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April 14, 2011

Margaret Hamburg, M.D.,
Commissioner
U.S. Food and Drug Administration
Department of Health and Human Services
WO 2200
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Hamburg:

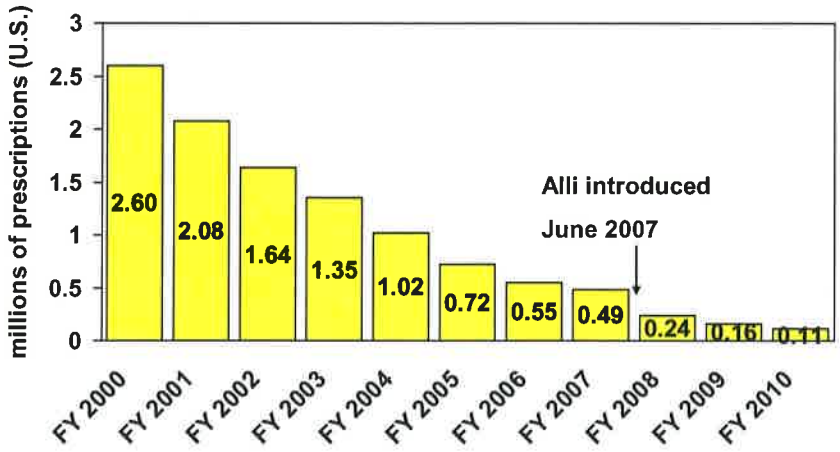
Public Citizen, representing more than 225,000 members and supporters nationwide, hereby petitions the Food and Drug Administration (FDA), pursuant to the Federal Food, Drug, and Cosmetic Act 21 U.S.C. Section 355(e)(3), and 21 C.F.R. 10.30, to immediately ban both the prescription drug, Xenical (orlistat; Hoffman-La Roche), and the over-the-counter (OTC) drug, Alli (orlistat; GlaxoSmithKline), because they expose patients to serious risks that greatly outweigh their minimal clinical benefits. The most serious risks include:

- Severe liver injury, which can lead to liver failure, need for liver transplantation, and death;
- Acute pancreatitis, which frequently results in hospitalization and can lead to death; and
- Acute renal failure secondary to acute oxalate nephropathy, and calcium oxalate nephrolithiasis (kidney stones).

Orlistat is a drug used to treat people who are either overweight or obese. Unfortunately, it has little clinical effectiveness and has the potential to damage a number of organs, including the liver, pancreas, and kidneys. As will be discussed in more detail later, orlistat not only can cause severe liver damage (as acknowledged in a recent FDA warning), but also can cause acute pancreatitis and kidney stones, as predicted by the FDA's Medical Officer before approval and as found in our own analysis of FDA's adverse reaction reports (47 cases of acute pancreatitis and 73 cases of kidney stones in patients receiving either Xenical or Alli).

Certainly related to the increased perception of risks greatly outweighing benefits, physicians have increasingly rejected prescribing Xenical, long before OTC Alli was available, as seen in the figure on the next page:

Rapidly Declining U.S. Prescriptions for Orlistat (Xenical)
(96% decrease from 2000-2010)
most of this decrease preceded Alli introduction



Data from FDA presentations and IMS

In addition, after a burst of promotion-induced sales in the first years of Alli marketing, its sales have also begun to significantly decrease in the U.S. Sales have dropped from $145 million in the first year of marketing (mid-2007 to mid-2008) to $84 million in the most recent year of marketing (mid-2009 to mid-2010), according to data from Nielsen surveys of food and drug store pharmacies (other sales data said to represent an approximately equal amount of sales were not available).

I. BACKGROUND

A. Current FDA-approved indications

Xenical (orlistat) was approved April 23, 1999, as a prescription drug for treatment of obesity at a dose of 120 mg up to three times a day to be taken with any meal containing fat. It is approved for obese patients 12 years of age or older with an initial body mass index (BMI) of ≥30 kilograms per meter squared of body surface area (kg/m^2) or a BMI of ≥27 kg/m^2 if patients have other risk factors, such as hypertension, diabetes, or dyslipidemia.[1]

Alli (orlistat) was approved for OTC use on February 7, 2007, at one-half the prescription dose for weight loss in "overweight" adults, ages 18 and over. A height-

[1] FDA-approved drug label for Xenical (orlistat). Updated December 17, 2010. Web pages 14 and 19. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020766s030lbl.pdf Accessed March 11, 2011.

weight combination table in the drug label indicates that the drug is "right" for those with a BMI ≥27 kg/m^2.[2,3]

B. Mechanism of action

Orlistat is an inhibitor of lipases, enzymes that break down fat (di- and triglycerides); lipase inhibition therefore stops fats from being broken down and subsequently absorbed in the small intestine. The label states that the inhibition is reversible, but since orlistat forms a covalent bond with the enzyme, this inhibition is, in reality, irreversible.[4] According to the FDA pharmacology reviewer, "reactivation of lipase is possible but, according to the sponsor, far too slow to have any significant pharmacological relevance in vivo"[5] as it would presumably involve the synthesis of new enzyme.

The Xenical label lists only gastric and pancreatic lipases as targets of inhibition, but the FDA pharmacology review provides a more comprehensive list: "Orlistat is not selective for gastrointestinal lipases but inhibits a broad range of physiological tri- and diacylglycerol lipases including gastric, pancreatic, carboxylester, lipoprotein, hepatic, and hormone-sensitive lipases."[6] Since orlistat can, to some extent, be absorbed, these cellular lipases would also be inhibited, causing the fat buildup in tissues that was seen in animal studies.

II. EFFICACY

A. FDA clinical efficacy review of Xenical (orlistat) (prior to its approval)

Because five of the seven randomized phase III studies evaluating Xenical (orlistat) (studies BM14119B, BM14119C, NM14161, BM14149, and NM 14185) employed similar study designs and included a homogeneous subject population, the FDA medical officer pooled the data from these five studies to obtain a more accurate assessment of orlistat's efficacy.[7]

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[2] FDA-approved drug label for Alli (orlistat). Approved February 7, 2007. Web page 13. http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021887lbl.pdf. Accessed March 11, 2011.

[3] The height-weight combinations provided in the FDA-approved label for Alli (orlistat) were converted to a BMI using the BMI calculator available at http://www.nhlbisupport.com/bmi/.

[4] Because the reaction is irreversible, the inhibition remains in effect for a long period of time.

[5] FDA pharmacology review for Xenical (orlistat). Web page 2. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed March 14, 2011.

[6] FDA pharmacology review for Xenical (orlistat). Web page 1. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed March 14, 2011.

[7] FDA medical officer's review of clinical data for Xenical (orlistat). Web page 3. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P1.pdf. Accessed February 28, 2011.

1. One-year efficacy data (Xenical)

At baseline there were 1,561 subjects in the 120 mg orlistat group, 452 in the 60 mg orlistat group, and 1,119 in the placebo group. Approximately 81% of the subjects were female, the mean age was 44 years (range 18-78 years), and nearly 92% were Caucasian; their mean body weight was 97 kg (213 pounds (lbs)), and the average BMI was 35 kg/m^2.[8]

The placebo-subtracted mean percent weight loss from baseline to week 52 was approximately 3% for the orlistat 120 mg group. In terms of absolute weight loss from baseline to week 52, the difference from placebo was -2.6 kg (-5.6 lbs) for the 60 mg orlistat group and -3.2 kg (-7.1 lbs) for the 120 mg orlistat group.[9]

2. Two-year efficacy data (Xenical)

Two-year efficacy data was available for subjects enrolled in four of the above-referenced studies (BM14119C, NM14161, BM14149, and NM 14185). At baseline, in the combined data, there were 606 subjects in the 120 mg group, 328 in the 60 mg group and 516 in the placebo group. Approximately 81% of these subjects were female, the mean age was 45 years (range 18-78 years), and approximately 94% were Caucasian; their mean body weight was 96.5 kg (212 lbs) and the average BMI was 35 kg/m^2.[10]

For all three groups, the mean body weight gradually increased from week 40 to week 104. After week 20, the difference in weight loss between the placebo and 120 mg orlistat groups remained fairly constant at approximately 3%. In terms of absolute weight loss, the difference was -2.4 kg (5.3 lbs) for the 60 mg orlistat group and -2.9 kg (6.5 lbs) for the 120 mg orlistat group.[11] This means that the average weight loss (beyond placebo) for the interval from 20 weeks to two years of treatment was only 6.5 lbs out of a starting weight of 212 lbs.

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[8] FDA medical officer's review of clinical data for Xenical (orlistat). Web page 4. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P1.pdf. Accessed February 28, 2011.

[9] FDA medical officer's review of clinical data for Xenical (orlistat). Web page 5. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P1.pdf. Accessed February 28, 2011.

[10] FDA medical officer's review of clinical data for Xenical (orlistat). Web page 9. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P1.pdf. Accessed February 28, 2011.

[11] FDA medical officer's review of clinical data for Xenical (orlistat). Web pages 9-10. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P1.pdf. Accessed February 28, 2011.

B. FDA statistical efficacy review of Alli (orlistat) (prior to its approval) (actual use study NM17247)

Only one study was submitted that specifically targeted the OTC patient population; data from other studies utilizing the 60 mg dose came from the New Drug Application (NDA) for orlistat prescription use and were targeted to a different population.

In the OTC study, subjects were randomized to either 60 mg of orlistat (N=196) or placebo (N=195) with each meal for four months. Enrollment criteria included BMI ≥25 kg/ m^2 and ≤28 kg/m^2, age18 or older, not pregnant or lactating, and no active gastrointestinal (GI) disorders. Most subjects were Caucasian (89%) and female (94%). The rates of subjects completing the study were 72% (placebo) and 78% (orlistat).

The FDA statistician who reviewed that data for OTC effectiveness did not find the weight loss adequate for approval, stating: "So, over a 4-month period, patients can only expect to lose approximately 1 to 2 kg [2.2 to 4.4 lbs] over [more than] diet and exercise alone with the use of orlistat 60 mg tid [three times a day]."[12] Since patients had a baseline weight of 161 lbs, losses ranged from 1% to 3% of initial weight. As a result, "This [statistical] reviewer concludes that though a statistically significant weight loss for orlistat 60 mg compared to placebo is seen, there is no evidence presented that a modest, transient weight loss due to orlistat will afford any long-term clinical benefit through either a change in behavior or a reduced risk of serious clinical diseases manifested by being overweight."[13]

C. FDA clinical efficacy review of Alli (orlistat) (prior to its approval)

The FDA medical officer did not approve the application for OTC orlistat. Her arguments were that "GlaxoSmithKline has *not* shown:"[14]

1) that consumers are able to lose more weight (either clinically or statistically) on orlistat *vs.* placebo;
2) that consumers can maintain their weight loss;
3) that those with a BMI of 25-28 lose a clinically significant amount of weight;
4) that orlistat has any impact on motivation on long-term health or weight loss outcomes;
5) that patients derive a health benefit from having a nonprescription drug available; and

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[12] FDA statistical review for Alli (orlistat). Web page 13. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_StatR.pdf. Accessed March 11, 2011.
[13] FDA statistical review for Alli (orlistat). Web page 21. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_StatR.pdf. Accessed March 11, 2011.
[14] FDA clinical review for Alli (orlistat). Web page 32. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P3.pdf. Accessed March 11, 2011.

6) that any benefit outweighs actual or theoretical risks including interactions with fat-soluble nutrients and drugs.

"Therefore, this reviewer is recommending a Not Approvable action."[15]

D. FDA advisory committee on the efficacy of Alli (orlistat) (prior to its approval)

Dr. Mary Tinetti, a member of the Nonprescription Drugs Advisory Committee that participated in a joint review of Alli with the Endocrinologic and Metabolic Drugs Advisory Committee, asked: "Is there any even epidemiologic data to show that this amount of risk factor change – a millimeter of mercury or two of blood pressure and maybe 3 mm/dl [millimoles per deciliter] in LDL – translate into prevention of stroke or MI?" The answer from the sponsor was, "I am not aware of any such data."[16]

Nevertheless, the current website for Alli misleadingly states that, "New studies show that overweight and obese people using alli® (orlistat 60 mg) with a reduced calorie, lower-fat diet can significantly reduce weight, visceral fat, and waist circumference and therefore may reduce their risk of type 2 diabetes, hypertension, heart disease and stroke."[17]

III. SAFETY

A. Severe liver injury

1. Severe liver injury – pre-clinical studies of Xenical (orlistat)

Early animal studies involving intravenous (IV) administration of orlistat revealed evidence of hepatic lipid accumulation and hepatocellular injury. For instance, in rats given up to 100 mg/kg/day of IV orlistat for two weeks, there was fat accumulation in the spleens and livers of most treated rats, and single-cell hepatic necrosis was seen in rats receiving high doses.[18]

Similar studies in dogs given IV orlistat at doses up to 125 mg/kg/day for two weeks revealed dose-related increases in plasma transaminases, alkaline phosphatase, and

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[15] FDA clinical review of Alli (orlistat). Web page 32. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P3.pdf. Accessed March 11, 2011.

[16] FDA Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee joint meeting transcript. January 23, 2006. Web page 293. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4201T.pdf. Accessed March 11, 2011.

[17] GlaxoSmithKline. Alli press room webpage. http://www.myalli.com/pressroom/alli-reduces-visceral-fat-jan2010.aspx. Accessed March 15, 2011.

[18] FDA pharmacology review for Xenical (orlistat). Web page 10. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed February 28, 2011.

bilirubin. Dogs in the high dose group developed "marked hepatic toxicity" as evidenced by yellow color and multifocal hepatitis with "marked fatty change."[19]
Although the Xenical label states that "[s]ystemic exposure to orlistat is minimal," the data from animal studies contradicts this assertion. Rats and dogs given an oral dose of orlistat labeled with radioactive carbon had "variable" absorption, "ranging from 1 to 22% under physiological conditions." The extent of absorption depended on the formulation of the drug, as well as the presence of food. Absorption was higher with oral doses administered mid-meal than doses administered during the fasting state (of note, orlistat is to be taken with meals). Furthermore, in an intravenous study in dogs, it took 130 hours (> 5 days) for the plasma level to decline to one-half its maximal value—i.e., once the drug was in the body, it took a very long time to be cleared.[20] For humans, "[t]he time to reach complete excretion (fecal plus urinary) was 3 to 5 days."[21]

The FDA pharmacology reviewer noted that the ability of orlistat to get into tissues was due to the "high lipophilicity [fat solubility] of the drug" indicating "extensive tissue penetration."[22] This would explain the fat accumulation seen in some tissues, since the drug's lipid solubility would enable it to cross cell membranes and, once inside, inhibit fat breakdown by tissue lipases.

When absorption of the drug is combined with its high solubility in fatty tissues, it is not surprising that, in male rats given radioactive orlistat orally for 30 days, orlistat accumulated in the liver and kidney to levels 3-fold higher than in plasma and accumulated in white fat to levels ≥5-fold higher than in plasma. Even following a single dose of radioactive orlistat in male rats, radioactivity was found in the liver, as well as the GI wall, urinary bladder, kidney, and white fat. Following multiple oral doses over 30 days, radioactivity was found in the adrenal glands, skin, bone marrow, pancreas, lung, thyroid, heart, and salivary gland. With higher oral doses, there was "fatty infiltration and fatty change" in adrenals, kidneys, bone marrow, and lumen of heart vessels.[23]

Similar gastrointestinal absorption and systemic exposure certainly occurs in humans. Therefore, given that the duration of exposure of patients to Xenical or Alli can be months to years, it is biologically plausible that significant hepatic accumulation of

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[19] FDA pharmacology review for Xenical (orlistat). Web page 11. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed February 28, 2011.
[20] FDA pharmacology review for Xenical (orlistat). Web page 5. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed February 28, 2011.
[21] FDA-approved drug label for Xenical (orlistat). Updated December 17, 2010. Web page 2. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020766s030lbl.pdf. Accessed March 11, 2011.
[22] FDA pharmacology review for Xenical (orlistat). Web page 10. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P4.pdf. Accessed February 28, 2011.
[23] FDA pharmacology review for Xenical (orlistat). Web pages 10-11. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P4.pdf. Accessed March 1, 2011.

orlistat can occur in patients and cause hepatic toxicity similar to that seen in animal studies.

2. Severe liver injury – FDA clinical safety review of Alli (orlistat)

The FDA medical officer discussed, in her March 2006 review, nine cases of orlistat associated with hepatic failure or cholestatic hepatitis, two of which resulted in death and one in liver transplantation. Although none of the reports demonstrated a "definitive" association, the medical officer found that, "similar to the discussion surrounding pancreatitis," an association cannot be ruled out.[24]

3. FDA acknowledges risk of severe liver injury by requiring revised label for Xenical and Alli

It took the FDA 11 years after Xenical was approved and 4 years after Alli was approved for the agency to be convinced of an association between orlistat use and severe liver injury when, on May 26, 2010, it approved a revised label for both Xenical and Alli that included information about 13 cases of severe liver injury, which resulted in two deaths from liver failure and an additional three liver transplants.[25]

B. Acute pancreatitis

1. Acute pancreatitis – FDA pre-clinical review of Xenical (orlistat)

As noted above in the discussion of severe liver injury, studies in dogs and rats demonstrated significant GI absorption of orlistat following oral administration.[26,27] Furthermore, in male rats given multiple oral doses over 30 days, radioactivity was found in the pancreas.[28]

Dogs treated with oral orlistat for two weeks while on a high fat diet were noted to have increases in serum α-amylase and lipase, which are key diagnostic indicators of

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[24] FDA clinical review of Alli (orlistat). Web page 7. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P5.pdf. Accessed March 1, 2011.

[25] FDA drug safety communication: completed safety review of Xenical/Alli (orlistat) and severe liver injury. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213038.htm. Accessed March 1, 2011.

[26] FDA pharmacology review for Xenical (orlistat). Web page 5. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed February 28, 2011.

[27] FDA pharmacology review for Xenical (orlistat). Web page 10. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P4.pdf. Accessed March 1, 2011.

[28] FDA pharmacology review for Xenical (orlistat). Web pages 10-11. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P4.pdf. Accessed March 1, 2011.

pancreatic injury.[29] The increase in α-amylase was observed in all treated dogs and at doses as low as 0.1 times that of the human dose (based on body surface area). Unfortunately, the FDA pharmacology reviews provided no such data for the one-year dog study or for the long-term studies in the mouse or rat (one and a half- and two-year studies, respectively). However, the FDA pharmacology review did note that for rats, at doses ≥450 mg/kg/day, plasma amylase activity was increased.[30]

Therefore, as with severe liver injury, it is biologically plausible that pancreatic accumulation of orlistat can occur in patients and cause pancreatic toxicity similar to that seen in animal studies.

2. Acute pancreatitis – FDA clinical safety review of Alli (orlistat)(prior to its approval)

In her review of the Adverse Event Reporting System (AERS) database, the FDA medical officer found 99 "raw" cases of pancreatitis in the database, of which 68 were confounded by other factors:[31] gallbladder disease (30 cases), dyslipidemia (13 cases), history of pancreatitis/gallstones (9 cases), alcohol use (8 cases) and diabetes (8 cases). The remaining 31 cases compared to a total of only 8 cases of pancreatitis identified in the AERS database for the FDA-approved anti-obesity drug, sibutramine.[32]

3. Acute pancreatitis – FDA advisory committee discussion on the safety of Alli (orlistat) (prior to its approval)

Dr. Alastair Wood, the advisory committee chairperson, listed three organs as targets of toxicity: the pancreas, liver, and kidney, but, in addition, he was concerned about a lack of oversight by health professionals.

He continued: "Other concerns--pancreatitis, liver toxicity and stones? I am not sure that the pancreatitis issue is entirely clear yet. It is interesting that the FDA is working on it, which sort of left you with a sense of some discomfort, I would say. Obviously, it wasn't fair to share that data with us."[33]

Dr. Wayne Snodgrass: [re: pancreatitis] "I would just say that this raises the issue of a need for post-marketing surveillance, at the minimum."

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[29] FDA pharmacology review of Xenical (orlistat). Web pages 9-10. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P3.pdf. Accessed March 1, 2011.

[30] FDA pharmacology review for Xenical (orlistat). Web page 8. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf. March 1, 2011.

[31] FDA clinical review for Alli (orlistat). Web pages 4-6. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P5.pdf. Accessed March 1, 2011.

[32] FDA clinical review for Alli (orlistat). Web page 6. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P5.pdf. Accessed March 1, 2011.

[33] FDA Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee joint meeting transcript. January 23, 2006. Web page 405. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4201T.pdf. Accessed March 11, 2011.

Dr. Thomas Carpenter was worried about the people who take this drug for "extended periods of time [beyond 6 months]" and wondering "where some level of oversight, if it is not the physician" will come from to "look for red flags in terms of toxicities that we are not aware of because the over-the-counter safety data is only at the six-month point."[34]

4. Acute pancreatitis – Published cases of orlistat-related pancreatitis

In our review of the medical literature, we found four case reports of orlistat-associated pancreatitis: a 36 year-old man,[35] a 73 year-old woman, a 45 year-old woman, [36] and a 53 year-old woman.[37] A fifth case of orlistat-associated pancreatitis occurring in a 49 year-old woman appeared in a Spanish publication.[38] The authors of these case reports concluded that a diagnosis of acute pancreatitis should be considered in patients taking orlistat and presenting with a new onset of abdominal pain.

5. Acute pancreatitis – Public Citizen's review of pancreatitis cases in the AERS database

The Public Citizen Health Research Group analyzed the FDA's post-marketing reports of pancreatitis. We used the Medical Dictionary for Regulatory Activities (MedDRA) and the Standardized MedDRA Query (SMQ) for "acute pancreatitis." Specifically, we looked at cases with the preferred term *Cullen's sign* or *pancreat*, or a combination of one of these terms (*abdom* or *ascites* or *fat necrosis* or *gastro* or *ileus paralytic* or *jaundice* or *nausea* or *vomit*) and one of these terms (*amylase* or *trypsin* or *lipase* or *pancreatic enzymes*).

We searched as drug names *orlistat* or Alli or *Xenical* as "primary suspect" drugs. We searched for dates through March 2010. We did a similar search for the recently-banned *sibutramine* or *Meridia* or *Reductil* through March 2010 as a comparison to another anti-obesity drug. We removed cases which had the preferred terms *gallbladder* or *chole* or *cystic fibrosis pancreatitis* or *pancreatic carcinoma* and also cases which from an initial analysis had too many different corresponding events.

Our AERS database search yielded 97 possible cases of acute pancreatitis for Xenical, 38 cases for Alli and seven cases for Meridia/Reductil.

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[34] FDA Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee joint meeting transcript. January 23, 2006. Web page 333. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4201T.pdf. Accessed March 11, 2011.

[35] Napier S, Thomas M. 36 year old man presenting with pancreatitis and a history of recent commencement of orlistat case report. Nutr J. 2006;5:19.

[36] Ahmad FA, Mahmud A. Acute pancreatitis following orlistat therapy: report of two cases. J Pancreas (online) 2010;11:61-63.

[37] Garg R, Hussey C, Ibrahim S. Pancreatitis associated with the use of sitagliptin and orlistat combination: a case report. Diabetic Medicine 2010;27:485-488.

[38] Auilera XG, Sanchez-Vegazo CT, Perez LC, et al. Acute pancreatitis induced by orlistat. Medicina Clinica 2008;130:557. http://adisonline.com/reactions/Fulltext/2009/12330/Orlistat__Acute_pancreatitis__case_report.49.aspx.

We then obtained from the FDA and reviewed the original MedWatch reports for all cases identified through our search of the AERS database. We eliminated from our findings cases where acute pancreatitis was not the primary event described in the MedWatch report and cases where there was evidence of more than occasional alcohol use, gallstones, gallbladder inflammation, inflammation or obstruction of the bile duct, liver disease, severe hypertriglyceridiemia, or pancreatic cancer that might provide other explanations for the pancreatitis. After removing these, we found 47 total cases of acute pancreatitis for orlistat (Xenical and Alli) (see below and Tables 1-3 in the Appendix).

For *Xenical*, we found 38 cases of acute pancreatitis, 32 of which required hospitalization (one of which died), between March 1999 and March 2010 (see Table 1 in the Appendix). Patients' ages ranged from 29 to 77 years. There were 24 patients with positive dechallenges (the patient improved once Xenical was removed). Data on the approximate duration of exposure prior to the onset of pancreatitis were available for 32 cases and ranged from two to 334 days. Six cases were reported from the U.S. and 32 from 11 foreign countries, including 13 cases from the United Kingdom and five from Germany.

For *Alli*, we found 9 cases of acute pancreatitis; seven required hospitalization and one resulted in disability (see Table 2 in the Appendix). Patients' ages ranged from 25 to 69 years. Data on the approximate duration of exposure prior to the onset of pancreatitis were available for eight cases and ranged from three to 140 days. Seven patients had a positive dechallenge after orlistat was removed. Six cases were reported from the U.S., one from the Netherlands and two from an unknown country of origin.

For sibutramine (*Meridia* or *Reductil*), we found six cases of acute pancreatitis, all of which required hospitalization (see Table 3 in the Appendix). Patients' ages ranged from 45 to 67 years. Five patients had a positive dechallenge. Data on the approximate duration of exposure prior to the onset of pancreatitis were available for all cases and ranged from three to 90 days. One case each was reported from the U.S., Belgium, Denmark, Germany, Lebanon and Sweden.

The limitations to using the AERS database combined with review of original MedWatch reports lie in missing and incomplete data.

Furthermore, many mild cases of acute pancreatitis may be missed because of masking by the common symptoms of abdominal pain and nausea that are associated with orlistat use.

C. Acute oxalate nephropathy and kidney stones (nephrolithiasis)

1. Acute oxalate nephropathy and kidney stones – FDA review of pre-clinical studies

Regarding pre-clinical studies submitted as part of the NDA for Xenical (orlistat), in rats treated for 6 or 9 months with oral orlistat while fed a high-fat, normal calcium diet, kidney mineralization, pelvic dilation, and progressive nephropathy were commonly

observed pathologic lesions on post-mortem histopathology examination.[39] Likewise, in female dogs treated for one year with oral orlistat while fed a high-fat diet, medullary mineralization of the kidney was seen on post-mortem histopathology examination.[40] Nephrocalcinosis (calcium deposits in the kidney), a pathologic process characterized by calcium oxalate and calcium phosphate accumulation in renal parenchyma has a similar pathophysiology to that seen in calcium oxalate (kidney) stone formation, and both disorders often occur together.

A more recent study in rats demonstrated that the administration of lipase inhibitors resulted in a "significant and marked increase in urinary oxalate . . . elevating the risk of oxalate stone formation."[41]

Several mechanisms related to steatorrhea (fatty diarrhea caused by inhibiting fat absorption) may play a role in the formation of kidney stones in animals and patients treated with orlistat. One early study in rats suggested that long-chain fatty acids may enhance the absorption of oxalate from the colon.[42] Another study showed that exposure of rat colonic mucosa to bile salts or fatty acids increased the permeability of the mucosa to oxalate.[43] Other investigators have proposed that unabsorbed bile acids and fat (present in the intestine as a consequence of fat malabsorption) react with calcium in the intestinal lumen forming soaps, thus limiting the available calcium for combination with oxalate. Oxalate is therefore free to be absorbed and, combining with calcium in the kidney, forms calcium oxalate crystals that can damage kidney function and lead to kidney stones.[44]

Given the results of these animal studies, it is highly biologically plausible that orlistat causes the formation calcium oxalate kidney stones.

<u>2. Acute oxalate nephropathy and kidney stones – FDA clinical safety review of Xenical (orlistat) (prior to its approval)</u>

The FDA medical officer analyzed pooled data for the 120 mg orlistat group subjects and placebo group subjects who participated in the randomized phase III studies evaluating Xenical (orlistat). Although not statistically significant, the data for patients

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[39] FDA pharmacology review for Xenical (orlistat). Web pages 6 and 8. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P3.pdf. Accessed March 1, 2011.

[40] FDA pharmacology review for Xenical (orlistat). Web pages 12-13. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P3.pdf. Accessed March 1, 2011.

[41] Ferraz RRN, Tiselius H-G, Heiberg IP. Fat malabsorption induced by gastrointestinal lipase inhibitor leads to an increase in urinary oxalate excretion. Kidney International 2004;66:676-682.

[42] Saunders DR, Sillery J, McDonald GB. Regional differences in oxalate absorption by rat intestine: evidence for excessive absorption by the colon in steatorrhea. Gut 1975;16:543-548.

[43] Kathpalia SC, Favus MJ, Coe FL. Evidence for size and charge permselectivity of rat ascending colon: effects of ricinoleate and bile salts on oxalic acid and neutral sugar transport. J Clin Invest 1984;74:805-811.

[44] Hill P, Karim M, Davies D, et al. Rapidly progressive irreversible renal failure in patients with pancreatic insufficiency. Am J Kidney Dis 2003;42:842-845.

who had normal baseline renal (kidney) ultrasounds indicated a tendency towards increased kidney stone development in the orlistat group subjects, as summarized in the table below:[45]

	Placebo	120 mg orlistat	P value
Renal ultrasounds			
After one year	0.2% (n=500)	0.8% (n=875)	P=0.12
After two years	0.3% (n=333)	1.1% (n=454)	P=0.15

Although there was the above-mentioned trend toward increased ultrasound-detected kidney stones in the orlistat group, no difference was seen between the two groups in the incidence of symptomatic renal colic episodes.

In study NM14161, levels of urinary oxalate were higher in the orlistat group subjects in comparison to placebo group subjects, but this difference did not reach statistical significance. However, a statistically significant higher number of subjects in the orlistat group had markedly elevated levels of 24-hour urine oxalate levels in comparison to control subjects. In discussing the results of these studies, the FDA medical officer concluded, "[t]hese data provide biological plausibility with which to link the use of orlistat with the development of nephrolithiasis [kidney stones]."[46]

3. Acute oxalate nephropathy and kidney stones – Published cases of acute renal failure secondary to acute oxalate nephropathy associated with orlistat

There are several reports in the medical literature of orlistat use in humans leading to the formation of calcium oxalate crystals resulting in acute renal failure.[47,48,49,50] In one case, the patient had normal baseline renal function prior to starting orlistat.[74] Renal biopsy in three cases revealed deposition of calcium oxalate crystals within tubular lumens consistent with acute oxalate nephropathy.[72,73,74] Two patients required hemodialysis, one of whom died of a cardiac arrest three weeks after the initiation of hemodialysis. As a result, Courtney et al. suggested that "all patients with renal impairment who are prescribed gastrointestinal lipase inhibitors have their renal function

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[45] FDA medical officer's review of clinical data for Xenical (orlistat). Web page 12. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P2.pdf. Accessed March 1,2011.

[46] FDA medical officer's review of clinical data for Xenical (orlistat). Web pages 12-13. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P2.pdf. Accessed March 1, 2011.

[47] Singh A, Sarkar SR, Gaber LW, et al. Acute oxalate nephropathy associated with orlistat, a gastrointestinal lipase inhibitor. Am J Kidney Dis 2007;49:153-157.

[48] Courtney AE, O'Rourke DM, Maxwell AP. Rapidly progressive renal failure associated with successful pharmacotherapy for obesity. Nephrol Dial Transplant 2007;22:621-623.

[49] Karamadoukis L, Shivashankar GH, Ludeman L, et al. An unusual complication of treatment with orlistat. Clinical Nephrology 2009;71:430-432.

[50] Sarica K, Akarsu E, Erturhan S et al. Evaluation of urinary oxalate levels in patients receiving gastrointestinal lipase inhibitor. Obesity 2008;16:1579-1584.

monitored" since "[e]arly detection of rapidly deteriorating renal function would allow discontinuation of the medication before irreversible end-stage renal disease is reached." Other authors suggested that patients with "undiagnosed mild forms of primary hyperoxaluria or secondary hyperoxaluria, who also take orlistat, may be predisposed to developing acute oxalate crystalluria [a predecessor to kidney stones]."[51]

Results of a six-month study of 55 patients on Xenical compared to 40 control patients showed that urinary oxalate excretion increased in 62% of the treated group leading the researchers to conclude that this "suggests that an increased risk of stone formation could be anticipated during long-term use" and "[t]hus, we recommend that all patients receiving such agents should be closely monitored for increased risk of oxalate excretion and possible stone formation,"[52] something that is unlikely to occur for an OTC drug.

4. Acute oxalate nephropathy and kidney stones – Public Citizen's review of nephrolithiasis cases in the AERS database

We utilized the same search techniques as described under Public Citizen's review of "pancreatitis" in this petition but using the MedDRA term "nephrolithiasis." Our AERS database search yielded 27 possible cases of nephrolithiasis for Xenical, 67 cases for Alli, and five cases for Meridia/Reductil.

We then obtained and reviewed the original MedWatch reports for all cases identified through our search of the AERS database. We eliminated from our findings cases where the report indicated that the patient had a history of chronic or recurrent kidney stones or an acute kidney stone episode during the preceding year.

We found 73 total cases of nephrolithiasis for orlistat (Xenical and Alli).

For *Xenical*, we found 22 cases of nephrolithiasis, 14 of which required hospitalization, between March 1999 and March 2010 (see Table 4 in the Appendix). Patients' ages ranged from 27 to 69 years. Data on the approximate duration of exposure prior to the onset of nephrolithiasis were available for 18 cases, and ranged between four and 442 days. Five cases were reported from the U.S., 13 from the United Kingdom, and one each from Australia, Sweden, Taiwan, and an unknown country of origin. In one case, the patient had acute renal failure and a renal biopsy revealed calcium oxalate crystals, a finding consistent with acute oxalate nephropathy.

For *Alli*, we found 51 cases of nephrolithiasis; nine required hospitalization and one resulted in disability (see Table 5 in the Appendix). Patients' ages ranged from 24 to 83 years. Data on the approximate duration of exposure prior to the onset of nephrolithiasis

[51] Karamadoukis L, Ludeman L, Williams AJ. Is there a link between calcium oxalate crystalluria, orlistat and acute tubular necrosis? Nephrol Dial Transplant 2008;23:1778-1779.
[52] Sarica K, Akarsu E, Erturhan E, et al. Evaluation of urinary oxalate levels in patients receiving gastrointestinal lipase inhibitor. Obesity 2008;16:1579-1584.

were available for 32 cases and ranged from three to 450 days. Fifty cases were reported from the U.S. and one from the Netherlands.

For sibutramine (*Meridia* or *Reductil*), we found five cases of nephrolithiasis, four of which required hospitalization (see Table 6 in the Appendix). Patients' ages ranged from 21 to 51 years. Data on the approximate duration of exposure prior to the onset of nephrolithiasis were available for four cases and ranged from 34 to 60 days. Three cases were reported from the U.S. and one each from Belgium and Switzerland.

D. Gastrointestinal (GI) tract adverse effects

1. GI tract adverse effects – Pre-clinical animal studies

Oral administration of orlistat to rats and dogs caused a significant increase in fecal fat excretion, leading to loose or soft stools, as would be expected for a drug that inhibits fat breakdown and absorption.[53]

2. GI tract adverse effects – FDA clinical safety review of Xenical (orlistat) prior to its approval

The FDA medical officer identified GI effects as one of the four major general categories of adverse events of orlistat. The most common GI adverse events were oily spotting, fecal urgency, flatus with discharge, and abdominal pain (latter in about 25% of patients).[54] The fact that orlistat commonly causes significant abdominal pain due to its local effects on the GI tract is important because this may mask pain that is due to concurrent mild acute pancreatitis or renal colic.

E. Interference with the absorption of fat soluble vitamins and lipophilic drugs

1. Interference with absorption – Pre-clinical animal studies

In spite of supplementation, hepatic stores of vitamin E decreased in all three species treated with oral orlistat in long-term studies (mice, rats, and dogs), and hepatic stores of vitamin A decreased in dogs.[55,56] Even with supplementation, vitamin E levels in liver decreased by 60% to 70% in male and female rats. Although plasma levels appeared

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[53] FDA pharmacology review for Xenical (orlistat). Web page 13. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P4.pdf. Accessed March 11, 2011.
[54] FDA-approved drug label for Xenical (orlistat). Updated December 17, 2010. Web page 20. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020766s030lbl.pdf. Accessed March 11, 2011.
[55] FDA pharmacology review for Xenical (orlistat). Web pages 2 and 7. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P2.pdf. Accessed March 1, 2011.
[56] FDA pharmacology review for Xenical (orlistat). Web page 10. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed March 1, 2011.

little affected, the liver reservoirs were depleted.[57] In rats, plasma vitamins A and E decreased while in dogs, plasma vitamins D and E decreased.[58] These decreases occurred because the fat-soluble vitamins are excreted along with the unabsorbed fat.

2. Interference with absorption – FDA clinical safety review of Xenical (orlistat) (prior to its approval)

Review of the individual phase III studies for Xenical indicated that, compared with placebo-treated subjects, subjects in the 120 mg orlistat group had reduced plasma levels of vitamin E and β-carotene. Some, but not all studies reported lower plasma levels of vitamin D in orlistat-treated subjects. Prothrombin times, the insensitive surrogate marker used to assess vitamin K levels, were not significantly different between orlistat and placebo group subjects.[59]

3. Interference with absorption – FDA clinical safety review of Alli (orlistat) (prior to its approval)

The FDA medical officer review noted that orlistat can interfere with the absorption of fat-soluble compounds including the fat-soluble vitamins (A, D, E, and K) and lipophilic drugs (e.g., cyclosporine and amiodarone). There is potential indirect interference with warfarin's safe use due to orlistat's lowering of vitamin K levels.[60]

Data from a published study in which 17 adolescents, 12 to 17.6 years of age (mean 14.7±2.0), were treated with orlistat along with multivitamin supplement showed that even with supplementation, vitamin D levels can decline. When tested after three to six months of treatment, mean plasma vitamin D levels were significantly reduced compared with baseline, leading the authors to comment that, "It may be prudent to monitor vitamin D concentrations in adolescents who take orlistat, even when a multivitamin is prescribed."[61] [Xenical is approved for children 12 to 16; Alli is approved for those 18 and over.]

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[57] FDA pharmacology review for Xenical (orlistat). Web page 4. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P4.pdf. Accessed March 1, 2011.
[58] FDA pharmacology review of Xenical (orlistat). Web page 2. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf. Accessed March 1, 2011.
[59] FDA medical officer's review of clinical data for Xenical (orlistat). Web page 12. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P2.pdf. Accessed March 1, 2011.
[60] FDA clinical review of Alli (orlistat). Web page 35. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P3.pdf. Accessed March 1, 2011.
[61] McDuffie JR, Calis KA, Booth SL, et al. Effects of orlistat on fat-soluble vitamins in obese adolescents. Pharmacotherapy 2002;22:814-822.

4. Interference with absorption – FDA advisory committee discussion on the safety of Alli (orlistat) (prior to its approval)

Dr. Alastair Wood, the advisory committee chairperson, expressed concern about fat-soluble vitamin malabsorption and lack of oversight by health professionals.[62]

Dr. Marie Griffin said that, "It worries me a little bit when the label says 'talk to your physician or pharmacist' about warfarin" because the physician doesn't have the "knowledge base" about orlistat's effect on vitamin K absorption.[63]

Dr. Neal Benowitz was concerned that the concentration of any lipophilic drug could be affected, not just cyclosporine and amiodarone. He noted that when there was an average 25% decrease in availability, it meant that some individuals could have had a 50% drop.[64]

Dr. John Dent (GlaxoSmithKline) responded that it would take 24 to 48 hours for the effects of orlistat to stop working, but that Roche is recommending taking any "highly lipophilic drug" two hours before or two hours after orlistat, but he admitted that the effect of this on availability had never been studied.[65]

IV. PUBLIC CITIZEN SUMMARY AND DISCUSSION

A. Efficacy Summary (Xenical, Alli)

The actual weight loss achieved for prescription- and OTC-strength orlistat in randomized controlled studies was minimal. The placebo-subtracted mean percent weight loss from baseline to week 52 was approximately 3% for subjects treated with 120 mg of prescription orlistat. In terms of absolute weight loss from baseline to week 52, the difference from placebo was -2.6 kg (-5.6 lbs) for the 60 mg orlistat group and -3.2 kg (-7.1 lbs) for the 120 mg orlistat group.[66]

For subjects treated for two years, weight steadily increased after week 40, and after week 20, the difference in weight loss between the placebo and 120 mg orlistat groups

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[62] FDA Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee joint meeting transcript. January 23, 2006. Web page 405. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4201T.pdf. Accessed March 11, 2011.

[63] FDA Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee joint meeting transcript. January 23, 2006. Web page 325. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4201T.pdf. Accessed March 11, 2011.

[64] FDA Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee joint meeting transcript. January 23, 2006. Web page 309. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4201T.pdf. Accessed March 11, 2011.

[65] FDA Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee joint meeting transcript. January 23, 2006. Web page 311. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4201T.pdf. Accessed March 11, 2011.

[66] FDA medical officer's review of clinical data for Xenical (orlistat). Web page 5. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P1.pdf. Accessed February 28, 2011.

remained fairly constant at approximately 3%. In terms of absolute weight loss, the difference was -2.4 kg (5.3 lbs) for the 60 mg orlistat group and -2.9 kg (6.4 lbs) for the 120 mg orlistat group.[67]

Subjects in the "actual use study" submitted for Alli approval had only a 1 to 2 kg (2.2 to 4.4 lbs) weight loss more than placebo (untreated) over the four-month treatment period, not enough for either the FDA statistician or medical reviewers to find the drug approvable. The Alli advisory committee concluded that this amount of weight loss would not result in any health benefits.[68]

One of the reasons proposed as to why there is minimal effect of orlistat on weight loss is that when calories are removed from the diet (in this instance by inhibiting fat absorption), appetite is increased to replace them. A study in healthy human volunteers fed a meal with and without 120 mg orlistat, found a reduction in postprandial plasma levels of gastrointestinal hormones that regulate appetite: cholecystokinin, peptide YY, and glucagon-like peptide-1. According to the authors, this "may raise appetite sensations and increase food consumption and should therefore be considered as potential side effects when applying lipase inhibitors for the treatment of morbid obesity."[69]

Another study of healthy volunteers, who were fed a meal with and without orlistat, confirmed the decline in cholecystokinin levels.[70] These authors concluded that "in healthy, lean subjects the acute inhibitory effect of fat on subsequent energy intake is attenuated by orlistat and the increase in energy intake approximates the energy lost due to fat malabsorption." Similar effects on appetite occurred in subjects who were fed a meal containing the fat substitute, olestra.[71] The FDA pharmacology reviewer noted the same finding in rats.[72]

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[67] FDA medical officer's review of clinical data for Xenical (orlistat). Web pages 9-10. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P1.pdf. Accessed February 28, 2011.

[68] FDA Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee joint meeting transcript. January 23, 2006. Web page 293. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4201T.pdf. Accessed March 11, 2011.

[69] Ellrichmann M, Kapelle M, Ritter PR, et al. Orlistat inhibition of intestinal lipase acutely increases appetite and attenuates postprandial glucagon-like peptide-1-(7-36)-amide-1, cholecystokinin, and peptide yy concentrations. J Clin Endocrinol Metab 2008;93:3995-3998.

[70] O'Donovan D, Feinle-Bisset C, Wishart J, Horowita M. Lipase inhibition attenuates the acute inhibitory effects of oral fat on food intake in healthy subjects. British J of Nutrition 2003;90:849-852.

[71] Cotton JR, Weststrate JA, Blundell JE. Replacement of dietary fat with sucrose polyester: effects on energy intake and appetite control in nonobese males. Am J Clin Nutr 1996:63:891-896.

[72] FDA pharmacology review for Xenical (orlistat). Web page 13. http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P4.pdf. Accessed March 11, 2011.

B. Safety Summary (Xenical, Alli)

1. Previously noted problems with orlistat from our earlier petition

Public Citizen opposed the expansion of the use of orlistat to the OTC population from its very inception.[73] In April 2006, Public Citizen petitioned FDA to remove orlistat from the market because of its ability to cause the development of aberrant crypt foci (ACF) in rats. The scientific literature identifies ACF as an early neoplastic colonic lesion and a putative precursor of colon cancer.

"The connection of ACF with carcinogenesis is so well recognized that the appearance of ACF in rats is used by many groups to test the potential carcinogenicity of chemicals. For example, the Environmental Protection Agency (EPA) uses an ACF assay in its tests of possible carcinogens. The ACF assay is also used to examine compounds that may prevent cancer, i.e., prevent ACF formation."[74]

Other safety issues noted in our original petition were GI toxicity, vitamin depletion, and increased cases of breast cancer.

2. New problems highlighted in our current petition

a. Severe liver injury

Prior evidence for hepatic toxicity exists from studies in rats and dogs where hepatic necrosis occurred in treated animals and from the clinical review of patient adverse effects.

On May 26, 2010, the FDA issued a warning concerning "severe liver injury." FDA identified 12 foreign reports of severe liver toxicity associated with Xenical and one domestic case for Alli. Two patients died of liver failure, and three required liver transplants. A revised label will instruct patients to contact their health professional if they develop itching, yellow eyes or skin, dark urine, loss of appetite or light-colored stools. However, as of March 2011, under FAQ [Frequently Asked Questions] on the Alli.com website, Novartis is still saying that, "The alli label is being updated to alert consumers to certain symptoms . . . of severe liver injury . . ."[75] It is most unlikely that OTC consumers will read the package label, recognize symptoms, and act in time to avoid liver damage. Healthcare professionals are now advised to tell patients to discontinue medications immediately and to run liver function tests. However, this is buried in the 32 page professional product label.

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[73] Wolfe SM, Barbehenn E. Testimony before the Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee joint meeting on possible switch of orlistat to OTC status. January 23, 2006. http://www.citizen.org/Page.aspx?pid=2736. Accessed March 11, 2011.
[74] Barbehenn E, Wolfe S, Pretlow TP, Pretlow TG. Petition to FDA to ban the diet drug orlistat (Xenical). April 10, 2006. http://www.citizen.org/Page.aspx?pid=667. Accessed March 11, 2011.
[75] Novartis. Alli website. http://www.myalli.com/faq.aspx. Accessed March 8, 2011.

b. Acute pancreatitis

One of the potentially most serious adverse events for patients taking Xenical or Alli is acute pancreatitis, which may be especially difficult to diagnose since orlistat's most common adverse effects relate to the gastrointestinal tract.[76] Abdominal pain and nausea were the two most commonly observed adverse events in clinical trials, the same symptoms seen in patients presenting with pancreatitis: a discussion on diagnosing this disease concluded that "the clinical diagnosis of acute pancreatitis is based on characteristic abdominal pain and nausea" along with elevated serum levels of pancreatic enzymes (amylase and lipase).[77]

The FDA clinical safety reviewer for Alli was particularly concerned about pancreatitis: "Because nonprescription drugs carry a greater burden of safety than prescription agents, . . .," the reviewing division revisited the issue of orlistat-induced pancreatitis with the result that "[a]n up-to-date accounting from FDA's Adverse Event Reporting System identifies a sizable imbalance in the number of reports of pancreatitis for orlistat in comparison to sibutramine."[78] The FDA found 17 cases of acute pancreatitis, as well as 73 cases of pancreatitis and 14 cases of increased amylase, which "should be interpreted as a potential signal that would require more investigation...." Dr. Golden noted that "it is not clear whether gallstones are a confounding factor or a potential causative mechanism."[79] The European Medicines Agency added pancreatitis to the adverse reaction section of their drug label in June 2008.[80]

Case reports from the literature, as well as our recent review of the AERS database cases, indicate that pancreatitis remains an area of continuing importance. In Public Citizen's analysis of MedWatch reports, we excluded from our case findings any cases where there was evidence of more than occasional alcohol use, gallstones, gallbladder inflammation, inflammation or obstruction of the bile duct, liver disease, severe hypertriglyceridiemia, or pancreatic cancer. After doing so, we found for Xenical and Alli (orlistat) 47 cases of pancreatitis, of which 39 required hospitalization (one of which died), whereas for Meridia and Reductil (sibutramine), we found only six cases of pancreatitis, all of which were hospitalized (see Tables 1-3 in the Appendix).

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[76] FDA-approved drug label for Xenical (orlistat). Updated December 17, 2010. Web page 21. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020766s030lbl.pdf. Accessed March 11, 2011.

[77] Whitcomb, DC. Acute pancreatitis. NEJM 2006;354:2142-2150.

[78] FDA Clinical Review for Alli (orlistat). Web page 5. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P5.pdf. Accessed March 11, 2011.

[79] FDA Clinical Review of Alli (orlstat). Web page 5. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P5.pdf. Accessed March 11, 2011.

[80] Summary of Product Characteristics. Web pages 6 and 24. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000154/WC500058428.pdf. Accessed March 10, 2011.

FDA estimates that, at most, 10% of prescription drug adverse reactions are reported. Comparable reporting data is missing for OTC drugs, but the percentage would presumably be much lower since, in general, it is consumers rather than physicians who are relied upon to report their adverse reactions from OTC drugs to the FDA. As a result, the numbers of cases of acute pancreatitis (and other adverse events) reported in the AERS database for both Xenical and Alli can probably be multiplied by a factor of more than 10 to obtain an estimate closer to reality.

The U.S. Xenical label states: "Pancreatitis has been reported with the use of XENICAL in postmarketing surveillance. No causal relationship or physiopathological mechanism between pancreatitis and obesity therapy has been definitively established." This is not helpful, to say the least.[81]

c. Acute oxalate nephropathy and kidney stones (nephrolithiasis)

There is overwhelming evidence that orlistat predisposes animals and patients to the development of acute oxalate nephropathy and calcium oxalate kidney stones. Given the mechanism of action of orlistat, it was completely predictable that this would be the case (see below).

There are several case reports in the medical literature of acute renal failure secondary to biopsy-proven acute oxalate nephropathy.

In Public Citizen's analysis of MedWatch reports, we excluded from our case findings any cases where the report indicated that the patient had a history of chronic or recurrent kidney stones or an acute kidney stone episode during the preceding year. After doing so, we found for Xenical and Alli (orlistat) 73 cases of nephrolithiasis (kidney stones), of which 23 were hospitalized. We also found one patient with acute renal failure in whom a renal biopsy revealed calcium oxalate crystals, a finding consistent with acute oxalate nephropathy.

For the same time period we found only five cases of nephrolithiasis for Meridia and Reductil (sibutramine), four of which were hospitalized (see Tables 4-6 in the Appendix).

As discussed for pancreatitis, there certainly is significant underreporting of cases of kidney stones associated with Xenical and Alli.

There are data indicating that obese patients have a baseline increased risk for kidney stones.[82,83] A prospective study examining such patients suggested "an association

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[81] FDA-approved drug label for Xenical (orlistat). Updated December 17, 2010. Web page 22. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020766s030lbl.pdf. Accessed March 11, 2011.

[82] Sarica K, Akarsu, Erturhan S, et al. Evaluation of urinary oxalate levels in patients receiving gastrointestinal lipase inhibitor. Obesity 2008;16:1579-1584.

[83] Semins MF, Shore AD, Makary MA et al. The association of increasing body mass index and kidney stone disease. J Urology 2010;183:571-575.

between the use of gastrointestinal lipase inhibitor medication and the urinary oxalate excretion." The authors of this study concluded that "Increased intestinal absorption of dietary oxalate due to this type of medication [orlistat] . . . may further place these individuals at even higher risk."

A recent review concluded that a patient with pre-existing renal disease who is taking orlistat needs to be monitored for any deterioration in renal function "to exclude the possibility of orlistat-induced oxalate nephropathy."[84] The European Medicines Agency listed kidney stones as an adverse effect of 60 mg orlistat use.[85]

Several mechanisms related to steatorrhea (fatty stools) may play a role in the formation of kidney stones in animals and patients treated with orlistat. One early study in rats suggested that long-chain fatty acids may enhance the absorption of oxalate from the colon.[86] Another study showed that exposure of rat colonic mucosa to bile salts or fatty acids increased the permeability of the mucosa to oxalate.[87] Other investigators have proposed that unabsorbed bile acids and fat (present in the intestine as a consequence of fat malabsorption) react with calcium in the intestinal lumen, forming soaps and thus limiting the available calcium for combination with oxalate. Oxalate is then free to be absorbed and form calcium oxalate crystals that can damage kidney function.[88]

Given the results of these animal studies, it is highly biologically plausible that orlistat causes the formation calcium oxalate kidney stones. Yet, there are currently no warnings about kidney stones in any of the labels for these drugs.

d. Interference with the absorption of fat soluble vitamins and lipophilic drugs

Data from pre-clinical animal studies and clinical studies demonstrates diminished absorption of fat-soluble vitamins in animals and humans taking orlistat orally.

Cyclosporine and amiodarone levels can be lowered below their point of efficacy as a result of binding to lipid that is not absorbed and leaving the body with feces. Warfarin efficacy is affected by the lowering of vitamin K levels. Effects on the levels of other fat-soluble drugs and supplements have not been tested but would presumably be similarly affected.

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[84] Ahmed MH. Orlistat and calcium oxalate crystalluria: an association that needs consideration. Renal Failure 2010;32:1019-1021.

[85] Summary of Product Characteristics. Web page 6. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000854/WC500024120.pdf. Accessed March 10, 2011.

[86] Saunders DR, Sillery J, McDonald GB. Regional differences in oxalate absorption by rat intestine: evidence for excessive absorption by the colon in steatorrhea. Gut 1975;16:543-548.

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V. RECOMMENDATION

The FDA Alli advisory committee concluded that the amount of weight loss would not result in any health benefits.[89] Public Citizen has reviewed the FDA documents, as well as the medical literature and the AERS reports, and concludes that there are serious safety concerns for all forms of orlistat. Because of their lack of clinically significant efficacy and risks of serious toxicity, Public Citizen recommends that the FDA immediately remove Xenical and Alli from the market.

VI. ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this petition will have an impact on the environment.

VII. CERTIFICATION

We certify that, to the best of our knowledge and belief, this petition includes all information and views on which this petition relies, and that it includes representative data and information known to the petitioners which are unfavorable to the petition.

Sincerely,

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[89] FDA Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee joint meeting transcript. January 23, 2006. Web page 293. http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4201T.pdf. Accessed March 11, 2011.

Appendix
Table 1. Xenical-Associated Cases of Acute Pancreatitis Found in FDA Adverse Event Reporting System Database

Mfr. Control #	Age (Years)	Sex	Approximate Duration of Drug Use (Days)	Dechallenge Tested and Successful	Outcome
213172 (also 205105)	29	F	65	Yes	
328126	29	M		Yes	HO
263581	34	F	45	Yes	HO
403104	36	F	15		HO
442063	36	M	5		HO
460840	37	F	61	Yes	HO
370064	39	M	32	Yes	HO
206304	40	F	30		HO
448180	40s	F			HO
314082	43	F	33		HO
473902	44	F	4	Yes	HO/LT
302752	45	F	2-3	Yes	OT
377091	45	F	334	Yes	HO
213693	48	F	62	Yes	
257987	50	F	45		OT
319690	52	F	17		HO
394729	52	F	121	Yes	HO
306878	53	F	39	Yes	OT
323565	53	F	182	Yes	HO
457457	54	F	14	Yes	HO
243969	60	F	90	Yes	HO
312909	62	F		Yes	HO/LT
320878	62		280	Yes	HO/LT
330304	62	F	4	Yes	HO
231385	64	F	190	Yes	HO/LT
301888	64	F	27	Yes	HO
239886	65	F	80		HO

361144	65	F	42	No	HO/DE
381972	65	F	92	Yes	HO
382949	67	F		Yes	HO
325994	77	F	68	Yes	HO
229048		F	12		HO
260703		F	22	Yes	HO
314518		F	42		OT
340371		M	14		HO
434753		F			OT
206010		M	9	Yes	HO
321239		M			HO

F=female; M=male; DE=Death; HO=hospitalization; LT=Life Threatening; OT=other. For empty cells, insufficient data was reported.

Table 2. Alli-Associated Cases of Acute Pancreatitis Found in FDA Adverse Event Reporting System Database

Mfr. Control # or FDA triage unit sequence #	Age (Years)	Sex	Approximate Duration of Drug Use (Days)	Dechallenge Tested and Successful	Outcome
A0759939A	25	F	3		HO
334871	37	F	10	Yes	HO
A0711185A	37	F	7	Yes	DS
309808	51	F	27	Yes	HO
510241	53	F	11	Yes	HO
B0597687A	57	M	120	Yes	HO
A0810114A	65	M		Yes	HO
A0753639A	69	M	140		HO
A0775830A		F	30	Yes	OT

F=female; M=male; HO=hospitalization; DS=Disability; OT=other.
For empty cells, insufficient data was reported.

Table 3. Sibutramine-Associated Cases of Acute Pancreatitis Found in FDA Adverse Event Reporting System Database

Brand Name and Mfr. Control #	Age (Years)	Sex	Approximate Duration of Drug Use (Days)	Dechallenge Tested and Successful	Outcome
Reductil 1440	45	F	30	Yes	HO
Reductil 10P-044-0618237-00	45	F	29	Yes	HO
Reductil 3700	48	F	90	Yes	HO
Meridia 04P-163-0283112-00	50	F	17		HO
Reductil 08P-013-0452772-00	56	F	31	Yes	HO
Reductil 06P-150-0354071-00	67	M	3	Yes	HO

F=female; M=male; HO=hospitalization.
For empty cells, insufficient data was reported.

Table 4. Xenical-Associated Cases of Nephrolithiasis Found in FDA Adverse Event Reporting System Database

Mfr. Control # or FDA triage unit sequence #	Age (Years)	Sex	Approximate Duration of Drug Use (Days)	Outcome
632894	27	F	6	HO
540864	32	M	89	OT
553465	33	F	136	OT
650506	36	F	70	OT
104070	40	M	262	HO
343073	41	F	4	HO
531039	45	F	8	HO
B0560572A	45	F	23	HO
502892	46	M	92	HO
339627	47	F		HO
545365	47	F	114	HO
618827	47	F	170	HO
515226	51	F	124	HO
509966	53	F	4	OT
508215	54	M	12	HO
512996	57	F	99	HO
445255	64	M	442	HO
342018	69	M	7	OT
334409		F		HO
379786		F	635	OT
391600				OT
533024				OT

F=female; M=male; HO=hospitalization; OT=other.
For empty cells, insufficient data was reported.

Table 5. Alli-Associated Cases of Nephrolithiasis Found in FDA Adverse Event Reporting System Database

Mfr. Control #	Age (years)	Sex	Approx. Duration of Drug Use (Days)	Outcome
A0765419A	24	F		HO
A0665678A	25	F	13	OT
A0777006A	26	F		OT
A0743058A	30	M	31	OT
A0796800A	31	F		OT
A0667819	36	F	14	OT
A0780090A	39	F		OT
A0717065A	40	F	110	OT
A0676632A	42	F	59	HO
A733377A	43	F		HO
A0778688A	43	F		OT
A0778877A	43	F	14	OT
A0659522A	44	M	7	OT
A0689991A	44	F	120	OT
A0746534A	45	F	90	OT
A0802032A	46	F		OT
A0800644A	47	F	7	OT
A0812338A	47	F	64	OT
A0732621A	48	F	180	HO
A0740902A	49	F	180	OT
A0669176A	51	F	19	HO
A0725230A	51	F	78	OT
A0727101A	51	F	30	HO
A0728233A	52	F	15	OT
A0666255A	53	F	5	OT
A0749198A	53	F	450	OT
A0770879	54	M	180	OT
B0583288A	55	F	4	OT
A0797886	56	F	180	OT

A0806671A	57	F		HO
A0752969A	58	F		OT
A0773377A	58	F		OT
A0673876A	59	F		OT
A0810303A	60	M	270	OT
A0677518A	61	F		OT
A0751944A	63	M	8	OT
A0717497A	64	F	270	OT
A0664704A	65	F	21	OT
A0809895A	66	F	90	OT
A0714418A	83	M	240	HO
A0670972A		M	3	OT
A0679087				OT
A0684258A		F	21	OT
A0685496A		F	61	HO
A0692019A				OT
A0693200A				OT
A0703311A				OT
A0716945A		F	90	DS
A0731100A				OT
A0746548A				OT
A0772709A				OT

F=female; M=male; DS=Disability; HO=hospitalization; OT=other.
For empty cells, insufficient data was reported.

Table 6. Sibutramine-Associated Cases of Nephrolithiasis Found in FDA Adverse Event Reporting System Database

Brand Name and Mfr. Control # or FDA triage unit sequence #	Age (Years)	Sex	Approx. Duration of Drug Use (Days)	Outcome
Meridia FDA# 238160	21	F	24	HO
Meridia 03P-163-0212834-00	33	F	60	HO
Reductil 06P-013-0351516-00	35	M	51	HO
Meridia 03P-163-0230216-00	48	M		HO
Reductil 10P-151-0623811-00	51	M	30-45	OT

F=female; M=male; HO=hospitalization; OT=other.
For empty cells, insufficient data was reported.