patient demographics and clinical data.

When analyzing the data across classes, we observed that Class III (or the complicated cases) contained both the pediatric case and the cases of patients who were 65 years and older. The duration of therapy was the longest for the patients in Class III; the average days of therapy was approximately 208 days. In addition, patients in Class III reported 13 (93%) of the 14 cases resulted in a cholecystectomy. See Table 4 for patient demographics and clinical data.

As stated earlier, there was only one pediatric case in this series, ISR #: 4080703. Based on the patient's clinical presentation, this case was classified as acute cholecystitis with gallstones (a Class III) and is described as follows: A 15-year-old female (BMI=30.3, weight=195.3 lbs), enrolled in a 54-week study of the efficacy and safety of orlistat in the weight management of obese pediatric patients, was ini [redacted] edication three times a day as per protocol on June 29, 2001. On [redacted], the patient developed right upper quadrant pain associated with vomiting. She was taken to a hospital and an abdominal ultrasound scan showed multiple gallbladder calculi. Her relevant laboratory test showed elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT), and white blood cell count ; values were (110 U/L, normal < 36), (66 U/L, normal < 52), and (119000/microliter; normal 4000-11000) respectively. The patient's last dose of study medication was on December 11, 2001. On unspecified dates, treatment with meperidine, esomeprazole, and dicyclomine was started. As she awaited surgery, it was reported that her condition worsened on December 13, 2001. On [redacted], the patient underwent a cholecystectomy, and on an unspecified date the patient was discharged. On January 18, 2002, treatment with study medication was re-started. On an unspecified date, the study ended; the drug code was broken and it was determined that the patient received orlistat, 120 mg three times a day. No information was provided regarding the patient's medical history or her concomitant medications.

The patient demographics and clinical data for the overall case series are detailed in Table 4 below.

Table 4: Patient Demographics and Clinical Data for Orlistat Case Series				
PATIENT CHARACTERISTICS	**Class I Asymptomatic** (n=7)	**Class II Symptomatic** (n=16)	**Class III Complicated** (n=14)	**Total** (N=37)
Gender				
Female	5	16	13	34
Male	2	0	1	3
Age (years)	n=4	n=7		n=34
Range	40-63	29-62	15-74	15-74
Mean	50.0	43.2	46.9	45.5
Median	48.5	42.5	43.5	43.0
Age Distribution	n=4			n=34
00-11	0	0	0	0
12-16	0	0	1	1
21-30	0	2	0	2
31-64	4	14	9	27
65-90	0	0	4	4
Unknown	3	0	0	3
Report Type				
15-Day	7	15	14	36
Periodic	0	1	0	1
Report Source *				
Consumer	2	9	3	14
Health Professional	5	7	11	23
Study	0	1	1	2
Outcome *				
Disability	0	0	2	2
Hospitalization	5	12	13	30
Other	2	4	1	7
Required Intervention	2	8	5	15
Weight (lbs)	n=4	n=15		n=33
Range	207.9-349.0	145.1-451.9	151.9-266.1	145.1-451.9
Mean	156.8	228.2	202.0	204.8
Median	207.9	225.1	197.0	210.1
Dose (mg/day)	n=4		n=13	n=33
Range	120-360	120-360	120-360	120-360
Mean	300.0	292.5	313.8	301.8
Median	360.0	300.0	360.0	360.0

Table 4: Patient Demographics and Clinical Data for Orlistat Case Series continued:				
PATIENT CHARACTERISTICS	**Class I Asymptomatic** (n=7)	**Class II Symptomatic** (n=16)	**Class III Complicated** (n=14)	**Total** (N=37)
Duration of Therapy (days)	n=5	n=15		n=34
Range	30-378	6-241	23-642	6-642
Mean	117.9	100.8	208.6	144.8
Median	60.0	94.0	165.5	108.0
Discontinued Drug	n=4	n=14		n=32
Yes	2	11	14	27
No	2	3	0	5
Unreported	3	2	0	5
Symptoms *		n=16	n=12	n=28
Abdominal Pain	0	16	11	27
Nausea/Vomiting	0	6	9	15
Fever	0	0	3	3
Confirmed by Imaging	n=3		n=10	n=29
Yes	3	16	9	28
No	0	0	1	1
Unreported	4	0	4	8
Baseline Gallbladder Imaging	n=0	n=1	n=1	n=2
Negative	0	1	1	2
Unreported	7	15	13	35
Cholecystectomy Performed	n=5	n=14		n=33
Yes	5	10	13	28
No	0	2	1	3
Planned	0	2	0	2
Unreported	2	2	0	4
Risk Factors *	n=6	n=16	n=14	n=36
Female gender	5	16	13	34
Obesity	4	15	14	33
Co-administered Drugs	1	5	8	14
Concurrent Disease States	2	5	5	12
1st degree relative with gallstones	0	0	1	1
Ethnicity	0	1	0	1
Multiparity	0	2	1	3
Pregnancy	0	1	1	2

* Events are not mutually exclusive.

7.2 Selected Case Narratives

Because only one domestic pediatric case was identified in this series, the case narratives of young adults (age less than or equal 30 years) are presented for clinical descriptive purposes.

ISR #: 3572356 *(Symptomatic Cholelithiasis)*
A 29-year-old female (BMI=36.4, weight=225.1 lbs) began orlistat therapy 120 mg three times a day with meals on March 3, 2000; occasionally experienced oily stools. Around May 1, 2000, the patient awakened with a sharp, constant pain in the right upper quadrant (RUQ) of her stand that lasted for an hour. Around June 1, 2000, she experienced another episode of sharp, constant RUQ pain that radiated to her back and last five hours; she also vomited. ON June 25, 2000, the patient took her orlistat, about two hours later she experienced RUQ abdominal pain; orlistat was discontinued. On June 27, 2000, the patient took orlistat with a low fat meal and again experienced RUQ abdominal pain. On an unreported date, an ultrasound scan of her gallbladder revealed multiple gallstones. On July 20, 2000, orlistat therapy was discontinued as advised by the patient's doctor. At the time of the report, surgery for removal of her gallbladder was planned. Her relevant medical history included two pregnancies both delivered via caesarean sections. Her concomitant medications included labetalol and hydrochlorothiazide.

ISR #: 3451428 *(Symptomatic Cholelithiasis)*
A 30-year-old female (BMI=49.1, weight =259.9 lbs) began orlistat 120 mg twice a day around July 15, 1999 for treatment of obesity. On December 17, 1999, the patient took a home pregnancy test which resulted in positive findings. Orlistat was discontinued on an unspecified date. On December 20, 1999, she visited her physician, and a blood test was positive for pregnancy. The patient developed severe abdominal pain on January 4, 2000, and an ultrasound scan performed that day showed many gallstones. On , the patient was hospitalized and a cholecystectomy was performed. The patient reported "feeling very well" on January 20, 2000. The patient had no relevant medical history; her mother died of breast and ovarian cancer, her father died of leukemia. She does not smoke or drink alcohol. No concomitant medications were reported.

7.3 Limitations of AERS
It is possible that there are other pediatric orlistat adverse event reports. The voluntary or spontaneous reporting of adverse events from health care professionals and consumers in the U.S reflects underreporting and also duplicate reporting.[14] 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.

8.0 DISCUSSION
Obesity is a chronic disease with serious health consequences. It is an important risk factor for many medical disorders, and certain disorders like gastro-esophageal reflux disease, gallstones, cholecystitis, and pancreatitis are more prevalent in obese people.[10] However, because of their weight obese people are at risk of developing gallstones and at

14 Ahmad SR Goetsch, GA, and Marks NS. Spontaneous Reporting in the United States. In: Strom BL, ed. Pharmacoepidemiology, 4th ed. West Sussex, England: Wiley and Sons; 2005: 135-159.

the same time, they are at an increased risk of developing gallstones during weight reduction.[10, 15]

One epidemiologic study found that over a 5-year period, new gallstones developed in 2.2% of the men and 2.9% of the women (aged 30 years and older).[16] In the United States, the incidence of gallstones occurs in approximately 10% (20 million) of persons 40 years and older; with a significantly higher prevalence in women compared to men (2:1).[15, 16] Our findings, with respect to age (n=33 cases age 30 years or older) and gender (n=34 cases of females), are similar to epidemiological sources.[15, 16] In addition, the majority of our cases were also associated with at least one factor that increased their risk for gallstones. (See Table 4: Patient Demographics and Clinical Data above and Appendix 1: Risk Factors for the Development of Gallstones below.)

Vauthey et al. stated that considering these numbers and the limited healthcare resources, treating every patient diagnosed with asymptomatic gallstones by cholecystectomy is not possible.[17] He stated that because the risk factors for symptoms, and possibly the complications of gallstones are cumulative, prophylactic cholecystectomy should be considered in some populations.[17] In our case series, we found that 75.7% of our cases (n=28) reported having a cholecystectomy and 2 had operations scheduled at the time of the reports. In Class I or the asymptomatic cases, five patients in that Class had a cholecystectomy (71%).

With respect to usage, orlistat use in the pediatric population (ages 0 to 16 years) represented 0.35% of the overall use; 0.27% use was within the indicated pediatric population (ages 12 to 16 years), and 0.08% use was in off-labeled use (a pediatric population age 0 to 11 years).[11] Our case series identified only one pediatric case. The patient's clinical presentation was similar to the adult complicated cases; her outcome was a cholecystectomy, which was the same treatment outcome reported in 13 (93%) of the 14 Class III cases. But AERS is largely a voluntary reporting system, and the extent of underreporting is unknown. It has been estimated that the FDA receives by direct report less than 1% of suspected serious adverse event reports.[14] Therefore, the cases spontaneously reported to any surveillance program may represent only a small portion of the number of cases that may have actually occurred.[14] Therefore, this one pediatric case could represent a significant number of actual pediatric cases obscured by underreporting.

The initial gastrointestinal effects of orlistat are well-documented. But it is the long-term biochemical effects of orlistat that are less well-known. Various clinical trials have been undertaken, designed to identify the drug's effect on the digestive system. But studies often utilize subjects similar to those in Ellrichmann et al. study. These subjects were considered healthy, young adults (aged 22 to 45 years), with no gastrointestinal or

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15 Cui H, Peralta R. Cholelithiasis. In: 5-Minute Clinical Consult 2007, The 15th Ed., online. Available at: http://online.statref.com. Accessed: February 2007.

16 Persely KM, Rajeev J. VI Gallstones and Biliary Tract Disease. In: ACP Medicine 2007, online. Available at: http://online.statref.com. Accessed: February 2007.

17 Vauthey JN, Saldinger PF. The natural history of gallstones and asymptomatic gallstones. In: Blumgart LH, Fong Y, eds. Surgery of the liver and biliary tract. 3 ed. W.B. Saunders; 2000: 643-49.

endocrine disorders, and who were not taking any medication.[9] These clinical characteristics of study subjects usually differ greatly from the patient characteristics of the treated population. As our case series has shown, the treated population usually consist of those who because of their obesity have various disease-related disorders and who are taking several concomitant medications which alone could have caused their symptoms.

Orlistat, a covalent inhibitor of digestive lipases, is derived from lipstatin which is a natural product of *Streptomyces toxytricini*. It covalently blocks the active site of lipase, inhibiting the hydrolysis of dietary triglycerides thereby reducing the intestinal absorption of monoglycerides (MGs) and free fatty acids (FFA).[9] Ellrichmann et al. stated that "the inhibition of intestinal lipolytic activity by orlistat results in reduced gallbladder emptying through inhibition of meal-mediated CCK release."[9] They hypothesized that "impaired gallbladder motility may represent a risk factor in chronic treatment of severe obesity using orlistat."[9] In addition, a study conducted by Matgus-Vliegen et al. concluded that "obese subjects with diabetes or hyperlipidemia, who are more at risk of gallstones, should be followed carefully" when using orlistat.[10]

While the physiological effect of orlistat could contribute to the incidences of cholelithiasis, the *CLINICAL PHARMACOLOGY, Other Short-term Studies* section of the product labeling states that in adults, "there were no clinically significant changes observed in gallbladder motility, bile composition, or lithogenicity…"[4] However, an overlay of orlistat for this adverse event is possibly suggested from the comparative data presented in the *PRECAUTIONS* section of the labeling which states that, "in a clinical trial of XENICAL for the prevention of type 2 diabetes, the rates of cholelithiasis as an adverse event were 2.9% (47/1649) for patients randomized to XENICAL and 1.8% (30/1655) for patients randomized to placebo."[4] In addition the labeling states that, in this trial the incidence of cholelithiasis was similar for XENICAL and placebo at similar amounts of weight loss, and that an increase in cholelithiasis with XENICAL was not seen in trials that were not evaluating the prevention of type 2 diabetes.[4]

With this background (biological plausibility of drug effect as well as clinical trials data), our current case series from postmarketing reports suggests that orlistat may have an effect on the gallbladder that results in the formation of gallstones over and above the tendency for this disease from the natural history of this population. This suggestion is for the overall treated population including adolescents. With one pediatric case in this case series which has a similar presentation as the adults, there is no safety concern that is specific to pediatrics at this time.

9.0 CONCLUSION AND RECOMMENDATIONS

In conclusion, effective drug products for the management of weight lost is medically important. In addition, understanding a drug's safety profile so that the right patient can be prescribed the right drug is equally important. However, there is a need to understand the overlay of the drug adverse effect over and above the natural history of gallstone disease in the obese population with variable co-morbidities. With regards to a specific

pediatric perspective, we have just one pediatric case in our case series. The clinical presentation and the outcome of this pediatric case were similar to those observed in the adult population and to the clinical findings of the supplemental review (S-018) for the pediatric indication.[18] This case did not generate concerns about orlistat use and cholelithiasis that are specific to pediatrics patients.

On the other hand, when the entire case series is taken into account, some concerns are generated about the association of cholelithiasis and orlistat use in all populations, particularly as the drug is used in obese patients with co-morbidities. With the findings from our case series, and a possible contributory mechanism of action by orlistat, DDRE will initiate further review on orlistat and cholelithiasis (with inclusion of postmarketing data for other anti-obesity drugs for perspective) to the DMEP. If warranted, we will make recommendations for changes to the orlistat product labeling in that future review.

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Concur:

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18 Clinical Review of Supplement 018/NDA 20-766. Available at: Division System Files. Accessed: February 2007.

APPENDIX 1

Risk Factors for the Development of Gallstones[15, 19]

- Obesity
- Profound weight loss
- Increased age (peak in 60s)
- Female sex
- Multiparity
- Prolonged fasting
- Cystic fibrosis
- Hypertriglyceridemia
- Hyperlipidemia
- Total parenteral nutrition
- Pregnancy
- High spinal cord injury
- Medications
  - Oral contraceptives
  - Octreotide
  - Estrogens/progesterones
  - Ceftriaxone
  - Clofibrate
- Ethnicity – Asian, Native-American (Pima Indian tribe), Scandinavia, Hispanics, Caucasians
- Chronic intravascular hemolysis – sickle cell anemia, blood dyscrasia,
- Liver disease -- alcoholic liver disease, cirrhosis, hepatitis
- Chronic parasitic infections
- Ileal disease, resection, or bypass
- Biliary infection
- Truncal vagotomy
- Duodenal diverticulum
- Primary biliary cirrhosis
- Diabetes
- Inflammatory Bowel Disease

19 Brady WJ, Aufderheide TP, Tintinalli JE. 85. Cholecystitis and Biliary Colic. In: Emergency Medicine: A Comprehensive Study Guide - 6th Ed. (2004), online. Available at: http://online.statref.com. Accessed: February 2007.

APPENDIX 2

Risk Factors for the Development of Acute Cholecystitis[20]

- Current gallstones
- Cardiac surgery
- Trauma
- Obesity: BMI >30
- First-degree relative with gallstones
- Estrogen use
- Rapid weight loss >1.5 kg per week
- Prolonged parenteral alimentation
- Pregnancy

20 Agresta T. Cholecystitis. In: 5-Minute Clinical Consult 2007, The 15th Ed., online. Available at: http://online.statref.com. Accessed: February 2007.

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