

MEMORANDUM

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

PID#: D030559

DATE: November 4, 2004

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Office of Drug Safety (ODS)

THROUGH: Mark Avigan, M.D., Director  
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TO: Solomon Iyasu, M.D., MPH, Team Leader  
Div. of Pediatric Drugs and Development, HFD-960  
Office of Counter-Terrorism and Pediatric Development, HFD-960

SUBJECT: ODS POSTMARKETING SAFETY REVIEW  
Consult: One-Year Post-Pediatric Exclusivity,  
Postmarketing Adverse Event Review  
Drug: Orlistat (Xenical®)  
NDA #: 020-766  
Pediatric Exclusivity Date: September 12, 2003

**Executive Summary**

As requested by the Office of Counter-Terrorism and Pediatric Development, this consult reviews the pediatric adverse events associated with orlistat (Xenical®) during a 12-month period beginning September 12, 2003 (pediatric exclusivity approval date) through September 12, 2004. October 12, 2004 was the data termination date to allow for a one-month lag time for report entry.

To identify the adverse events, two Adverse Event Reporting System (AERS) searches were conducted in the adult and pediatric age groups for the following time periods: 1) April 23, 1999 (approval date) to September 12, 2004, and 2) September 12, 2003 through September 12, 2004.

Our AERS searches yielded only one pediatric report for the 12-month time period after pediatric exclusivity was granted. 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**

AERS searches including all sources - U.S. and foreign.

AERS search dates include two time periods: a) April 23, 1999 (approval date) to September 12, 2004, and b) September 12, 2003 through September 12, 2004.

A. Adverse events from marketing approval date (April 23, 1999) to September 12, 2004:

1. Raw Counts of AERS Reports: see Table 1

Table 1: Raw Counts of AERS Reports †			
	All reports (US)	Serious (US)	Death (US)
All ages ‡	6261 (4989)	6128 (4910)	58 (19)
Adults (≥17)	3828 (2710)	3729 (2651)	54 (18)
Pediatrics (0-16)	22 (13)	21 (13)	0 (0)

† Count may include duplicate reports

‡ Includes null ages

Figure 1: Reporting trend for U. S. pediatric reports from approval date

Calendar Year	Number of U.S. Pediatric Cases
2000	6
2001	3
2002	3
2003	1

2. Top 20 reported event preferred terms (PT) and labeling status of these events (Underlined denotes Unlabeled):

**All Ages:**

steatorrhea (1129); constipation (1119); diarrhea (569); weight increased (566); abdominal pain (565); flatulence (487); frequent bowel movements (336); abdominal distension (285); nausea (272); feces discolored (267); loose stools (244); headache (231); anorectal disorder (222); dizziness (215); vomiting (179); rectal hemorrhage (176); condition aggravated (175); defecation urgency (162); fatigue (160); dyspnea (156)

**Adults:**

steatorrhea (753); constipation (470); abdominal pain (444); diarrhea (431); flatulence (347); weight increased (258); frequent bowel movements (249); nausea (224); loose stools (188); abdominal distension (179); headache (173); dizziness (171); feces discolored (161); condition aggravated (159); vomiting (151); anorectal disorder (149); rectal hemorrhage (134); dyspnea (132); fatigue (130); defecation urgency (128)

**Pediatrics:**

complications of maternal exposure to therapeutic drugs (6); pregnancy (6); steatorrhea (5); caesarean section (4); feces discolored (3); maternal drugs affecting fetus (3); flatulence (2); jaundice neonatal (2); neonatal disorder (2); abdominal pain (1); abnormal feces (1); accidental exposure (1); accidental overdose (1); acne (1); asthenia (1); bowel sounds abnormal (1); bradycardia fetal (1); cardiac murmur (1); cataract (1); cholelithiasis (1)

**B. Adverse events from Pediatric Exclusivity approval date (September 12, 2003) through September 12, 2004:**

**1. Table 2: Counts of reports**

<b>Table 2: Raw Counts of AERS Reports <sup>†</sup></b>			
	<b>All reports (US)</b>	<b>Serious (US)</b>	<b>Death (US)</b>
<b>All ages <sup>‡</sup></b>	211 (71)	211 (71)	6 (2)
<b>Adults (≥17)</b>	159 (50)	159 (50)	6 (6)
<b>Pediatrics (0-16)</b>	1 (0)	1 (0)	0 (0)

<sup>†</sup> Count may include duplicate reports

<sup>‡</sup> Includes null ages

**2. Top 20 reported event preferred terms (PT) and labeling status of these events (Underlined denotes Unlabeled):**

**All Ages:**

cholelithiasis (17); abdominal pain (11); diarrhea (11); dizziness (8); drug interaction (8); drug ineffective (7); hepatitis (7); circulatory collapse (6); hypoglycemia (6); international normalized ratio increased (6); maternal drugs affecting fetus (6); pancreatitis (6); pulmonary embolism (6); steatorrhea (6); depression (5); flatulence (5); hematochezia (5); loose stools (5); pregnancy (5); rectal hemorrhage (5)

**Adults:**

cholelithiasis (13); abdominal pain (10); diarrhea (10); dizziness (8); drug interaction (8); circulatory collapse (6); pulmonary embolism (6); hematochezia (5); hypoglycemia (5); international normalized ratio increased (5); pancreatitis (5); rectal hemorrhage (5); steatorrhea (5); asthenia (4); convulsion (4); depression (4); diverticulum (4); drug ineffective (4); dysarthria (4); dyspnea (4)

**Pediatrics:**

Caesarean section (1); congenital hip deformity (1); maternal drugs affecting fetus (1)

**Postmarketing Review of All Pediatric Adverse Event Reports from (September 12, 2003) through September 12, 2004**

**A. Case Narrative**

ISR #: 4203266-6, Foreign

A 29 year-old female was prescribed orlistat 120 mg three times a day on May 9, 2001, for obesity. On approximately, June 24, 2002, the patient became pregnant; orlistat was subsequently discontinued. On February 6, 2003, the patient delivered a normal female infant by caesarean section. Upon the infant's follow-up visit to her physician, it was determined that the infant had an unstable hip and was referred to orthopedics. X-ray review of infant at 28 weeks revealed a normal hip. The mother reported no concomitant medications except use of a contraceptive implant which was removed five months prior to the pregnancy. Maternal medical history was positive for smoking.

**B. Comment regarding labeling status of the top 20 adverse events and if they are similar to adult adverse event profile.**

There are no adverse events specific to the fetus similar to the adult adverse event profile. However, the adverse event term - 'maternal drugs affecting fetus' was identified in both the pediatric and the 'all age' groups during the post-exclusivity time period.

**C. Comment and analyze any events not recognized for adult population. Recommend actions.**

There are no recommended actions.

**D. Comment and analyze if any events are uniquely identified in pediatric population but are not reported in adult population, including increased frequency of any expected events. Recommend actions.**

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

**E. Summarize and comment on the death reports.**

There were no pediatric deaths identified in this consult.

**F. Summarize all pediatric reports during period if appropriate and develop an adverse event risk profile.**

Because on one pediatric case was identified, an adverse event risk profile can not be determined at this time.

**Conclusion**

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.

**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.*

November 4, 2004

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Joslyn Swann, Pharm.D.  
Safety Evaluator

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Date Signed

Concur:

November 4, 2004

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Lanh Green, Pharm.D., MPH  
Team Leader

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Date Signed

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/s/

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