

# **One Year Post Exclusivity Adverse Event Review: Orlistat**

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**Hari Cheryl Sachs, MD, FAAP  
Medical Officer  
Division of Pediatric Drug Development  
Center for Drug Evaluation and Research  
Food and Drug Administration**



# Background Drug Information

- **Drug:** Xenical<sup>®</sup> (orlistat)
- **Therapeutic Category:** lipase inhibitor
- **Sponsor:** Roche
- **Original Market Approval:** April 23, 1999
- **Pediatric Exclusivity Granted:** September 12, 2003
- **Mechanism of action:** inhibits absorption of dietary fats

# Background Drug Information

- **Indication (12 years and older):**
  - Obesity management in conjunction with weight loss
  - Body Mass Index (BMI)  $> 30 \text{ mg/m}^2$  or  $27 \text{ mg/m}^2$  with risk factors (hypertension, diabetes, dyslipidemia)
- **Adult and Adolescent Dosage:** 120 mg TID

# Drug Use Trends in Outpatient Settings: Orlistat

- Dispensed prescriptions for all age groups have decreased from 1.6 million (Oct 2001- Sept 2002) to 1 million (Oct 2003- Sept 2004).<sup>1</sup>
- Orlistat is prescribed mainly in adults (male: female ratio of 1:3).<sup>2</sup>
- Pediatric patients (ages 1-16) account for <1 % (approximately 4,000) prescriptions annually.<sup>1,2\*</sup>

<sup>1</sup>IMS Health, National Prescription Audit *Plus*<sup>TM</sup>, Oct 2001 – Sept 2004, Data Extracted Nov 2004

<sup>2</sup>Caremark Dimension Rx<sup>TM</sup>, Nov 2001 – Oct 2004, Data Extracted Dec 2004

\*Calculation based on application of proportions of pediatric orlistat prescriptions in Caremark Dimension Rx<sup>TM</sup> to IMS Health, National Prescription Audit *Plus*<sup>TM</sup> to estimate number of orlistat prescriptions dispensed nationwide to pediatric population

# Drug Use Trends in Outpatient Settings: Orlistat

- Prescribers (Oct 2003 to Sept 2004)<sup>1</sup>
  - Internists, family practitioners and osteopathic medicine practitioners accounted for nearly 70% of the prescriptions written.
  - Pediatricians wrote <1%.
- Diagnosis<sup>2</sup>
  - Adults: obesity
  - Pediatric use was not recorded during sampling period.

<sup>1</sup>IMS Health, National Prescription Audit *Plus*<sup>TM</sup>, Oct 2003 – Sep 2004, Data Extracted Nov 2004

<sup>2</sup>IMS Health, National Disease and Therapeutic Index<sup>TM</sup>, Jan 2004 – Sep 2004, Data Extracted Nov 2004

- <http://www.fda.gov/cder/pediatric/Summaryreview.htm>

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### Summaries of Medical and Clinical Pharmacology Reviews of Pediatric Studies as of December 28, 2004

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**Summaries of Medical and Clinical Pharmacology Reviews**

Drug	Sponsor	Review Summary	
Ofloxacin - Ocuflax	Allergan	<a href="#">Medical</a> 	Clinical Pharmacology
Orlistat - Xenical	Hoffmann-La Roche	<a href="#">Medical</a> 	<a href="#">Clinical Pharmacology</a> 
Oseltamivir - Tamiflu	Roche	<a href="#">Medical</a> 	<a href="#">Clinical Pharmacology</a> 

# Pediatric Exclusivity Studies: Orlistat

Studies performed:

- 3 week effect of orlistat on mineral balance
- 54 week efficacy and safety study
- Population PK study as subset of both studies

# Pediatric Exclusivity Studies: Orlistat

- 3 week in-patient double blind, randomized, placebo-controlled study in obese adolescents (n=32)
- Reduced calorie diet plus 120 mg orlistat TID and multivitamin
- Mineral balance:
  - Calcium, copper, iron, magnesium and zinc
  - Plasma and urine sodium and potassium
  - Urine creatinine
- Fecal fat (daily)

# Pediatric Exclusivity Studies: Mineral Balance Results

- No effect on balance of Ca, Mg, PO<sub>4</sub>, Zinc, copper, or creatinine
- Iron balance decreased by 49.7 μmoles/24 hours in orlistat group and decreased by 32.9 μmoles/24 hours in placebo group
- Fecal fat: orlistat treatment increased fecal fat 15.9 grams/day vs. 4.1 grams/day in placebo group
- 94% completed trial

# Pediatric Exclusivity Studies: Safety and Efficacy

- Double blind, placebo controlled, 54 week efficacy and safety trial of obese adolescent patients (age 12-16 years, n=539)
- All patients received reduced calorie diet, nutritional and behavioral counseling, and vitamin supplementation.
- Efficacy Endpoints
  - Primary: BMI (percent of patients achieving 5 or 10% reduction BMI)
  - Secondary: change in body weight, lipids, blood pressure, glucose tolerance and insulin levels

# Pediatric Exclusivity Studies: Safety and Efficacy

- Safety Endpoints
  - Linear growth, Tanner Stage and sex hormone levels
  - Gastrointestinal tolerability
  - Body composition assessment by DEXA scan
  - Fat soluble vitamins, Beta-carotene, serum calcium levels
  - Gallbladder and renal ultrasound
  - EKG

# Pediatric Exclusivity Studies: Efficacy Results

- ~65% completed in each treatment group
- Orlistat vs. placebo significantly:
  - Decreased BMI (-0.55 kg/m<sup>2</sup> vs. +0.31 kg/m<sup>2</sup>, p=.001)
  - Decreased waist and hip circumference
  - Increased percent with 5 or 10% reduction in BMI
    - 5% - 26.5% vs. 15.7% (p=.005)
    - 10% - 13.3% vs. 4.5% (p=.002)
  - Decreased weight gain
  - Increased percent with 5 or 10% reduction weight
    - 5% - 19% vs. 11.7% (p<.05)
    - 10% - 9.5% vs. 3.3% (p<.05)

# Pediatric Exclusivity Studies: Safety Results

- Orlistat compared with placebo
  - No statistically significant differences
    - BP
    - Glucose and insulin levels
    - Lipid parameters
  - Statistically significant differences
    - Lower serum Vitamin E ( $p=.089$ ) and Beta-carotene levels ( $p=.001$ ) in orlistat vs. placebo
    - Increased fatty/oily stools

# Labeling Changes Resulting from Exclusivity Studies

- Precautions
  - Take multivitamin supplement containing fat-soluble vitamins
  - Pediatric patients
    - Clinical trial described
- Adverse Reactions
  - Profile similar to adults

# Additional Relevant Safety Labeling

- Contraindication
  - Chronic malabsorption syndrome
  - Known cholestasis
- Precautions
  - Adhere to dietary guidelines
  - GI symptoms with high fat diet
  - Multivitamin including fat-soluble
  - Increased urinary oxalate
- Misuse in anorexia

# Relevant Safety Labeling

- Pregnancy Category B
- Adverse events
  - Oily stools
  - Infectious diarrhea
  - Nausea
  - Rectal pain/discomfort
  - Vomiting

# Adverse Event Reports since Market Approval: Orlistat 04/23/99 - 10/12/04

- Total number of reports, all ages<sup>†\*</sup>:
  - 6,261 reports (4,989 US)
    - 6,128 serious (4,910 US)
      - 58 deaths (19 US)
- Pediatric reports<sup>\*</sup>:
  - 22 reports (13 US)
    - 21 serious (13 US)
      - No deaths

<sup>†</sup>Includes reports with unknown age

<sup>\*</sup>Counts may include duplicate reports

# Top 20 Reported Adverse Events since Approval (Adults: n=3,828)

## Labeled

Steatorrhea

Abdominal pain

Flatulence

Frequent bowel movements

Nausea

Headache

Dizziness

Vomiting

Fatigue

Defecation urgency

## Unlabeled

Constipation

Diarrhea

Weight increased

Loose stools

Abdominal distension

Feces discolored

Condition aggravated

Anorectal disorder

Rectal hemorrhage

Dyspnea

# Top 20 Reported Adverse Events since Approval (Pediatrics: n=22)

## Labeled

Steatorrhea  
Flatulence  
Abdominal pain

## Unlabeled

Maternal exposure to therapeutic drug  
Pregnancy  
Caesarian section  
Feces discolored  
Maternal drugs affecting fetus  
Neonatal jaundice  
Neonatal disorder  
Abnormal feces

Accidental exposure  
Accidental overdose  
Acne  
Asthenia  
Bowel sounds abnormal  
Fetal bradycardia  
Cardiac murmur  
Cataract  
Cholelithiasis

# Adverse Event Reports during the One-Year Post-Exclusivity Period: Orlistat 09/12/03 – 10/12/04

- Total number of reports, all ages<sup>†\*</sup>:
  - 211 reports (71 US)
    - 211 serious (71 US)
      - 6 deaths (2 US)
- Pediatric reports:
  - 1 report (0 US)
    - 1 serious (0 US)
      - No deaths

<sup>†</sup>Includes reports with unknown age

\*Counts may include duplicate reports

# Top 20 Serious Adverse Events during the One-Year Post- Exclusivity Period (Adults: n=159)

## Labeled

Abdominal pain  
Dizziness  
Steatorrhea  
Depression

## Unlabeled

Cholelithiasis  
Diarrhea  
Drug interaction  
Circulatory collapse  
Pulmonary embolism  
Hematochezia  
International normalized  
ratio increased

Hypoglycemia  
Pancreatitis  
Rectal hemorrhage  
Asthenia  
Convulsion  
Diverticulum  
Drug ineffective  
Dysarthria  
Dyspnea

# **Pediatric Adverse Event during the One-Year Post-Exclusivity Period (n=1)**

- Term neonate with suspected developmental hip dysplasia, normal x-rays with orthopedic follow-up
- Maternal tobacco exposure
- Contraceptive implant removed 5 months prior to pregnancy

# Summary: Orlistat

- Minimal use in pediatric patients
- Insufficient events to draw any conclusions
- Reports of cholelithiasis during trial and post-marketing surveillance (relationship to therapy vs. underlying obesity and rapid weight loss unclear)
- FDA recommends continued monitoring of AEs, particularly for the risk of cholelithiasis, for this drug in all populations.
- Does the Advisory Committee concur?

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