7.1.12.1 Studies from the Original NDA

7.1.12.1.1 Bone Metabolism

Two studies from the prescription NDA specifically evaluated bone metabolism: BM14119C and BM14149. Findings from study BM14119C were ultimately published in the International Journal of Obesity in 2001.[39] In this study, bone mineral content and density by DEXA, serum concentrations of ionized calcium, PTH, alkaline phosphatase, osteocalcin, and vitamin D, and urinary hydroxyproline/creatinine and calcium/creatinine ratios were measured in 14 placebo- and 16 orlistat 120 mg-treated subjects at baseline and at one year. After one year of treatment, no differences in bone mass or density were seen between groups (Table 7.1.12.1.1.A), although bone marker data is suggestive of an increase in bone turnover in favor of resorption in the orlistat group (Table 7.1.12.1.1.B). It should be noted, however, that mean weight loss was not significantly different between groups, which may have minimized any findings on bone.

Table 7.1.12.1.1.A.
Table 4 BMC and BMD values measured by DXA before and after 1 y of treatment with either OLS or placebo; mean and s.d. are given

	OLS		Placebo		
	Baseline	After 1 y	Baseline	After 1 y	One year change, OLS vs placebo
TBMC (kg)	3.01 (0.48)	2.98 (0.47) NS	2.97 (0.40)	2.93 (0.40) NS	NS
TBMD (g/cm^2)	1.10 (0.12)	1.10 (0.12) NS	1.09 (0.11)	1.12 (0.11)*	NS
BMC_h (g)	56.3 (11.3)	57.2 (10.5) NS	54.7 (8.7)	55.1 (9.1) NS	NS
BMD_h (g/cm^2)	1.13 (0.17)	1.13 (0.16) NS	1.18 (0.15)	1.19 (0.14) NS	NS
$BMC_{forearm}$ (g)	3.91 (0.87)	3.82 (0.71)**	3.92 (0.66)	3.74 (0.55) NS	NS
$BMD_{forearm}$ (g/cm^2)	0.49 (0.08)	0.48 (0.07)**	0.51 (0.06)	0.49 (0.06)*	NS

Within OLS and placebo groups, effect of treatment was tested by Student's t-test for paired data. Differences between the group changes were tested by Student's t- test for unpaired data.
*P < 0.05; **P < 0.01; NS = not significant.
Gotfredson A, et al. Int J Obes Relat Metab Disord. 2001 Aug;25(8):1154-60.

Table 7.1.12.1.1.B.
Table 5 Biochemical markers of calcium metabolism and bone turnover before and after 1 y of treatment with either OLS or placebo; mean and s.d. are given

	OLS		Placebo		
	Baseline	After 1 y	Baseline	After 1 y	One year change, OLS vs placebo
s-Ca ion (mmol/l)	1.20 (0.02)	1.21 (0.02)*	1.18 (0.11)	1.21 (0.04) NS	NS
s-iPTH (pmol/l)	2.32 (0.74)	3.16 (0.95)*	2.29 (1.08)	3.49 (2.47) NS	NS
s-Alk. phosph. (U/l)	115 (26)	125 (29)**	108 (19)	117 (27) NS	NS
s-25(OH)D_2 + D_3 (nmol/l)	68.3 (19.0)	49.8 (20.6)***	73.1 (25.7)	53.6 (23.5)***	NS
s-1,25$(OH)_2D_3$ (pmol/l)	140 (39)	111 (45)*	103 (32)	94 (35) NS	NS
s-Osteocalcin (µg/l)	3.64 (2.27)	3.67 (3.28) NS	3.26 (1.87)	4.01 (2.52) NS	NS
fU-OHpr/creat (10^{-3})	12.0 (4.7)	20.1 (10.2)***	10.9 (3.3)	13.2 (5.4)*	*
fU-Ca/creat (10^{-3})	229 (169)	387 (271)*	218 (151)	252 (202) NS	NS

Within OLS and placebo groups, effect of treatment was tested by Student's t-test for paired data. Differences between the group changes were tested by Student's t-test for unpaired data.
*P < 0.05; **P < 0.01; ***P < 0.001; NS = not significant.
Gotfredson A, et al. Int J Obes Relat Metab Disord. 2001 Aug;25(8):1154-60.

In study BM14149, bone mineral content and density were assessed at baseline and following one year of treatment in 17 placebo-, 20 orlistat 60 mg-, and 18 orlistat 120 mg-treated subjects. After two years of treatment, data were available in 15 placebo-, 19 orlistat 60 mg, and 18 orlistat 120 mg-treated subjects. There were essentially no changes in BMD or BMC after one

or two years of treatment in any of the groups. However, as Dr. Colman noted in his review,[28] it is difficult to make definitive conclusions regarding these DEXA data given the relatively small sample size of these studies. Moreover, obese individuals are known to have higher bone density than individuals of lower weight,[54] and therefore, orlistat may exert more clinically relevant effects on bone in a low overweight population.

7.1.12.1.2 Mineral Balance, Serum and Urinary Electrolytes, Osteocalcin, Hydroxyproline, Fecal Fat, and Biliary Acids

Study ND14458 was a four-week, single-center, randomized, placebo-controlled study of 11 female and 11 male obese subjects that was conducted to evaluate the effects of orlistat 120 mg on:

- Mineral balance (calcium, phosphate, magnesium, iron, copper, and zinc) and electrolyte concentrations in the urine and serum (sodium, potassium, magnesium, calcium, phosphate, oxalate, uric acid and bicarbonate).
- Markers of bone formation (osteocalcin and hydroxyproline).
- Composition of fecal fat and fecal biliary acids (cholic and chenodeoxycholic, deoxycholic, lithocholic, and ursodeoxycholic acids).

It is unclear to this reviewer what the primary outcome measure of this study was, and therefore, what measure the power calculations were based on.

The mineral balance portion of this study was limited because the fecal marker sitostanol was deemed to be unreliable by the sponsor. In the orlistat group there were statistically significant reductions from baseline in fecal copper, urinary magnesium, and fecal and urinary phosphorus. Similar reductions were seen in urinary magnesium and urinary phosphorus in the placebo group. There were no statistically significant differences between the two groups in the changes of any other mineral concentrations. There were no clinically significant changes in any of the serum electrolyte concentrations in either group. Urinary concentrations of oxalate increased in the orlistat group, but the change was not statistically significant.

There were no statistically significant changes noted in the concentrations of serum osteocalcin or urinary hydroxyproline in the orlistat group.

As for total fat, free fatty acids (FFA) and total bile acids in fecal material, the concentrations of total fat and FFA in the stool increased significantly in the orlistat group when compared with baseline values and changes in the placebo group. The concentrations of total bile acids decreased significantly in the orlistat group as compared to baseline and placebo values. The decrease in the concentration of individual bile acids was greater in the orlistat as compared with the placebo group; this decrease was statistically significant with lithocholic acid. The concentration of neutral fecal fats decreased significantly in the orlistat group when compared with baseline and to the change in the placebo group.

54 Frost HM. Bone. 1997 Sep;21(3):211-4.

7.1.12.1.3 Colonic Mucosa Cell Turnover

As discussed in Section 7.1.11, study NP15138 was reviewed by Dr. Gallo-Torres from the Division of Gastrointestinal and Coagulation Drug Products for the original NDA. Although mean changes in the biomarkers of cell proliferation were not statistically significantly different between orlistat and placebo groups (N = 10 and 12, respectively), there was some suggestion of a direct correlation between increased concentrations of fecal total fat and FFA with increased activity of the biomarkers for proliferation in the orlistat group, but not the placebo group. The clinical significance of these findings is unclear to this reviewer.

7.1.12.2 Other Safety Issues

7.1.12.2.1 Kidney Stones

Animal data suggest that the use of orlistat (particularly with diets rich in oxalate or fat) can lead to significant increases in urinary oxalate.[55] This is presumably due to the binding of unabsorbed fat and bile acids interacting with calcium in the intestinal lumen, thereby freeing oxalate to be absorbed and subsequently excreted in the urine. These animal findings are consistent with oxalate data generated in study NM14161, which demonstrated that more subjects on orlistat compared with placebo had markedly elevated levels of 24-hour urinary oxalate. In fact, as noted by Dr. Colman in his original review of the nonprescription NDA,[28] two individuals in the 60 mg group who had elevated levels of urinary oxalate developed nephrolithiasis during the trial. Moreover, although the absolute numbers are low, there was a slightly higher incidence of new renal stones visualized by ultrasound after two years of treatment [2 of 413 (0.5%) placebo subjects, 4 of 262 (1.5%) orlistat 60 mg subjects, and 5 of 476 (1.1%) orlistat 120 mg subjects].

This reviewer speculates that the incidence may be higher in the real-world situation in which compliance with the low-fat diet will not be monitored. It is important to note, however, that the incidence of *symptomatic* renal and ureteral calculi was not increased over two years in these trials [3 of 524 placebo subjects (0.6%), 1 of 334 (0.3%) orlistat 60 mg subjects, and 2 of 613 (0.3%) orlistat 120 mg subjects].

7.1.12.2.2 Hepatobiliary Findings

7.1.12.2.2.1 Gallstones

In contrast to a possible mechanistic link to lithogenicity in the kidney with orlistat, the data supporting such a mechanism for gallstone formation are somewhat conflicting. One published study demonstrated an impairment of gallbladder motility up to one year with 60 and 120 mg of orlistat compared to placebo,[56] whereas a second study demonstrated no alteration in gallbladder motility in a single dose study with orlistat and meals of differing fat contents.[57] A third study demonstrated that orlistat actually inhibited the adverse changes in biliary lipid composition that

55 Ferraz RR, et al. Kidney Int 2004 Aug;66(2):676-82.
56 Mathus-Vliegen EM, et al. Aliment Pharmacol Ther. 2004 Mar 1;19(5):601-11.
57 Froehlich F, et al. Dig Dis Sci. 1996 Dec;41(12):2404-8.

can lead to gallstones in subjects undergoing dietary weight loss,[58] suggesting a possible *beneficial* effect. Clinical pharmacology studies conducted in obese and normal volunteers in support of the prescription orlistat NDA demonstrated that orlistat treatment did not alter gallbladder motility, the cholesterol saturation index, or gastrin or secretin concentrations. Plasma concentration of post-prandial cholecystokinin (CCK) was lowered by orlistat.

As described in Dr. Colman's review of the studies supporting the prescription orlistat NDA,[28] gallbladder ultrasounds at one year in subjects with normal baseline studies demonstrated that 3.6% of both placebo- and orlistat 120 mg-treated subjects developed gallstones and 0.2% of placebo- and 0.5% of orlistat-treated patients developed sludge. After two years, 2.8% and 3.9%, respectively, developed gallstones and 1.0% and 0%, respectively, developed sludge. However, in subjects with *abnormal* baseline ultrasounds, 3.3% of placebo and 6% of orlistat subjects developed gallstones and 0% and 0.9% developed sludge after one year.

It is well-established that weight loss can increase the risk of cholelithiasis. Symptomatic gallbladder disease was similar between groups in the pooled clinical trials supporting safety; see Section 7.1.2 for a discussion of the findings of SAE*s* of cholelithiasis and cholecystitis at six months and one year. In the four-year XENDOS trial, the rates of patients with cholelithiasis as an adverse event were 2.9% (47/1649) for orlistat 120 mg and 1.8% (30/1655) for placebo.[52]

7.1.12.2.2.2 Pancreatitis

In 2002, based on spontaneous reports of pancreatitis in patients treated with orlistat, the European Agency for the Evaluation of Medicinal products requested that Roche add pancreatitis to the Undesirable Effects section of the European Union (EU) orlistat package insert.

Based on review of data from controlled clinical trials, the Company's Global Drug Safety Database (used to calculate the proportional reporting ratio for pancreatitis), a general epidemiological database from the UK, preclinical studies, and relevant published literature, Roche concluded that there was no evidence for a causal relationship between orlistat and pancreatitis. The current EU label does not include pancreatitis in the Undesirable Effects section.

Based on an initial review of the orlistat-pancreatitis question, the Division of Metabolism and Endocrinology Products intended to request that Roche include in the prescription orlistat labeling information the increased incidence of cholelithiasis in orlistat *vs.* placebo-treated subjects from a large, four-year controlled trial (results discussed above in Section 7.1.12.2.2.1, gallstones); however, this request has not yet been conveyed.

Because nonprescription drugs carry a greater burden of safety than prescription agents, GlaxoSmithKline's proposal to take orlistat over-the-counter led the Division of Metabolism and Endocrinology Products to revisit the orlistat-pancreatitis issue.

In addition to an update on the number of reports of pancreatitis in subjects exposed to orlistat, a

58 Trouillot TE, et al. Am J Gastroenterol. 2001 Jun;96(6):1888-94.

count of reports of pancreatitis associated with sibutramine, the only other drug FDA-approved for long-term weight loss, was requested from FDA's Office of Drug Safety. Sibutramine serves as a crude control for the potential confounding effect of weight loss on the incidence of gallstones.

Sibutramine was approved by FDA in November 1997 and orlistat in April 1999. Since 1999, the number of prescriptions for orlistat in the US is estimated to be approximately 1.5 to 1.7 times that of sibutramine.[59] As of January 2006, there were a total of 99 unique reports of acute pancreatitis (29 from the US) for orlistat and 8 for sibutramine (1 from the US) in FDA's Adverse Event Reporting System.

Based on a number of different analyses, Roche concluded in 2003 that there was no evidence to support a causal association between orlistat and pancreatitis. An 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 with sibutramine. As Dr. Cynthia Kornegay from the Office of Drug Safety stated in her review of this issue:

To examine the possibility of comparator bias, a preliminary PRR analysis was performed in AERS for orlistat. Unlike the sponsor analysis, the AERS investigation did not exclude any terms, and was adjusted by age, gender, and FDA receipt date. As expected, the gastro-intestinal events commonly associated with orlistat showed as very strong, significant signals. Acute pancreatitis (17 cases), pancreatitis (73 cases), and blood amylase increased (14 cases) had less strong associations, but were also statistically significant. If, as could be the case, the signals for gastro-intestinal disorders are biasing the PRR, then the actual safety signal might be stronger than these initial results indicate. This is not a confirmation of a safety signal, but should be interpreted as a potential signal that would require more investigation, including a detailed case analysis.[60]

This reviewer's preliminary review of post-marketing pancreatitis cases both with orlistat and sibutramine (Table 7.1.12.2.2.2.A) indicate that determining a mechanism of action is difficult. Furthermore, it should be noted that the differential in reporting between the two weight loss drugs may reflect confounding by labeling differences and prescribing patterns. It is not clear at this point whether gallstones are a confounding factor or a potential causative mechanism (acknowledging that no causative association has been confirmed). Additionally, an idiosyncratic or hypersensitivity reaction cannot be ruled out.

59 Internal data.
60 Kornegay C. ODS Review of Potential Association between Orlistat and Pancreatitis.

Table 7.1.12.2.2.2.A. Pancreatitis Cases with Potential Confounders or Other Related Issues	
	No. Cases*
Orlistat – Total	**99**
Gallbladder disease	30
Dyslipidemia	13
History of pancreatitis/gallstones	9
Alcohol use	8 (4 specifically described as occasional/moderate)
Diabetes mellitus	8
Estrogen use	4
Deaths	3 (1 pancreatic cancer)
"Toxic hepatitis"	3
Xenical allergy	1
Pancreatic abscess	1
Perforated ulcer	1
Parasite	1
Sibutramine – Total	**8**
Gallbladder disease	3
Dyslipidemia	2
History of pancreatitis/gallstones	2
Regular alcohol use	1
Diabetes mellitus	1
Death	1
* Individuals may be counted more than once	

Finally, it should be noted that although there were no adverse events of 'pancreatitis' reported in the datasets submitted with the NDA, the narratives revealed that one subject in study NM14302 randomized to orlistat 60 mg developed symptomatic cholecystitis on day 56 of treatment (gallstones noted on screening ultrasound) and additionally experienced an elevation of liver and pancreatic enzymes (amylase = 737 U/L). Presumably, this subject developed gallstone pancreatitis. After laparoscopic cholecystectomy, all laboratory values returned to normal.

The Division's investigation of the orlistat-pancreatitis data continues as of this writing, and awaits results from a follow-up analysis requested from Roche. Regardless of the outcome of this inquiry, the Division will, at a minimum, require prescription orlistat labeling to reflect the gallstone findings from the XENDOS study.

7.1.12.2.2.3 Liver findings

The effect of orlistat on the liver was reviewed in the literature and in the clinical trial database. As of this writing, there are four published case reports of hepatotoxicity temporally associated with the use of orlistat.[61, 62, 63, 64] In two of these reported cases, the patient developed subacute hepatic failure requiring liver transplantation.[61, 64] A causal relationship cannot be definitively established from these reports; however, in the case of the two cases of liver failure requiring transplant, neither of the patients was on any other drug therapy and there was a clear temporal relationship to orlistat administration.

61 Montero JL, et al. J Hepatol. 2001 Jan;34(1):173.
62 Lau G, et al. Med Sci Law. 2002 Oct;42(4):309-12.
63 Kim DH, et al. Taehan Kan Hakhoe Chi. 2002 Sep;8(3):317-20.
64 Thurairajah PH, et al. Eur J Gastroenterol Hepatol. 2005 Dec;17(12):1437-8.

This reviewer, in an exploratory search of AERS, found nine unique cases of orlistat associated with acute or subacute hepatic failure or cholestatic hepatitis. Two of these cases were reported in the literature as discussed above.[61, 62] Two other cases resulted in death, and one case resulted in liver transplantation. Several of the patients were on concomitant medications and one consumed excessive alcohol. None of these case reports demonstrate a definitive association between orlistat and hepatic failure or hepatitis. Similar to the discussion surrounding pancreatitis, a rare idiosyncratic or hypersensitivity reaction cannot be ruled out in the consideration of an association between orlistat and an outcome such as hepatotoxicity.

As seen in Section 7.1.7 on laboratory findings, the incidence of markedly abnormal ALT, AST, and total bilirubin in the clinical studies supporting safety was similar between treatment groups, and several authors have in fact reported an improvement in steatohepatitis associated with orlistat-induced weight loss.[45, 65, 66]

One subject in the clinical studies (orlistat 30 mg, study NM14302) had an ALT value 46x the upper limit of normal on study day 78. She was diagnosed with hepatitis A (IgM antibody positive). She discontinued the study, and follow-up laboratory values demonstrated improvement.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Because orlistat is systemically absorbed to a very limited extent and is not believed to affect the central nervous system, the sponsor considers the risk of abuse potential, that is, physical dependence, to be low. The gastrointestinal side effects of orlistat are typically a deterrent to its misuse or of dietary indiscretion. Nevertheless, the use of orlistat as a purgative after binge episodes has been reported in four patients with bulimia nervosa.[17, 18, 19] In such cases, orlistat has actually been shown to have the opposite of the desired effect on eating behavior, where it is used during a high-fat binge, in some sense, enabling the maladaptive eating behavior. A misconception soon after orlistat arrived on the market was that one could eat whatever he or she wanted while taking the drug and still lose weight.[67] The concern certainly remains that this misconception will prevail, particularly with the greatly broadened availability and marketing that occurs with switching a drug to nonprescription status. Furthermore, given the prevalence of weight concern experienced by adolescents and even younger children,[68] this reviewer believes there is likely going to be some degree of inappropriate use of nonprescription orlistat in this population, despite limiting its use to adults through labeling.

65 Hatzitolios A, et al. Indian J Gastroenterol. 2004 Jul-Aug;23(4):131-4.
66 Harrison SA, et al. Aliment Pharmacol Ther. 2004 Sep 15;20(6):623-8.
67 Garrow J. BMJ. 1998 Sep 26;317(7162):830-1.
68 Field AE, et al. Pediatrics. 2001 Jan;107(1):54-60.

7.1.14 Human Reproduction and Pregnancy Data

As specified in the current approved prescription label of orlistat 120 mg, orlistat is categorized as a Pregnancy Category B drug based on non-clinical data and information received on subjects who became pregnant during the clinical study program. Periodic reviews of post-marketing information as of 1999 to date have not revealed any new information that would necessitate a revision in the prescription labeling. Below is the information on pregnancy provided in the current orlistat 120 mg package insert.[11]

Pregnancy:
Teratogenic Effects: Pregnancy Category B.

Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryotoxicity or teratogenicity. This dose is 23 and 47 times the daily human dose calculated on a body surface area (mg/m^2) basis for rats and rabbits, respectively.

The incidence of dilated cerebral ventricles was increased in the mid- and high-dose groups of the rat teratology study. These doses were 6 and 23 times the daily human dose calculated on a body surface area (mg/m^2) basis for the mid- and high-dose levels, respectively. This finding was not reproduced in two additional rat teratology studies at similar doses.

There are no adequate and well-controlled studies of cryostat in pregnant women. Because animal reproductive studies are not always predictive of human response, orlistat is not recommended for use during pregnancy.

Nursing Mothers: *It is not known if orlistat is secreted in human milk. Therefore, orlistat should not be taken by nursing women.*

Although the above comments regarding orlistat's teratogenic effects are correct, this reviewer notes that essential fatty acids, particularly, omega-3 fatty acids, are important for the developing fetus, and guidelines regarding intake during pregnancy have been established by the Institutes of Medicine Food and Nutrition Board Dietary Reference Intakes (DRI).[69] As for vitamin D, a recent review notes that in cases of poor maternal vitamin D stores, fetal growth may be retarded, mineral accretion may be reduced, neonatal hypocalcaemia is more common, and postnatal linear growth and weight gain may be reduced. [70] Weight loss is not recommended during pregnancy.[71] Therefore, this reviewer believes strongly that a woman should discontinue orlistat, in addition to any weight loss program, as soon as she discovers she is pregnant.

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69 Food and Nutrition Board, Institute of Medicine (2002) Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). A report of the Panel on Macronutrients, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 2002 National Academy Press Washington, DC.
70 Pawley N, et al. Am J Clin Nutr. 2004 Dec;80(6 Suppl):1748S-51S.
71 Int J Gynaecol Obstet. 1993 Oct;43(1):67-74.

7.1.15 Assessment of Effect on Growth

As is further discussed in Section 8.3.1, 539 obese children 12-16 years of age were evaluated in a one-year study in for the safety and efficacy of orlistat *vs.* placebo for weight loss. Dr. Theresa Kehoe, medical officer in the Division of Metabolism and Endocrine Drug Products, reviewed this study.[72] Findings from her review related to growth, include:

- Tanner Stage: Patients in both the orlistat treatment group and the placebo treatment group experienced normal sexual maturation during the study and there were no notable differences between treatment groups.
- Height: Patients in both treatment groups grew during the study and were taller at the end of treatment than at baseline. The change in height from baseline to the end of the study was similar in both treatment groups (1.91 cm in the placebo group versus 1.82 cm in the orlistat group).
- BMI: Orlistat use resulted in a statistically significant decrease in BMI when compared to placebo (-0.55 kg/m^2 vs. 0.31 kg/m^2; $p = 0.001$). Overall, 26.5% of orlistat-treated patients and 15.7% of placebo-treated patients had a 5% reduction of their baseline BMI ($p = 0.005$), while 13.3% of orlistat-treated patients and 4.5% of placebo-treated patients had a 10% reduction of their baseline BMI ($p = 0.002$).
- DEXA: Changes in body weight were accounted for mostly by decreases in body fat and increases in fat free mass (soft tissue), with the orlistat group demonstrating significantly greater decreases in fat mass than the placebo group. No significant differences between groups were found in mean BMC or BMD changes.

7.1.16 Overdose Experience

In the clinical pharmacology program, single doses of orlistat up to 800 mg and doses of up to 1200 mg/day in divided doses given for 15 days were not associated with adverse events other than gastrointestinal events. In phase 2 studies, 240 mg orlistat TID for six months was associated with a similar adverse event profile as 120 mg TID except for a slightly greater higher incidence of gastrointestinal events.

The sponsor reviewed post-marketing data and found 16 cases of overdose (defined as at least twice the normal dose); they noted that these cases revealed for the most part that patients either had no adverse events related to the overdose or adverse events similar to that with the recommended dose. In the case of an extreme overdose, the appropriate course of action is to observe the patient. Local effects in the gastrointestinal tract should not last beyond 48-72 hours. Given the limited systemic exposure, the effect on other body systems is unlikely.

7.1.17 Post-Marketing Experience

The Xenical label[11] includes the following language on post-marketing findings, such as hypersensitivity:

72 Kehoe T. Medical Officer Review of Study NM16189, NDA 20-766.

Rare cases of hypersensitivity have been reported with the use of XENICAL. Signs and symptoms have included pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis. Very rare cases of bullous eruption, increase in transaminases and in alkaline phosphatase, and exceptional cases of hepatitis that may be serious have been reported. No causal relationship or physiopathological mechanism between hepatitis and orlistat therapy has been established. Reports of decreased prothrombin, increased INR and unbalanced anticoagulant treatment resulting in change of hemostatic parameters have been reported in patients treated concomitantly with orlistat and anticoagulants.

In clinical trials in obese diabetic patients, hypoglycemia and abdominal distension were also observed.

Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when XENICAL was coadministered with cyclosporine.

Specific safety issues evaluated with post-marketing data are discussed in other sections of this review; in particular, pancreatitis. This section reviews the safety findings from a post-marketing surveillance (PMS) study conducted between March 1999 and April 2000 in primary health care centers in Germany, entitled the XXL (Xenical ExtraLarge) Study.[73] Subjects were 11131 women and 4418 men with a mean age of 48 years, mean BMI 34.7 kg/m^2, and mean duration of obesity 13.7 years. Physicians who were routinely visited by field representatives of Roche were asked to participate in this PMS study. Physicians were advised to treat their patients as usual, without any obligation to prescribe a given drug. If the physicians chose to prescribe orlistat, they were instructed to follow the European Prescribing Guidelines. Patients with a BMI 28 kg/m^2 in whom treatment with orlistat was indicated could be included. Patients with contraindications were excluded from participation.

Patients were treated for a mean of 7.1 months, with a follow-up visit 32 days after recruitment. Adverse events were reported in 1.5% of patients and were mainly gastrointestinal in nature. Diarrhea or liquid stools (n = 64), fatty stools (n = 50), flatulence (n = 23), and nausea (n = 7) were the most frequently reported adverse events. Headaches were reported by six patients; reports of all other adverse events were given by four (0.03%) patients or fewer. No specific information regarding serious adverse events was provided.

As noted by the authors, the lower number of adverse events reported by the patients than those reported in previous controlled studies may be explained by the fact that in PMS studies patients report adverse events only spontaneously and detailed data are unavailable for patients prematurely terminating their treatment with orlistat.

73 Wirth A. Diabetes, Obesity and Metabolism 2005; 7:21-27.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The reader is referred to Section 4.1 for a discussion of the safety database and Section 4.2 for a presentation of the trials supporting this application in tabular form. The following is a description of studies evaluated for safety that were not described in Section 6, the Integrated Review of Efficacy.

Study NM14302 included a 60 mg treatment arm but was not included in the evaluation of efficacy because the main objective of this study was to assess the efficacy of orlistat in preventing weight regain after six months of diet-induced weight loss. This study is pooled with studies BM14149 and NM14161 in the analysis of safety. The original objectives of study NM14302 were to determine the weight loss maintenance and prevention of weight gain effects of orlistat (30 mg, 60 mg, or 120 mg) or placebo TID for 52 weeks after losing weight by conventional diet therapy. During the 24-week lead-in period, subjects (BMI 28 - 38 kg/m^2) were placed on a hypocaloric diet [(BMR x 1.3) - 1000 kcal/d] with 30% calories as fat. On day 1, subjects who lost at least 8% of their initial body weight were randomly assigned to receive orlistat or placebo in a 1:1:1:1 randomization to be administered for 52 weeks. On day 1, subjects were placed on a eucaloric diet.

The phase 2 study BM14150 was a 24-week dose-ranging study conducted under the original prescription NDA. This study evaluated orlistat at doses of 30, 60, 120, and 240 mg compared to placebo in subjects with BMIs 28 - 43 kg/m^2. It is a supportive study in this nonprescription NDA, and its results are presented separately. The original objectives were to determine the weight loss effect and tolerability of orlistat 30 mg, 60 mg, 120 mg, and 240 mg versus placebo, in combination with a hypocaloric diet [(BMR x 1.3) - 600 kcal/d] and 30% of calories as fat for 24 weeks.

Study NM14185 from the original prescription NDA also contained a 60 mg treatment arm but was not included in the current NDA since treatment with orlistat 60 mg TID occurred only after one year of treatment with orlistat 120 mg TID.

Study NM17285 was the actual use trial, and was reviewed in detail by Dr. Karen Feibus, medical officer in the Division of Nonprescription Clinical Evaluation, Office of Nonprescription Products.[16] The primary objectives of this study were to evaluate the ability of consumers to correctly select orlistat for their own use based on labeled directions, to provide initial information regarding how consumers use orlistat in the absence of physician supervision, and to evaluate the adverse event profile in an actual use setting. The study was designed as a multi-center, pharmacy-based, open-label, three-month trial. Subjects were self-selecting individuals

18 years of age or older, who were able to give written informed consent and able and available to participate in telephone follow-up interviews. Notable exclusion criteria included: allergy to orlistat; previously treated with Xenical; treated with medication for diabetes, warfarin, or cyclosporine; or pregnant or breast feeding. Subjects were instructed to take 1-2 capsules (60-120 mg) three times a day for up to six months. The following materials were included in an 'OTC package': one bottle of 90 orlistat 60 mg capsules, the Orlistat User Guide, a Personal Food Diary, a Pocket Fat Gram Counter, a Fat Gram Wheel and a portion size information card. In addition, the Orlistat Diet Success Planner was provided to each purchaser with the first purchase. The Orlistat Diet Success Planner provided lifestyle information designed to help consumers in their weight loss efforts. The package received in repeat purchases was identical to that of the first purchase. Subjects could purchase up to three product packages of 90 count bottles of 60 mg capsules at any one time and were not limited on how often they could return to the pharmacy for additional drug.

Study RCH-ORL-002 was a four-week consumer use study administered in a naturalistic setting. The primary objective was to determine the feasibility and consumer satisfaction of 60 mg orlistat given three times a day plus diet over a four-week in-home-use period. RCH-ORL-002 was designed as an open-label, multi-center, non-randomized, uncontrolled study in which subjects were recruited by mall intercept. Recruitment for this study took place at 16 shopping malls in the United States, where shoppers were intercepted and a concept interview was performed. The interview consisted of model questions, attributes, category usage, and demographics. Any subjects expressing "Top Three Box" purchase intent (i.e., definitely would buy, probably would buy, might or might not buy) were eligible for being a candidate subject to participate in the clinical portion of the study. Subjects were then asked to read and sign an informed consent form. A West Pharmaceutical Services (WPS) nurse reviewed the consent via telephone and addressed and responded to all study-related questions. Notable inclusion criteria included: having an interest in losing weight; being considered by the shopping mall research agency interviewer and the Central Medical Operations Group (CMOG), composed of a nurse and physician from WPS, to be motivated to participate in and complete the study as instructed; understanding and signing an informed consent form; being in good health as assessed by a medical history conducted by the CMOG of WPS; and being willing and able to use the study drug and complete the diary as instructed, participate in the follow-up telephone interview, and return the unused product, product packaging material, and diary at the end of the study. Notable exclusion criteria included: BMI < 27 kg/m^2 based on self-reporting, being pregnant or breastfeeding, chronic malabsorption, gallbladder problems, taking cyclosporine or warfarin, or having an eating disorder such as anorexia nervosa or bulimia. The enrolled subjects were instructed to use the study drug during the four-week study period according to the label on the drug bottle, the Product Information Sheet (adaptation of the approved package insert of Xenical), and the Product Brochure (modified from the patient brochure currently in use by patients taking Xenical). The subjects received the Project Information Sheet and the Product Brochure along with the study drug after enrollment. During the four-week study period, subjects were told to take 60 mg of orlistat three times a day with diet. Subjects were also instructed to take daily multivitamins and to eat a nutritionally balanced, reduced-calorie diet containing no more than 30% fat. The enrolled subjects were instructed to record product usage,

concomitant medications, initial and final body weight, and adverse events on a diary during the study period.

In the pooled safety studies BM14149, NM14161, and NM14302 (BMI 28-43 kg/m^2), 543 (87%) of 623 subjects on orlistat 60 mg TID and 537 (85%) of 632 subjects on orlistat 120 mg TID completed at least 24 weeks of study drug treatment. In NM17247, the four-month trial in subjects with a BMI 25-28 kg/m^2, 154 (79%) of the 196 orlistat subjects and 139 (71%) of the 195 placebo subjects were treated within the four-month window (99-140 days; orlistat, maximum: 129 days; placebo, maximum: 138 days).

As seen in Table 7.2.1.1.A, in all seven studies supporting NDA 21-887 combined, there were 671 subjects with a BMI < 30 kg/m^2 exposed to orlistat 60 or 120 mg. Of these subjects, 135 and 136 in the 60 mg and 120 mg groups, respectively, were in the study for at least 24 weeks. Although this is a relatively small number of subjects with a BMI < 30 kg/m^2 who have been exposed to orlistat for greater than six months, there is a considerable body of data regarding the safety of the 120 mg dose in those with a higher BMI. Study NM14302 has a proportionately higher number of subjects with a BMI < 30 kg/m^2 because the subjects underwent six months of dietary weight loss before being randomized to drug treatment.

Table 7.2.1.1.A. Extent of Exposure in Subjects with BMI < 30 at Randomization; Safety Population

Study	Treatment Period (weeks)	Dose	N	Time on study medication					
				>1 wk n (%)	>4 wks n (%)	>12 wks n (%)	>24 wks n (%)	>36 wks n (%)	>48 wks n (%)
BM14150	24	60 mg	23	23 (100.0)	23 (100.0)	22 (95.7)	---	---	---
		120 mg	23	23 (100.0)	23 (100.0)	21 (91.3)	---	---	---
BM14149	52[a]	60 mg	33	33 (100.0)	33 (100.0)	32 (97.0)	28 (84.8)	26 (78.8)	26 (78.8)
		120 mg	43	42 (97.7)	42 (97.7)	40 (93.0)	40 (93.0)	36 (83.7)	34 (79.1)
NM14161	52[a]	60 mg	14	14 (100.0)	14 (100.0)	14 (100.0)	12 (85.7)	11 (78.6)	11 (78.6)
		120 mg	12	11 (91.7)	11 (91.7)	11 (91.7)	9 (75.0)	9 (75.0)	8 (66.7)
NM14302	52	60 mg	105	104 (99.0)	103 (98.1)	98 (93.3)	95 (90.5)	89 (84.8)	82 (78.1)
		120 mg	110	108 (98.2)	104 (94.5)	96 (87.3)	87 (79.1)	77 (70.0)	75 (68.2)
NM17247	16	60 mg	196	189 (96.4)	178 (90.8)	158 (80.6)	---	---	---
NM17285[b]	---	60-120 mg	94	94 (100.0)	80 (85.1)	37 (39.4)	---	---	---
RCH-ORL-002	4	60 mg	33	30 (90.9)	27 (81.8)	---	---	---	---

Cell entries are number and % of subjects who entered the time interval.
[a] Data from year 1 of studies BM14149 and NM14161 are tabulated.
[b] Study NM17285 (actual use study): subjects could take 1-2 60 mg capsules for up to 90 days.
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7.2.1.2 Demographics

Demographics and baseline characteristics for the pooled efficacy studies BM14149 and NM14161, and pivotal study NM17247 (ITT population), were presented in Section 6.1.4.2. Table 7.2.1.2.A includes study NM14302 in the other two pooled phase 3 studies for safety.

Demographic characteristics in this pooled safety population are generally balanced between treatment groups. There were slightly more males in the orlistat 60 mg group and slightly more

Blacks and Hispanics in the orlistat 120 mg group. Although the distribution of placebo subjects in the BMI groups was slightly different than that of the orlistat groups, the mean weight and BMI was similar between treatment groups.

Baseline characteristics such as blood pressure, lipids, medical history, and concomitant medications were generally well-matched between treatment groups in the individual prescription phase 3 studies.

Table 7.2.1.2.A. Demographic Characteristics; Pooled Phase III Studies (BM14149, NM14161, NM14302)

	Placebo (N=634)		Orlistat 60 mg TID (N=623)		Orlistat 120 mg TID (N=632)	
	n	(%)	n	(%)	n	(%)
Sex						
Male	106	(16.7)	138	(22.2)	107	(16.9)
Female	528	(83.3)	485	(77.8)	525	(83.1)
Race						
Caucasian	594	(93.7)	591	(94.9)	578	(91.5)
Black	25	(3.9)	21	(3.4)	29	(4.6)
Hispanic	12	(1.9)	7	(1.1)	23	(3.6)
Other Race	3	(0.5)	4	(0.6)	2	(0.3)
Age category						
< 65 years	615	(97.0)	608	(97.6)	617	(97.6)
≥ 65 years	19	(3.0)	15	(2.4)	15	(2.4)
BMI category						
≥ 25 – < 28 kg/m^2	6	(0.9)	0	(0.0)	3	(0.5)
≥ 28 – < 30 kg/m^2	58	(9.1)	52	(8.3)	51	(8.1)
≥ 30 – < 35 kg/m^2	269	(42.4)	299	(48.0)	309	(48.9)
≥ 35 kg/m^2	299	(47.2)	270	(43.3)	268	(42.4)
Missing	2	(0.3)	2	(0.3)	1	(0.2)
Age (years)						
Mean +/- SD	44.0 +/- 10.33		44.3 +/- 10.51		44.2 +/- 10.64	
(Min, Max)	(18, 72)		(20, 72)		(18, 78)	
Weight (kg)						
Mean +/- SD	97.1 +/- 14.60		97.7 +/- 14.27		96.0 +/- 14.00	
(Min, Max)	(62.3, 155.5)		(67.3, 152.0)		(63.5, 147.3)	
BMI (kg/m^2)						
Mean +/- SD	34.8 +/- 3.89		34.8 +/- 3.72		34.6 +/- 3.59	
(Min, Max)	(27.0, 45.8)		(28.0, 44.0)		(27.4, 43.4)	

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Table 7.2.1.2.B presents the demographic data for the safety population for study NM17247. Treatment groups were well-matched for the described variables. Both treatment groups were generally well-matched for baseline characteristics such as lipids, blood pressure, pulse, glucose, and concomitant medications. Most patients (placebo 85%; orlistat, 91%) had at least one concomitant disease during the study. The most frequently reported concomitant diseases occurred in the nervous system, the musculoskeletal system, and the respiratory system; about one-third of patients in each treatment group reported concurrent or previous diseases in these body systems. The most frequently reported specific concurrent diseases included headache,

migraine, back pain, seasonal rhinitis, drug hypersensitivity, hypertension, depression, and hypercholesterolemia, each occurring in > 10% of patients in at least one of the treatment groups. There were no meaningful differences between treatment groups in the incidence of any specific concurrent diseases.

Table 7.2.1.2.B. Demographic Characteristics 4-Month Phase III Study

	Placebo (N=195)		**Orlistat 60 mg TID (N=196)**	
	n	**(%)**	**n**	**(%)**
Sex				
Male	11	(5.6)	12	(6.1)
Female	184	(94.4)	184	(93.9)
Race				
Caucasian	174	(89.2)	174	(88.8)
Black	14	(7.2)	18	(9.2)
Other Race	7	(3.6)	4	(2.0)
Age (years)				
Mean ± SD	46.5 ± 10.97		45.8 ± 11.87	
(min, max)	(19, 72)		(20, 80)	
Weight (kg)				
Mean ± SD	72.9 ± 6.94		72.7 ± 6.95	
(min, max)	(56.2, 106.6)		(57.4, 102.5)	
BMI (kg/m^2)				
Mean ± SD	26.8 ± 0.95		26.8 ± 0.96	
(min, max)	(23.7, 28.6)		(24.5, 29.0)	

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Table 7.2.1.2.C describes the demographics and baseline characteristics for subjects from the supportive study BM14150. Slightly more subjects were male and White in the orlistat 60 mg treatment group compared to the other groups.

Table 7.2.1.2.C. Demographic Characteristics; 6-Month Phase II Study (BM14150)						
	Placebo (N=124)		Orlistat 60 mg TID (N=123)		Orlistat 120 mg TID (N=120)	
	n	(%)	n	(%)	n	(%)
Sex						
Male	27	(21.8)	30	(24.4)	25	(20.8)
Female	97	(78.2)	93	(75.6)	95	(79.2)
Race						
Caucasian	117	(94.4)	120	(97.6)	108	(90.0)
Black	5	(4.0)	3	(2.4)	8	(6.7)
Other Race	2	(1.6)	0	(0.0)	4	(3.3)
Age (years)						
Mean +/- SD	42.6 ± 11.2		42.2 ± 11.3		40.4 ± 10.7	
(Min, Max)	(18, 65)		(19, 68)		(20, 66)	
Weight (kg)						
Mean +/- SD	94.8 ± 13.6		95.0 ± 13.6		94.9 ± 13.0	
(Min, Max)	(70.0, 135.6)		(71.0, 132.2)		(70.7, 128.4)	
BMI (kg/m^2)						
Mean+/- SD	34.7 ± 3.7		34.4 ± 3.8		34.7 ± 3.8	
(Min, Max)	(27.7, 43.2)		(27.3, 43.5)		(28.8, 43.5)	

Table 7.2.1.2.D describes the demographic and baseline characteristics in the actual use study, NM17285. Although this study's design and results is discussed in depth by Dr. Feibus, this table is included to highlight the following points. First, only one third of subjects who self-selected for purchase actually met the BMI criteria for overweight, and 8% were in fact normal weight. The BMI ranged from 21 to 54 in the purchasers group. Second, although there are no subjects < 18 years old in any group, such subjects were prohibited from screening and therefore the potential for purchase in this group was not studied.

Table 7.2.1.2.D. Demographic Information; Study NM17285				
	All Screened Subjects N = 703	Eligible Subjects N = 681	Purchasers Group N = 262	Users Group N = 237
Sex n (%)				
Male	143 (20.3)	140 (20.6)	38 (14.5)	34 (14.3)
Female	558 (79.4)	539 (79.1)	223 (85.1)	202 (85.2)
Missing	2 (0.3)	2 (0.3)	1 (0.4)	1 (0.4)
Race n (%)				
White/Caucasian	562 (79.9)	540 (79.3)	214 (81.7)	194 (81.9)
African American	42 (6.0)	42 (6.2)	9 (3.4)	6 (2.5)
Native American	10 (1.4)	10 (1.5)	4 (1.5)	4 (1.7)
Asian	11 (1.6)	11 (1.6)	6 (2.3)	6 (2.5)
Hispanic, Spanish, Latino	55 (7.8)	55 (8.1)	17 (6.5)	15 (6.3)
Other	22 (3.10)	22 (3.2)	12 (4.6)	12 (5.1)
Missing	1 (0.1)	1 (0.1)	0	0
Age (years)				
Mean	45.8	45.4	45.0	44.9
Std Dev	14.64	14.46	13.55	13.44
Median	45.0	45.0	45.0	45.0

Table 7.2.1.2.D. Demographic Information; Study NM17285				
	All Screened Subjects N = 703	**Eligible Subjects N = 681**	**Purchasers Group N = 262**	**Users Group N = 237**
Range (min, max)	18, 85	18, 85	18, 80	18, 75
N	699	677	262	237
Height (in)				
Mean	65.6	65.6	65.5	65.3
Std Dev	3.45	3.47	3.30	3.29
Median	65.0	65.0	65.0	65.0
Range (min, max)	57, 80	57, 80	59, 80	59, 80
Weight (lb)				
Mean	202.8	203.1	196.2	195.3
Std Dev	47.39	47.47	43.44	43.05
Median	196.5	197.0	190.0	191.0
Range (min, max)	114, 407	114, 407	118, 353	118,353
N	696	674	262	237
BMI at beginning of study (kg/m^2)				
Mean	33.0	33.1	32.0	32.0
Std Dev	6.70	6.68	5.98	5.84
Median	32.1	32.1	31.7	31.6
Range (min, max)	20.8, 62.6	20.9, 62.5	20.9, 54.5	20.9, 53.3
N	696	674	262	237
BMI group				
< 25	54 (7.7)	49 (7.2)	20 (7.6)	18 (7.6)
25-29.9	187 (26.6)	181 (26.6)	85 (32.4)	76 (32.1)
≥ 30	455 (64.7)	444 (65.2)	157 (59.9)	143 (60.3)
Missing	7 (1.0)	7 (1.0)	0	0

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In study RCH-ORL-002, the 162-subject safety population was primarily female (83.9%), with a mean age of 36.7 years (range 18 to 73 years). The safety population was primarily White (71.0%); other racial subgroups included: Hispanic (13.6%), Black (13.0%), and others (2.5%). At baseline, the mean weight was 97.4 kg (range 69.4 to 177.3 kg) and the mean BMI of the group was 34.7 kg/m^2 (range 27 to 57 kg/m^2).

7.2.1.3 Extent of exposure (dose/duration)

As the sponsor noted in its background package for the Advisory Committee meeting January 23, 2006, orlistat has been studied in over 100 clinical trials, including four 2-year and one 4-year double-blind, placebo-controlled studies. The sponsor further noted that the 120 mg dose was approved for marketing in the US in 1999 and has been approved and marketed in over 145 countries, with over 22 million patients treated. Therefore, there is a considerable amount of data available on the safety of this drug.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No secondary studies were provided to support safety other than those already discussed.

7.2.2.2 Post-marketing experience

Considerable post-marketing data were available for this review, as orlistat has been available on the prescription market in the U.S. since 1999 and is additionally widely available globally. The FDA Office of Drug Safety was consulted to provide analyses of the AERS database with regard to specific safety issues such as drug-drug interactions and pancreatitis.

7.2.2.3 Literature

In the original submission (i.e., not including the safety update), the sponsor provided those references related to safety between the dates of April 1, 2004 and November 30, 2004. This reviewer did not find a list of references over a seven-month period to be particularly useful. Instead, the literature was queried using PubMed for safety topics of interest.

7.2.3 Adequacy of Overall Clinical Experience

The clinical experience of orlistat is generally adequate; however, the issue of whether the data provided in the NDA was adequate is addressed in Section 7.2.8.

As discussed in Section 8.3.2, only approximately 2.4% of orlistat-treated subjects were aged 65 years or older (about 15 per group in the pooled safety studies). It is therefore difficult to make any conclusions about safety of orlistat in this population based on these studies.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The adequacy of the preclinical program was addressed in the reviews of the prescription NDA.

7.2.5 Adequacy of Routine Clinical Testing

Clinical testing was fully conducted under studies supporting the prescription orlistat approval. For a nonprescription product, it is appropriate for clinical testing to be kept to a minimum, as was done in the studies designed and conducted for the nonprescription NDA.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The adequacy of the clinical pharmacology program was addressed in the reviews of the prescription NDA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Evaluation for the potential adverse events of orlistat was generally adequate in the nonprescription NDA; however, a placebo-controlled actual use study with spontaneous adverse event reporting would provide more information regarding adverse events in the nonprescription setting.

7.2.8 Assessment of Quality and Completeness of Data

The safety database is considered limited because study NM14185, as well as two other studies from the original NDA that included only the 120 mg dose (i.e., those without a separate 60 mg dose arm) and the four-year XENDOS study, were excluded. This reviewer has referred, when appropriate, to the prescription NDA review and the literature for relevant safety data for the 120 mg dose.

Because of an agreement made during the pre-NDA meeting, the sponsor was only required to provide pooled datasets and an Integrated Summary of Safety for studies from the original prescription NDA. Pooled datasets were complete for adverse events, safety laboratory tests, and vital signs. Datasets did not include special testing, such as that of fat-soluble vitamin concentrations, ultrasounds, and electrocardiograms.

In the event that it is determined that nonprescription orlistat is more appropriate as a chronically-used drug (rather than having a six-month limitation), the NDA as submitted is inadequate to assess its safety in such a setting.

Although not a safety issue, per se, it is worth noting that discrepancies were found between the original sponsor's (Roche) study report for NM17247 and the Integrated Summary of Efficacy provided by the nonprescription NDA sponsor (GSK) with regard to conduct of the study. This was discussed in Section 6.1.3.4. Dr. Feibus will address the quality and completeness of the data from GSK's study NM17285, the actual use study.

7.2.9 Additional Submissions, Including Safety Update

No new studies were ongoing when the NDA safety update was submitted. The safety update, therefore, primarily consisted of an update of the post-marketing databases and literature from December 1, 2004 to August 15, 2005. Because post-marketing data and literature are most useful when queried for particular safety concerns, this reviewer did not find the safety update particularly useful. FDA AERS data are accessed in real-time, which enabled this reviewer, in consultation with the Office of Drug Safety, a more meaningful approach to evaluating post-marketing safety. Furthermore, the literature was regularly reviewed throughout the review cycle. Post-marketing and literature findings are incorporated in relevant sections of this review.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Gastrointestinal adverse events, such as fatty and oily stool, are common with orlistat use and are considered to be pharmacologic effects of the drug. This safety issue is discussed in detail in Section 7.1.4.1. These adverse events can be modified by decreasing the amount of fat in the diet. The pharmacologic effect of the drug is observed within 24-48 hours, and following discontinuation of the drug, fecal fat excretion returns to normal within 48-72 hours. Other safety issues such as lithogenicity, hepatitis, or pancreatitis are concerning, but have not been definitively determined to be drug-related.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data *vs.* individual study data

Subjects were initially randomized to a 60 mg orlistat TID dosing regimen in four phase 3 trials: BM14149, NM14161, NM14302, and NM17247. Safety data from studies BM14149, NM14161, and NM14302 were summarized together. Safety data from the four-month phase 3 study NM17247 were summarized separately.

Demographic, adverse event, laboratory, and vital sign data from studies BM14149, NM14161, NM14302, and NM17247 were pooled into common data structures.

7.4.1.2 Combining data

Data from the first year of the two-year studies BM14149 and NM14161 were pooled with data from the one-year treatment period of study NM14302. No special weighting of studies was done, meaning that the denominator was a simple sum of the N*s* of the individual studies.

7.4.2 Explorations for Predictive Factors

Because certain gastrointestinal adverse events, such as fatty and oily stool, are considered to be clearly drug related, the following explorations for predictive factors were done for those drug-related gastrointestinal adverse events.

7.4.2.1 Explorations for dose dependency for adverse findings

As seen in Table 7.4.2.1.A and predicted by the pharmacodynamic effect of the drug, orlistat 60 mg has slightly fewer drug-related adverse events than orlistat 120 mg.

Table 7.4.2.1.A. GI Adverse Events with Incidence ≥ 1% during 6 Months of Treatment; Pooled Phase 3 Studies						
WHO-ART Preferred Term	**Placebo (N=634)**		**Orlistat 60 mg TID (N=623)**		**Orlistat 120 mg TID (N=632)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Fecal urgency	50	(7.9)	117	(18.8)	148	(23.4)
Oily spotting	7	(1.1)	110	(17.7)	137	(21.7)
Flatus with discharge	12	(1.9)	108	(17.3)	126	(19.9)
Fatty/oily stool	17	(2.7)	107	(17.2)	137	(21.7)
Oily evacuation	4	(0.6)	72	(11.6)	85	(13.4)
Increased defecation	17	(2.7)	44	(7.1)	52	(8.2)
Fecal incontinence	5	(0.8)	29	(4.7)	49	(7.8)
Table includes events with orlistat incidence ≥ 5% and at least twice the placebo incidence						

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The incidence of the gastrointestinal AEs within the first week of treatment is presented in Table 7.4.2.1.B. The sponsor provided this table to demonstrate that tolerability is better with the orlistat 60 mg dose in the first week. It is therefore implied that early adherence will be improved with the availability of the 60 mg dose.

Table 7.4.2.1.B. Gastrointestinal Adverse Events within the First Week of Treatment; Pooled Phase 3 Studies						
WHO-ART Preferred Term	**Placebo (N=634)**		**Orlistat 60 mg TID (N=623)**		**Orlistat 120 mg TID (N=632)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Flatulence	60	(9.5)	56	(9.0)	59	(9.4)
*Fecal urgency	21	(3.3)	52	(8.4)	68	(10.9)
*Flatus with discharge	4	(0.6)	47	(7.6)	70	(11.2)
*Abdominal pain	19	(3.0)	38	(6.1)	39	(6.2)
*Oily spotting	1	(0.2)	37	(6.0)	64	(10.2)
*Fatty/oily stool	3	(0.5)	36	(5.8)	59	(9.4)
*Oily evacuation	1	(0.2)	36	(5.8)	42	(6.7)
Stools soft	8	(1.3)	19	(3.1)	13	(2.1)
Increased defecation	6	(1.0)	19	(3.1)	31	(4.9)
Liquid stools	8	(1.3)	15	(2.4)	27	(4.3)
Nausea	8	(1.3)	12	(1.9)	17	(2.7)
Fecal incontinence	0		9	(1.4)	16	(2.5)
Decreased defecation	9	(1.4)	5	(0.8)	3	(0.5)
Fullness abdominal	3	(0.5)	2	(0.3)	1	(0.2)
Abdominal discomfort	2	(0.3)	2	(0.3)	5	(0.8)
Studies BM14149, NM14161, NM14302 *Orlistat incidence ≥ 5% and at least twice the placebo incidence in pooled phase 3 studies.						

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7.4.2.2 Explorations for time dependency for adverse findings

As discussed in Section 7.1.4.1.1, this reviewer's exploratory analysis suggests that in the six-month completers, the majority of the gastrointestinal adverse events were in the first few weeks. Furthermore, the sponsor notes that the first gastrointestinal event in the majority of subjects

occurred within the first 12 weeks, with very few subjects experiencing their first episode after six months.

7.4.2.3 Explorations for drug-demographic interactions

This reviewer performed the following explorations of drug-related gastrointestinal adverse events by age, sex, and race (Tables 7.4.2.3.A, 7.4.3.2.B, and 7.4.3.2.C, respectively). Although the sample sizes for some sub-groups were small, in general, there were no important differences between groups.

Table 7.4.2.3.A. Explorations for Gastrointestinal Adverse Events and Age

	< 65			≥ 65		
	Placebo N = 615	**Orlistat 60 mg N = 608**	**Orlistat 120 mg N = 617**	**Placebo N = 19**	**Orlistat 60 mg N = 15**	**Orlistat 120 mg N = 15**
Gastro-Intestinal System Disorders	315 (51.2)	422 (69.4)	463 (75.0)	11 (57.9)	6 (40.0)	9 (60.0)
Fecal Urgency	48 (7.8)	116 (19.1)	146 (23.7)	2 (10.5)	1 (6.7)	2 (13.3)
Fatty/Oily Stool	17 (2.8)	107 (17.6)	137 (22.2)	0	0	0
Oily Spotting	7 (1.1)	106 (17.4)	134 (21.7)	0	4 (26.7)	3 (20.0)
Flatus With Discharge	12 (2.0)	107 (17.6)	124 (20.1)	0	1 (6.7)	2 (13.3)
Oily Evacuation	4 (0.7)	72 (11.8)	85 (13.8)	0	0	0
Fecal Incontinence	5 (0.8)	28 (4.6)	47 (7.6)	0	1 (6.7)	2 (13.3)

Table 7.4.2.3.B. Explorations for Gastrointestinal Adverse Events and Sex

	Male			Female		
	Placebo N = 106	**Orlistat 60 mg N = 138**	**Orlistat 120 mg N = 107**	**Placebo N = 528**	**Orlistat 60 mg N = 485**	**Orlistat 120 mg N = 525**
Gastro-Intestinal System Disorders	42 (39.6)	87 (63.0)	74 (69.2)	284 (53.8)	341 (70.3)	398 (75.8)
Fecal Urgency	7 (6.6)	18 (13.0)	15 (14.0)	43 (8.1)	99 (20.4)	133 (25.3)
Fatty/Oily Stool	6 (5.7)	24 (17.4)	24 (22.4)	11 (2.1)	83 (17.1)	113 (21.5)
Oily Spotting	2 (1.9)	16 (11.6)	21 (19.6)	5 (0.9)	94 (19.4)	116 (22.1)
Flatus With Discharge	3 (2.8)	20 (14.5)	17 (15.9)	9 (1.7)	88 (18.1)	109 (20.8)
Oily Evacuation	0	10 (7.2)	10 (9.3)	4 (0.8)	62 (12.8)	75 (14.3)
Fecal Incontinence	0	4 (2.9)	7 (6.5)	5 (0.9)	25 (5.2)	42 (8.0)

Table 7.4.2.3.C. Explorations for Gastrointestinal Adverse Events and Race

	White			Non-White		
	Placebo N = 594	**Orlistat 60 mg N = 591**	**Orlistat 120 mg N = 578**	**Placebo N = 40**	**Orlistat 60 mg N = 32**	**Orlistat 120 mg N = 54**
Gastro-Intestinal System Disorders	305 (51.3)	400 (67.7)	427 (73.9)	21 (52.5)	19 (86.4)	45 (83.3)
Fecal Urgency	45 (7.6)	108 (18.3)	137 (23.7)	5 (12.5)	10 (45.5)	11 (20.4)
Fatty/Oily Stool	17 (2.9)	101 (17.1)	130 (22.5)	0	2 (9.1)	7 (13.0)
Oily Spotting	7 (1.2)	101 (17.1)	130 (22.5)	0	5 (22.7)	7 (13.0)
Flatus With Discharge	11 (1.9)	94 (15.9)	109 (18.9)	1 (2.5)	9 (40.9)	17 (31.5)
Oily Evacuation	4 (0.7)	68 (11.5)	77 (13.3)	0	3 (13.6)	8 (14.8)
Fecal Incontinence	5 (0.8)	27 (4.6)	48 (8.3)	0	1 (4.5)	1 (1.9)

7.4.2.4 Explorations for drug-disease interactions

Because subjects in the safety studies provided in this NDA were generally healthy, this reviewer does not consider the exploration of orlistat-related gastrointestinal adverse events and disease to be meaningful. Studies in subjects with type 2 diabetes,[46] hypercholesterolemia,[74] and hypertension[34] generally had a similar pattern of gastrointestinal adverse events.

7.4.2.5 Explorations for drug-drug interactions

Drug-drug interactions are discussed in detail in Section 8.2. This reviewer does not consider the exploration of orlistat-related gastrointestinal adverse events and drugs to be meaningful.

7.4.3 Causality Determination

Adverse events that are common in the clinical studies and clearly related to the pharmacologic action of orlistat are those of the gastrointestinal tract, as discussed in other sections of this review. Other safety issues, for which causality has yet to be determined, such as pancreatitis, hepatitis, gallbladder disease, and nephrolithiasis, are discussed in Section 7.1.12.2.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The prescription dose of orlistat is 120 mg TID. GSK is proposing the nonprescription sale of a 60 mg dose, to be administered 1-2 capsules TID. The pharmacological effect (fecal fat excretion) describes the mechanism of action of orlistat's weight loss effect, that is, caloric deficit, as well as the biological plausibility for the increase in gastrointestinal (GI) side effects. Given that orlistat 60 mg is associated with approximately 25% fecal fat excretion, and orlistat 120 mg is associated with approximately 30% fecal fat excretion, it is expected that the 60 mg dose would be slightly less efficacious and cause fewer GI side effects than the 120 mg dose. This is supported by clinical data.

The pharmacological effect of orlistat also predicts that the more fat there is in the diet, the greater the drug effect. An individual who consumes a diet of 40% fat will experience a higher proportion of daily calories being excreted than someone consuming 20% fat if both individuals have the same amount of daily caloric intake.

However, not all of the weight loss achieved with orlistat may be directly attributable to its pharmacology. Some have suggested that individuals taking orlistat may reduce their dietary fat intake to levels below the recommended 30% of total calories in an effort to reduce or eliminate adverse GI side effects. A dramatic reduction in dietary fat intake may in and of itself reduce

74 Muls E, et al. Int J Obes Relat Metab Disord. 2001 Nov;25(11):1713-21.

weight, but only if individuals do not compensate for the reduction in fat calories by increasing intake of carbohydrate or protein.

One might also conjecture that some individuals will avoid taking orlistat when they know they will be eating out in a social situation, or eating a high-fat meal, in order to avoid embarrassing GI side effects. We know that 3 - 5% of subjects in the first 4 - 6 months of treatment discontinue orlistat due to GI side effects as compared to 1% of placebo-treated subjects.

8.2 Drug-Drug Interactions

The two drugs for which clinically important drug-drug interactions with orlistat have been established are warfarin and the immunosuppressive agent, cyclosporine (see Section 5, Clinical Pharmacology, as well as Sections 8.2.1 and 8.2.2, below).

Unfortunately, we cannot necessarily assume that the labeling for nonprescription orlistat will adequately alert patients to the potential dangers of concomitant use with cyclosporine or warfarin. Indeed, data from the orlistat actual use study NM17285 illustrate that only one half of subjects who were on cyclosporine or warfarin at the time of screening initially recognized that orlistat was not appropriate for their use (Table 8.2.A).

Table 8.2.A. Subjects with Unconditional Labeled Exclusions: Appropriate Initial Selection Decision; Eligible Subjects Study NM17285

	N	Initially said appropriate?	n (%)	Appropriate initial selection decision	
				Total	n (%)
Taking cyclosporine	2	Yes	1 (50.0)	0	1 (50.0)
		No	1 (50.0)	1	
		Don't know	0	0	
Taking warfarin	14	Yes	6 (42.9)	0	7 (50.0)
		No	7 (50.0)	7	
		Don't know	1 (7.1)	0	

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8.2.1 Cyclosporine

A reduction in the serum concentration of cyclosporine has been seen with co-administration with orlistat. Because weight gain is fairly common after organ transplantation, the concomitant use of cyclosporine and orlistat is more than a theoretical possibility, and may lead to sub-therapeutic immunosuppression.[13] Fourteen unique cases of drug interactions between the two drugs were reported in the AERS database (Table 8.2.1.A), and a case of a 'nonsignificant acute rejection episode' (ISHT grade 1B) in a transplanted heart was reported in the literature.[14] In that case report, the decrease from and subsequent re-establishment of an adequate trough cyclosporine level was temporally associated with the starting and stopping of orlistat, respectively.

Table 8.2.1.A. Unique Reports of Cyclosporine-Orlistat Interaction in FDA's Adverse Event Reporting System (AERS) Database				
Age	**Sex**	**Cyclosporine Indication**	**Outcome**	**Referenced Publications**
58	M	Renal transplant	Orlistat discontinued, reestablished cyclosporine concentration	
61	M	Heart transplant	Orlistat discontinued, reestablished cyclosporine concentration	Nagele H, et al.[75]
54	M	Heart transplant	Orlistat discontinued, reestablished cyclosporine concentration	
45	M	Liver transplant	Altered cyclosporine dose	
61	M	Nephrotic syndrome	Orlistat discontinued, reestablished cyclosporine concentration	
Unknown	M	Heart transplant	Unknown	
64	M	Unknown	Unknown	
65	M	Heart transplant	Switch to Neoral improved concentrations	Le Beller C, et al.[76]
43	M	Heart transplant	**Transplant rejection (ISHT-3A = moderate rejection)**	
71	M	Heart transplant	Separated dosing improved concentrations	
Unknown	F	Heart transplant	Increased dose of cyclosporine	
37	F	Unknown	Unknown	
40	F	Lung transplant	Orlistat discontinued, reestablished cyclosporine concentration	Johansson M, et al.[77]
Unknown	Unknown	Heart transplant	Unknown	

8.2.2 Warfarin

A placebo-controlled study evaluating the effect of orlistat on warfarin in healthy volunteers did not demonstrate significant alterations of the pharmacokinetics or pharmacodynamics of warfarin with concomitant orlistat therapy.[44] However, a case report described a patient receiving warfarin who had an increased international normalized ratio (INR) associated with the addition of orlistat to his drug regimen.[78] In addition, because orlistat may be associated with a decline in serum vitamin K concentrations,[22] the prescription orlistat label recommends that patients on chronic stable doses of warfarin who are prescribed orlistat be monitored closely for changes in coagulation parameters.

The FDA Office of Drug Safety provided this reviewer with a raw count of spontaneously reported drug interactions between orlistat and warfarin in the AERS database. A total of 39 reports were found of prolonged or abnormal prothrombin time (PT) or international normalized ratio (INR) with concomitant orlistat use. One of these cases resulted in death, although a causal mechanism with orlistat or warfarin was not established. One patient reportedly had an INR reaching 12.2. Potentially clinically important preferred terms listed include hemarthrosis,

75 Nagele H, et al. Eur J Clin Pharmacol. 1999 Nov;55(9):667-9.
76 Le Beller C, et al. Transplantation. 2000 Nov 27;70 (10):1541-2.
77 Johansson M, et al. Information from the Medical Products Agency. 2000; 4:80-82.
78 MacWalter RS, et al. Ann Pharmacother. 2003 Apr ;37(4) :510-2.

gastrointestinal hemorrhage, and hemorrhage. Four other reports were found suggesting a shortening of PT.

8.2.3 Amiodarone

A recent study of the impact of orlistat on the pharmacokinetics on amiodarone (a lipophilic antiarrhythmic drug), demonstrated that the absorption of amiodarone was reduced by approximately 20-25% when administered with orlistat.[23] The authors assert that the clinical significance of this reduction in systemic exposure is unclear. The amiodarone (Cordarone) label indicates that plasma concentrations of amiodarone with chronic dosing are approximately dose proportional and food increases the rate and extent of absorption. The mean terminal half-life is 58 days and antiarrhythmic effects persist for weeks or months after the drug has been discontinued. The label also states that there is no well-established relationship of plasma concentration to effectiveness; however, it is noted that concentrations much below 1 mg/L are often ineffective, and within-individuals, dose reductions and ensuing decreased plasma concentrations can result in loss of arrhythmia control.[79]

FDA's Office of Drug Safety identified two reports of sudden death with concomitant administration of orlistat and amiodarone in the AERS Database. However, these narratives provide no conclusive evidence that any drug-drug interaction occurred, and no plasma amiodarone concentrations were provided.

- A 65-year-old man being treated with orlistat for overweight (BMI 27.7 kg/m^2), cyclosporine for heart transplant rejection prophylaxis, and amiodarone for arrhythmia, was hospitalized for nonspecific pain and later died suddenly at home. The reporter suspected that the patient's death might have been due to a drug interaction between orlistat and amiodarone. Of note, the most recent serum cyclosporine concentration prior to death was reported to be therapeutic, although this patient had experienced previous subtherapeutic cyclosporine concentrations, thought to be a result of concomitant orlistat administration.
- A 60-year-old man was being treated with orlistat for weight loss and amiodarone for an unknown indication (although the narrative states he had a history of ischemic cardiomyopathy). He was also on multiple other medications. The patient suffered an arrest in a public place, was resuscitated, but died a few hours later. The ECG possibly revealed electrical dissociation but not ventricular fibrillation. The patient's cardiologist (the reporter) did not think the patient's death was related to orlistat.

8.3 Special Populations

8.3.1 Children and Adolescents

To support the labeled indication for Xenical use in adolescents (patients aged 12-16), Roche submitted two studies under NDA 20-766 for review by the Agency under a written request for

79 Cordarone package insert.

pediatric exclusivity: 1) a 21-day placebo-controlled mineral balance study in 32 subjects (results published October 2003[42]), and 2) a 54-week placebo-controlled study, including a two-week placebo lead-in, of 539 obese (BMI > 97th percentile) subjects (results published June 2005[80]). The indication for use in this age group was approved December 12, 2003.

The mineral balance study was discussed in Section 7.1.7.3.1.2.2. There were no deaths or serious adverse events in this 21-day study, with the majority of adverse events from the gastrointestinal system (81% orlistat, 56% placebo). One Black female subject had an increase of ALT from 23 U/L at baseline to 79 U/L on day 22, AST from 15 U/L to 33 U/L, and GGT from 52 U/L to 76 U/L. There were no follow-up values in this subject.

The primary objectives of the 54-week study were to characterize the efficacy and safety of orlistat 120 mg TID as an adjunct to diet in the treatment of obese pediatric patients. Safety was defined by gastrointestinal tolerability; linear growth and Tanner pubertal stage assessment; bone mineral content and body composition; fat-soluble vitamin, beta-carotene; and gallbladder and renal ultrasound. All subjects received a multivitamin. After one year, orlistat use resulted in a statistically significant decrease in BMI as compared to placebo (-0.55 kg/m^2 versus +0.31 kg/m^2, p = 0.001). In the subgroup of subjects who underwent dual-energy x-ray absorptiometry (DEXA) evaluation, subjects in the orlistat group gained a similar amount of fat-free body mass and lost significantly more fat mass than those in the placebo group.

Gastrointestinal adverse events were more common in the orlistat-treated group. Two female subjects underwent cholecystectomy; one was for cholelithiasis and one was for functional disorder of the gallbladder. No subject developed cholecystitis during the study. Of the subjects with normal gallbladder ultrasounds at baseline, six orlistat-treated subjects and one placebo-treated subject had gallstones at the end of the study. There was no evidence that orlistat treatment impacted growth, sex hormone concentrations, or sexual maturation. In the subgroup of subjects who underwent DEXA, bone mineral content and bone mineral density increased similarly in the two treatment groups independently of sex. The mean concentrations of measured fat soluble vitamins and beta-carotene increased in both groups, as a result of multivitamin supplementation. The adjusted mean difference from placebo in beta-carotene was significantly different (-2.4 µg/dL, p < 0.001), and there was a trend toward a difference between orlistat and placebo in vitamin E (adjusted mean difference: -40.26 µmol/L, p = 0.089). In subjects with normal renal ultrasound at baseline, there were two abnormalities seen in the orlistat group (mild left hydronephrosis and 6 mm echogenic focus) and none in the placebo group.

There are limited studies in the literature that examine the effects of treatment with orlistat in obese adolescents or children; all studies have been open-label and do not appear to have uncovered any additional concerns.

As discussed in Section 7.1.13, although misuse is a possibility in this population, there are no published reports of adolescents with eating disorders misusing orlistat. One case report

80 Chanoine JP, et al. JAMA. 2005 Jun 15;293(23):2873-83.

discusses the case of a 16-year-old female who developed significant gastrointestinal side effects from combining orlistat with olestra.[81] In this patient, discontinuing olestra use improved the adverse side effects.

Finally, and most importantly, it is clear that the diagnosis and treatment of obesity in children and adolescents requires the involvement of a learned intermediary, both to exclude organic causes of obesity and to provide the requisite interdisciplinary services to these children. Therefore, although the safety profile of orlistat in the pediatric population is similar to that of adults, nonprescription drug treatment of obesity in this population is considered inappropriate.

8.3.2 Elderly

Older people can derive significant benefit from intentional weight loss. It can ameliorate disease complications, improve mobility, and enhance quality of life. However, aging is associated with a loss of lean body mass and bone, and therefore, weight loss in older individuals should be undertaken with care to avoid further losses of these tissues. Ruling out concomitant illness and addressing nutritional issues are two important roles for the health care provider in the management of weight loss in the elderly population. In addition, the potential for multiple drug-drug interactions is increased as older people are maintained on more medications. This section will briefly discuss the limited data on orlistat-mediated weight loss in the elderly population.

Current guidelines for the management of obesity in older adults[26] assert that the available data from drug trials are insufficient to determine the efficacy and safety of pharmacotherapy for obesity in older persons because these trials tend to exclude older subjects. In the clinical trials primarily supporting efficacy and safety in this application (BM14149, NM14161, NM14302, and NM17247), mean age was approximately 45 years, with a range up to 80 years. However, because only approximately 2.4% of orlistat-treated subjects were aged 65 years or older (about 15 per group in the pooled safety studies), it is difficult to make any conclusions about safety or efficacy of orlistat in this population based on these studies.

The distribution of subjects in the following age groups: 60-69 years, 70-79 years, and $\geq$ 80 years from the actual use study NM17285, is presented in Table 8.3.2.A. Approximately 15% of subjects in the purchasers and users groups were 60 years of age or older, and 4.2-4.6% of subjects were 70 years of age or older. The mean age of subjects in the consumer use study, RCH-ORL-002 was 36 years with a range of 18-73 years.

81 Heck AM, et al. Ann Pharmacother. 2002 Jun;36(6):1003-5.

Table 8.3.2.A. Number and Percent of Subjects ≥ 60 Years by Group, Study NM17285								
Age Group	**All Screened Subjects N = 703**		**Eligible Subjects N = 681**		**Purchasers Group N = 252**		**Users Group N = 237**	
	n	%	n	%	n	%	n	%
60-69 Years	100	(14.2)	96	(14.1)	29	(11.1)	24	(10.1)
70-79 Years	36	(5.1)	29	(4.3)	11	(4.2)	11	(4.6)
≥ 80 Years	4	(0.6)	4	(0.6)	1	(0.4)	0	

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To the knowledge of this reviewer, there have been no studies conducted with orlistat designed specifically to address the safety and efficacy of this drug in the elderly population. Specific safety concerns beyond that of general weight loss include: nutritional deficiencies such as that of vitamin D, drug-drug interactions, and gastrointestinal intolerability, which may result in social or hygiene problems.

Therefore, given the limited data and multiple complexities with weight management in this population, further consideration should be given to the nonprescription availability of orlistat to the elderly.

8.4 Pediatrics

Orlistat (Xenical) 120 mg TID is not specifically labeled for use in children, although results from a year-long placebo-controlled study in children 12-16 years (see Section 8.3.1) are included in the prescription label. The sponsor is requesting a waiver of pediatric studies in children less than 12 and a deferral for those ages 12-17 years.

According to the sponsor, the February 14, 2005 Pediatric Advisory Committee recommended usage in the 12-16 year age group be monitored for an additional year and reported back to the committee. They determined that further evaluation of data in this age group should be completed before considering clinical evaluation at a lower age. Clinical evaluations below the age of 12 years should be completed in the context of prescription usage with considerable physician and dietician oversight.

The sponsor views product usage in the age group 0-11 years to be potentially ineffective and/or unsafe in a nonprescription setting and further states that there are no data to indicate pharmacotherapy for weight loss in this age group would be effective in a nonprescription setting. This reviewer notes that there are no placebo-controlled data to demonstrate efficacy in a nonprescription setting for *any* age group.

The limited time and relative absence of prescribing for this population were given as reasons for extending this oversight period for orlistat usage in this population. The sponsor agrees that additional post-marketing experience is warranted before considering marketing the nonprescription product in this age group.

In terms of the 12-17 year age group, the sponsor claims they would like to establish marketing history on the prescription product. Apparently this will help to determine if the dietary guidance, behavioral support and education/advertising messages developed with an adult population in mind are appropriate for a younger age group. This reviewer notes that there are no data to evaluate how children in this age group would respond to advertising planned for the adult age group.

The sponsor states that a pediatric plan considering use by children ages 12-17 years could be submitted approximately 18 months after NDA approval. Study completion is estimated between 18 and 24 months.

In a discussion of the appropriateness of nonprescription availability to the pediatric patient, Dr. Lisa Mathis, Acting Director of Division of Pediatric Drug Development, Office of Counter-Terrorism and Pediatric Drug Development provided the following insight in a memorandum written for the January 23, 2006 Advisory Committee meeting:

OTC availability of a weight loss drug for children may be dangerous as obese pediatric patients require a multidisciplinary approach to their weight loss. There is a need for a workup to ensure that there is not an organic etiology for their weight. There are several comorbidities with obesity in kids, including hypertension, high cholesterol, and behavioral issues. Any delay in diagnosis and multidisciplinary treatment could be detrimental for the child. Any weight loss without behavioral intervention results in weight regain, and no net benefit for the child.[82]

This reviewer agrees with this assessment, and notes that a similar argument could be made for the treatment of obese adults.

8.5 Advisory Committee Meeting

The following question responses and discussion points are excerpted and paraphrased from the quick minutes from the January 23, 2006 Joint Meeting of the Nonprescription Drugs and the Endocrinologic & Metabolic Drugs Advisory Committee:

1. Has clinical effectiveness been demonstrated with orlistat 60 mg TID and 120 mg TID in the nonprescription setting? For each of these doses, please comment on the following:
    a. A 6-month duration of use
    b. Repeated use or chronic use
    c. Use in the overweight individual
    d. Use in the obese individual (with and without multiple co-morbid conditions)
    e. Use with the proposed educational materials

        a. Yes: 15
        No: 0
        Abstain: 0

82 Mathis L. Consultation for NDA 21-887.

b. Question was dismissed due to lack clinical data in nonprescription setting presented on repeated use.

c. This question was divided into two groups; overweight individuals with: (1.) BMI of 25-28 and (2.) individuals with a BMI of 28-29.9.

C1.	C2.
a. Yes: 9	a. Yes: 15
b. No: 5	b. No: 0
c. Abstain: 1	c. Abstain: 0

d. Yes: 15
No: 0
Abstain: 0

e. Question was withdrawn by the FDA.

Discussion: *The committee's vote above reflects decisions regarding the data presented on patients without co-morbid conditions.*

2. Are the safety and tolerability characteristics of orlistat 60 mg -120 mg TID acceptable for a nonprescription drug? Specifically comment on the following safety concerns and the ability of labeling to convey these concerns to the consumer.
   a. Fat-soluble vitamins
   b. Drug-drug interactions (specifically, cyclosporine and warfarin)
   c. Other concerns? (e.g., pancreatitis, liver toxicity, lithogenicity)

   Yes: 12
   No: 3
   Abstain: 0

3. This proposed nonprescription product is targeted for overweight adults ≥ 18 yrs of age. Do you have specific concerns regarding possible use in the following populations?
   a. Pediatric patients
   b. Underweight or normal-weight individuals or in those with eating disorders
   c. Obese individuals (with and without multiple co-morbid conditions)

   Discussion: *FDA requested that the committee discuss the adequacy of labeling presented, specifically, what mechanisms could be instituted that would discourage use of orlistat in the above population and the possible adversities if used. The Committee agreed that labels should clearly state product is not for use in individuals under the age of 18 and individuals with normal weight or eating disorders. The committee further recommended implementing a plan that would require the sponsor to provide usage data*

in these populations and revisit the issue recommending alternative strategies if necessary.

4. Based on data from the label comprehension study, did subjects demonstrate adequate comprehension to support safe and effective use of orlistat by consumers? Please describe the factors or data you considered in making your decision.

   Yes: 13
   No: 1
   Abstain: 0
   Absent members: 1

5. Do the results from the actual use study suggest:
   a. That consumers make correct self-selection/de-selection decisions?

      Yes: 7
      No: 7
      Abstain:
      Absent members: 1

   b. That consumers comply with dosing directions?

      Yes: 13
      No: 1
      Abstain: 0
      Absent members: 1

6. Do you believe that the potential benefits of nonprescription orlistat outweigh the risks?

   Yes: 11
   No: 3
   Abstain: 0
   Absent member: 1

7. Should orlistat be approved for nonprescription use?
   a. If no, please discuss the deficiencies of the clinical program.
   b. If yes, is the adult population for which orlistat is targeted in the prescription setting different from the adult population in the nonprescription setting? If so, how would each of the two populations be identified?

   Yes: 11
   No: 3
   Abstain: 0
   Absent member: 1

8.6 Literature Review

The following is an alphabetical list of guidances and published literature referenced throughout the review.

Anonymous. Nutrition during pregnancy. ACOG Technical Bulletin Number 179. Int J Gynaecol Obstet. 1993 Oct;43(1):67-74.

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Dattilo AM, et al. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr. 1992 Aug;56(2):320-8.

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FDA Guidance for the Clinical Evaluation of Weight-Control Drugs; Sept. 1996.

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Field AE, et al. Peer, parent, and media influences on the development of weight concerns and frequent dieting among preadolescent and adolescent girls and boys. Pediatrics. 2001 Jan;107(1):54-60.

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8.7 Postmarketing Risk Management Plan

The post-marketing risk management plan was included in the summary clinical section of the NDA, and states:

The GSK Safety Database will capture all information on OTC orlistat adverse events received from spontaneous, solicited, literature and regulatory reports, and clinical studies (serious reports). All serious adverse events received will be actively followed up to ensure all relevant clinical information is received. Serious adverse events will be reviewed by Product Safety (Consumer Healthcare) at GlaxoSmithKline (GSK) to identify and monitor any safety signals. All spontaneous reported adverse events will be summarized in periodic safety reports which are submitted to the FDA. These reports include an extensive review of safety data (serious and non-serious reports) from all sources including clinical trials, spontaneous reports, published literature, and from post-marketing surveillance studies.

This plan details activities expected from the sponsor of an approved drug product. No post-marketing study proposals were provided for this review.

8.8 Other Relevant Materials

All reviewed materials were discussed in other sections of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Orlistat 60-120 mg TID has been demonstrated in controlled clinical trials to be safe and efficacious in the treatment of individuals with a BMI $\geq$ 28 kg/m^2 under a physician's care. In this setting, the use of orlistat results in a 2-3% weight loss over placebo after six months of treatment and contributes to weight maintenance and prevention of weight regain when taken chronically. The prescription product (Xenical 120 mg TID, Hoffman-La Roche)[1] was approved based on achievement of an efficacy criterion defined as a statistically greater percentage of subjects on orlistat losing greater than or equal to 5% of their baseline weight as compared to those on placebo.[2]

GlaxoSmithKline Consumer Healthcare is proposing that orlistat 60 mg be available as a nonprescription weight loss aid for overweight adults. There are several issues that concern this reviewer with regard to this application in particular and the approval of a nonprescription weight loss agent in general.

6. Defining the population

The National Institutes of Health's *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*[3] defines normal weight as a body mass index (BMI) of 18.5 – 24.9 kg/m^2, overweight as a BMI of 25 – 29.9 kg/m^2, and obese as a BMI $\geq$ 30 kg/m^2. The guidelines recommend weight loss through a combination of diet modification, increased physical activity, and behavior therapy for obese patients, and for patients who are overweight or have a high-risk waist circumference, when accompanied by two or more risk factors. In the event that lifestyle changes do not promote weight loss after six months, drugs should be considered as adjunctive therapy for select patients who have a BMI $\geq$ 30 kg/m^2, or a BMI $\geq$ 27 kg/m^2 if concomitant obesity-related risk factors or disease exist. This mirrors FDA's current approach to the evaluation and approval of prescription weight-loss drugs.

The recommendation to limit the use of weight-loss drugs to individuals with a BMI $\geq$ 30 kg/m^2 or $\geq$ 27 kg/m^2 if accompanied by obesity-related risk factors, represents an attempt to maximize the therapeutic risk-benefit profile by targeting drug therapy to those individuals whose risk for weight-related disease is high and is likely to outweigh the risks associated with any given pharmacological agent. As is emphasized in the guidelines: *In those patients with a lower level of obesity risk, nonpharmacological therapy is the treatment of choice.*[3]

A risk-benefit analysis cannot be done when the benefit aspect of the equation (or the risk of having a particular condition) is not quantifiable. Thus, this reviewer cannot quantify the benefit of drug-induced cosmetic weight loss in a healthy overweight population.

7. Determining the duration

Obesity and overweight tend to be chronic conditions.[4] Successful drug treatment is therefore expected to be chronic. To assess the long-term efficacy and safety of prescription weight-loss drugs, FDA currently recommends that pre-approval trials be at least one year in duration.

It is well-known that once treatment with a weight-loss drug is stopped, lost weight is regained and improvement in co-morbidities reversed.[5] Furthermore, two-year data from the prescription NDA suggest that if orlistat is continued but salutary lifestyle changes are modified or stopped, lost weight is regained. This underscores the critical role lifestyle modification plays in determining the efficacy of orlistat, as is discussed further, below.

It is unclear to this reviewer what the proposed six-month duration of therapy will achieve in terms of durable weight loss. However, weight loss drugs previously considered appropriate for nonprescription use were imposed with an even stricter duration limitation than six months. The Advanced Notice of Proposed Rulemaking (ANPR) for Weight Control Products for Over-the-Counter Human Use published on February 26, 1982,[6] stated that:

Attempts at weight reduction which involve the use of this product should be limited to periods not exceeding 3 months, because that should be enough time to establish new eating habits.

In the last 10 years or so, the medical community has shifted its thinking on this issue such that overweight and obesity are now considered to be chronic conditions, as stated above. Therefore, although a tentative monograph for nonprescription weight loss aids currently exists, a three-month limitation on a weight control therapy no longer seems to make medical or scientific sense. There are *no* data to suggest that a three-month treatment duration allows for the establishment of new eating habits. This reviewer would even go so far as to posit that such establishment of new eating habits is a lifelong undertaking, and one in which the addition of a drug is unlikely to impact. Of some concern is that the opposite of the desired effect may occur such that an individual may abandon healthful lifestyle changes with the promise of a weight-loss pill.

8. Concomitant lifestyle modification

Because the standard of care is to administer orlistat, as is the case with all obesity drugs, in conjunction with lifestyle modification, the efficacy of orlistat without some degree of lifestyle intervention has not been studied. We do know that lifestyle modification is critical both for weight loss and maintenance. This concept has been highlighted in a recent study that demonstrated greater successes with sibutramine – a centrally-acting obesity drug approved for long-term weight loss – in combination with health care provider visits.[7] Sibutramine plus intensive behavioral modification was the most successful treatment, followed by intensive

behavioral modification alone and sibutramine plus brief visits with the primary care physician. Least successful was the group randomized to sibutramine therapy alone. Similar success of lifestyle therapy as compared to drug has been demonstrated in other studies of disease prevention. For example, the Diabetes Prevention Program demonstrated that intensive lifestyle modification was significantly more efficacious than metformin therapy in the prevention of type 2 diabetes in individuals at risk for the disease.[8]

All placebo-controlled clinical trials for orlistat utilized some form of dietary/lifestyle intervention along the spectrum of brief physician visits to intensive dietary intervention. The actual use trial, a three-month pilot study that utilized written materials similar to those planned for labeling of the nonprescription product, did not employ a control group; therefore, a reliable assessment of efficacy in this setting cannot be made.

An additional concern, which illustrates this reviewer's discomfort with the entire concept of a nonprescription weight loss product, is that a consumer may actually *replace* a healthful lifestyle with the use of a drug. The development of overweight and obesity occurs because of an imbalance in energy intake *vs.* expenditure. Resetting this balance often involves changing one's relationship with food and physical activity, and is frequently accompanied by psychological, behavioral, emotional, and social disruption. This reviewer feels strongly that the attainment of durable weight loss cannot be accomplished solely by the available weight-loss drug treatments. The decision to be treated for obesity with a medication, including orlistat, is one that the health care provider and the patient should make together, only after a conversation about the patient's commitment to making the appropriate lifestyle changes. Current recommendations state that that pharmacotherapy for obesity is to be initiated only after six months of attempted weight loss with diet and other lifestyle intervention has been inadequate.[3]

9. Efficacy issues

Given the sponsor's proposal to market nonprescription orlistat for short-term use, the six-month time point was chosen as the efficacy endpoint of interest from the two prescription NDA clinical studies (BMI 28 - 43 kg/m^2). In these studies, which were pooled due to similar study designs and patient populations, 42% of subjects treated with orlistat 60 mg, 45% of subjects treated with orlistat 120 mg, and 23% of those treated with placebo achieved a weight loss of $\geq$ 5% at six months ($p < 0.001$, orlistat *vs.* placebo). Placebo-subtracted mean weight loss in the two prescription NDA clinical studies at six months was 2.3 kg (~2.4%) in subjects on the 60 mg dose and 2.9 kg (~3.1%) in those on the 120 mg dose.

By contrast, in the nonprescription NDA clinical study (BMI 25 - 28 kg/m^2), 36% of orlistat 60 mg-treated subjects *vs.* 28% of placebo-treated subjects lost at least 5% of their baseline body weight at four months (between-group difference non-significant, $p = 0.104$). In the nonprescription NDA clinical study, after four months of treatment with orlistat 60 mg, the placebo-subtracted mean weight loss was 1.2 kg (~1.6%).

These findings raise the possibility that orlistat may be less effective in mildly overweight individuals (i.e., BMIs 25 - 28 kg/m^2) than in obese subjects. However, because the sponsor has

not studied the effects of six months of orlistat therapy in mildly overweight subjects, we can only make assumptions about the six-month efficacy in this group.

Because the two prescription studies in subjects with BMI 28 - 43 kg/m^2 had differing degrees of lifestyle intervention (one study utilized dieticians and regular collection of food records were used to provide feedback, and the other occurred in the primary care physicians' offices where subjects were provided general encouragement, but no specialized counseling), the differential findings help inform efficacy issues related to dietary compliance. For example, there was less of a treatment and dose effect in the study with intensive lifestyle modification, although overall, weight loss (and weight maintenance over two years) was greater in this study.

10. Safety issues

Due to its low bioavailability, orlistat is considered a relatively safe drug in the prescription setting. The most common adverse events are gastrointestinal (GI) in nature, such as fatty and oily stool. Although these drug-related side effects are likely to be important to consumers, from a clinical perspective, this reviewer considers the GI side effects to be primarily tolerability rather than safety concerns.

On the other hand, fat-soluble vitamin and drug malabsorption are clearly important safety concerns with this drug, particularly in a nonprescription setting. The prolonged use of orlistat without appropriate vitamin supplementation may lead to clinically relevant fat-soluble nutrient malabsorption. Vitamin D may especially be a concern because deficiency of this nutrient is common in the United States, particularly among females, the elderly, and minorities,[9] and is associated with the risk for osteoporosis and other chronic diseases.[10] Furthermore, vitamin K malabsorption may put individuals taking warfarin at risk for development of supratherapeutic prothrombin time and consequently, bleeding.

Decreased concentrations of cyclosporine with concomitant use of orlistat have been documented,[11] and may, in the worst case scenario, result in transplanted organ rejection. Although there were very few subjects on either warfarin or cyclosporine in the actual use study, the preliminary findings, in which 50% of individuals on these drugs made an inappropriate purchase decision, raise concern that the messages regarding these drug interactions may not be effectively communicated.

9.2 Recommendation on Regulatory Action

GlaxoSmithKline (or previously, Roche) has shown in randomized, placebo-controlled clinical trials that: 1) subjects with BMIs $\geq$ 28 kg/m^2 lose a clinically significantly[2] greater amount of weight loss on orlistat as compared to those on placebo when receiving lifestyle intervention under the supervision of a health care provider; 2) subjects with BMIs $\geq$ 25 kg/m^2 lose a statistically, but not necessarily a clinically, significantly greater amount of weight with orlistat than placebo when receiving lifestyle intervention under the supervision of a health care provider; 3) changes in co-morbidities are what one would expect with the observed changes in

body weight; and 4) under health care provider supervision, when orlistat is discontinued, weight is regained, irrespective of the concomitant lifestyle intervention received.

GlaxoSmithKline has *not* shown: 1) that consumers are able to lose more weight (either clinically or statistically) on orlistat *vs.* placebo under "actual use" conditions; 2) that consumers are able to maintain weight loss beyond the duration of orlistat use in the actual use setting; 3) that subjects with a BMI in the 25 - 28 kg/m^2 range lose a clinically significant amount of weight with orlistat than placebo; 4) that having access to a weight loss drug has any impact on motivation, dietary or exercise compliance, or long-term health or weight loss outcomes; 5) that individuals derive a health benefit from having orlistat, or any other weight loss drug, as a nonprescription agent; and 6) that any cosmetic benefit achieved with orlistat being available as a weight loss drug outweighs actual or theoretical risks of orlistat; in particular, interactions with fat-soluble nutrients and drugs.

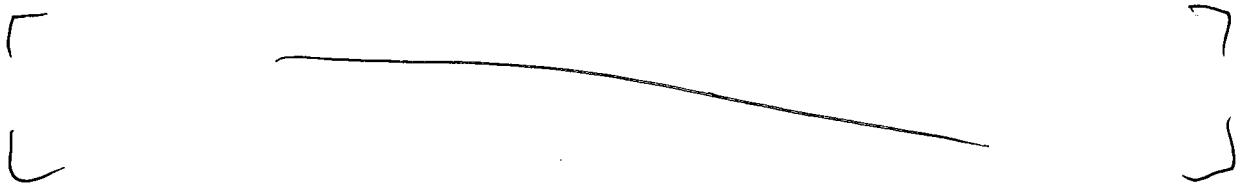
Although the answers to deficiencies 1, 2, and 3, above, could be achieved with further study, such as a well-designed, placebo-controlled, year-long actual use study, this reviewer does not believe that further study will satisfy the inherent deficiencies outlined in 4, 5, and 6. Therefore, this reviewer is recommending a Not Approvable action.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Risk management recommendations are being deferred at this time. However, in the event of nonprescription orlistat approval, the sponsor should be required to demonstrate that subjects on cyclosporine (or, more preferably, status post an organ transplant) have 100% compliance, or as close as possible, with the labeled cyclosporine/organ transplant warning.

9.3.2 Required Phase 4 Commitments



9.3.3 Other Phase 4 Requests

This reviewer has no recommendations for other phase 4 requests at this time.

9.4 Labeling Review

Please see the Appendix, Section 10.5 for a line-by-line labeling (Drug Facts) review. Comments on the accompanying written materials (dietary guides) are pending further internal discussion.

The following are key suggested changes to the Drug Facts label:

- Do not use if you are taking cyclosporine or have had an organ transplant must be bolded, highlighted, and in large font on all packaging.
- Orlistat has demonstrated clinical benefit in the prescription setting for individuals with a BMI ≥ 28 kg/m^2. Therefore, it is suggested that a BMI chart (designed for ease of use and re-tested) be included with the package to direct appropriate use towards this BMI group.
- Change "ask a doctor or pharmacist before use" to "ask a doctor before use" in cases of warfarin treatment. A pharmacist does not have access to important history surrounding warfarin use. For example, achieving the target prothrombin time (PT) is much more crucial for individuals with mechanical heart valves than those with atrial fibrillation. In addition, prolonged PT may be much more concerning in patients prone to falls or in whom a bleeding episode could be devastating, such as a patient who has had a recent stroke.
- [redacted]
- The label should be revised to reflect Roche's original intent with regard to co-morbidities. This reviewer does not think it is appropriate for patients with diabetes, especially those on medications for diabetes, to start a weight-loss program (and particularly a weight-loss program that includes a drug) without a physician's input. Other medical conditions best managed under a physician's care include individuals with hypertension and dyslipidemia.
- Given the importance of a lifestyle program with the use of orlistat, this reviewer recommends that there should be no distinction between the "starter pack" and "refill pack". The lifestyle program always *must* be provided with the drug.
- Although this reviewer thinks that a six-month limitation on a weight-loss drug is not reasonable, the sponsor has not submitted an NDA that supports nonprescription chronic use. Therefore, this reviewer is unable to comment on the time limitation suggested on the label.
- Change the following sentence from: "to ensure adequate vitamin absorption, you should take a multivitamin once a day, 2 hours before or after taking orlistat capsules", to "to ensure adequate vitamin absorption, take a multivitamin once a day, 2 hours before or after taking orlistat capsules".

9.5 Comments to Applicant

Detailed comments to the applicant will be deferred pending final action. In the event that orlistat is deemed approvable, this reviewer recommends that the sponsor conduct a year-long actual use (i.e., very minimal intervention, preferably with subject and study staff blinded to body weight measurement), placebo-controlled study. A label comprehension study will likely need to be done prior to this actual use study to ensure that the appropriateness of the label; however, specifics on this recommendation will be deferred to the Division of Nonprescription Evaluation. Internal discussion regarding a clinically meaningful primary outcome measure will need to occur before comments can be conveyed to the sponsor. Furthermore, the sponsor will need to demonstrate that subjects on cyclosporine (or, more preferably, status post an organ transplant) have 100% compliance, or as close as possible, with the labeled cyclosporine/organ transplant warning. If orlistat is to be used chronically, the submitted NDA should demonstrate its safety for chronic use.

10 APPENDICES

10.1 Narratives of Deaths

NM14302

Subject 13144/0083 (Diet Lead-in): A 40-year-old obese white female weighing 81.0 kg at screening (BMI = 34.6) died on day 107 of the weight loss lead-in period due to a closed head trauma resulting from being struck by an automobile. On day 105 of the weight loss lead-in period, the subject was struck by an automobile while crossing the road. She experienced blunt trauma to her head, neck, thorax, abdomen, and upper and lower extremities. She was hospitalized and experienced complications due to increased brain swelling which necessitated surgery. On day 106, a partial frontal lobectomy and placement of an intracranial pressure catheter was performed. The subject died the next day, on day 107, due to a cerebral hemorrhage.

BM14149

Subject 12823/M019 (60 mg TID): A 61-year-old obese white male weighing 96.8 kg (BMI = 32.7) at screening died after 449 days of treatment due to a myocardial infarction. The subject presented at screening with a significant past medical history of ischemic cerebral insult and a myocardial infarction (MI) seven years before the study. The subject was known to have a history of coronary heart disease for eight years. Ongoing coronary heart disease was treated with acetylsalicylic acid (250 mg/day), pravastatin (20 mg/day), and magnesium (121.6 mg/day). The subject was a non-smoker and had a waist circumference > 100 cm. The ECG done 28 days before randomization was abnormal, indicating left axis deviation, supraventricular premature contractions, ST segment elevation (leads Vl to V5), and evidence of an old MI; it was considered clinically significant by the investigator. Serum lipid values assessed at screening were normal. Fasting insulin was elevated at screening (39 mU/L; normal range 0-14) and remained abnormal during the study. Creatine phosphokinase (CPK) values were elevated at screening (387 U/L; normal range 0-250) and also at baseline (316 U/L) and remained abnormal throughout the study. The subject refused an ECG scheduled at the baseline visit. An ECG performed on day 367 showed no new changes from the screening ECG. The lipid profile was normal, except for an elevated lipoprotein [a] (1000 U/L; normal range 0-800). CPK was also elevated at 403 U/L. On study day 449 the subject experienced heartburn and took Kompensan® (1 tablet). He was subsequently found unconscious. Cardiac resuscitation was attempted but was not successful. The cause of death as stated by the investigator was sudden cardiac death from severe coronary artery disease complicated by angina. An autopsy was not performed and no additional information is available.

NM14161

Subject 12329/408 (120 mg TID): A 55-year-old obese white male weighing 122.8 kg (BMI=38.8) at screening, died of an acute myocardial infarction on study day 317. At screening, the subject indicated that he had never smoked and had no history of hypertension, hypercholesterolemia, or diabetes mellitus. Also, he had no other significant medical history and required no concomitant medications. There was no known family history of cardiac disease. His screening and baseline ECGs were within normal limits, as was his baseline chest x-ray. The subject's waist circumference at baseline was > 100 cm. Baseline lipid results were within normal limits. Fasting glucose measured before randomization was abnormal (310 mg/dL; normal range 60-125), with a 3+ glucose in urine (normal range 0-0). Both were abnormal sporadically during the study. An oral glucose tolerance test performed at baseline indicated impaired glucose tolerance. After 122 days of double-blind treatment, the subject was diagnosed with hypertension. On day 205 of treatment, antihypertensive therapy with lisinopril 10 mg/day was begun. On day 301, the subject developed an upper respiratory infection, which was treated with erythromycin 1 g/day until day 311. Late in the evening of day 316, the subject experienced chest pain for two hours and later vomited. He went to the emergency department early on day 317 and he suddenly died from an acute myocardial infarction. The subject's weight was last recorded at 128.2 kg. The subject had no other adverse events and did not take medications other than those described during the study.

BM14150

Subject BR13966/0373 (placebo lead-in period) died due to respiratory failure (asthma) on day 24 of the lead-in period. The subject, a 45 year-old obese white female, had a history of chronic obstructive pulmonary disease. There was no autopsy performed.

10.2 Narratives of Serious Adverse Events, Study NM17247

Patient 37460/2401 (orlistat 60 mg), a 47 year-old white female weighing 67.6 kg (BMI = 25.8 kg/m^2) at baseline, was hospitalized on study day 35 for repair of an umbilical hernia. The patient had secondary diagnoses of chronic sinusitis, fibromyalgia, migraines, headache, heartburn, dysmenorrhea/symptomatic fibroid uterus, Epstein-Barr virus, biliary dyskinesia, lower-back pain, hypertension, decreased defecation, osteoarthritis and mononucleosis. At the time of the event she weighed 68.5 kg (BMI = 26.14 kg/m^2) and was taking guafenesin, venlafaxine, dyazide, sumatriptan, rofecoxib, ibuprofen, Metamucil, Centrum multivitamins, and calcium carbonate. On study day 22 the patient was diagnosed with an umbilical hernia, repair of which was performed on study day 35. In addition to the hernia repair, the patient elected to undergo total abdominal hysterectomy with bilateral salpingo-oopherectomy for a pre-existing condition of symptomatic fibroid uterus that was not worsening. She received pitressin, bisacodyl, vasotec, morphine sulfate, propoxyphere with acetaminophen and ibuprofen. Study medication was interrupted from study day 34 to study day 36. The investigator considered this event to be moderate in intensity. The event resolved on study day 35 and patient was discharged on study day 37. The patient completed study drug administration and took the last dose of study medication on study day 111.

Patient 37466/2701 (orlistat 60 mg), a 41 year-old white female weighing 80.1 kg (BMI = 27.15 kg/m^2) at baseline, was hospitalized on study day 79 for lower back pain due to herniated disk reinjury. The patient had a history of herniated disk and secondary diagnosis of allergy to codeine and furodantin. At the time of the event she weighed 78 kg (BMI = 26.4 kg/m^2) and was taking co-enzyme Q10 and Centrum multivitamin as supplements. On study day 49 the patient reported the onset of lower-back pain, for which she started taking Vioxx on study day 51. She stopped taking Vioxx on study day 78 and commenced taking percocet. On study day 75 a MRI revealed large disc extrusion at L4-L5 compressing the right L5 nerve root and disc degeneration at L1-L2 and L3-L4. A lumbar disectomy and lumbar laminectomy were performed on study day 79. The event was considered moderate to severe in intensity and resolved on study day 81. Study medication was interrupted due to this event. The patient did not complete the study and the last dose of study medication was taken on study day 98.

10.3 Adverse Events

10.3.1 Serious Adverse Events; Pooled Safety Studies: First Year

Serious Adverse Events in Year 1 of Treatment
Safety Population

Studies: XN14148, XN14361, XN14302

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=155) n	(%)	NAE	Orlistat 60 mg tid (N=825) n	(%)	NAE	Orlistat 120 mg tid (N=832) n	(%)	NAE
SUBJECTS WITH AT LEAST 1 SERIOUS ADVERSE EVENT	37	(5.8)	38	12	(5.5)	12	37	(5.9)	42	34	(5.4)	38
REPRODUCTIVE DISORDERS, FEMALE	4	(0.6)	4	0		0	2	(0.3)	3	5	(0.8)	5
NEOPLASM BREAST FEMALE	0		0	0		0	1	(0.2)	1	3	(0.6)	3
TUMOR BREAST	0		0	0		0	0		0	1	(0.2)	1
UTEROVAGINAL PROLAPSE	0		0	0		0	0		0	1	(0.2)	1
VAGINAL PROLAPSE	0		0	0		0	0		0	1	(0.2)	1
CARCINOMA CERVIX	0		0	0		0	1	(0.2)	1	0		0
CERVICAL DYSPLASIA	0		0	0		0	1	(0.2)	1	0		0
MENORRHAGIA	2	(0.3)	2	0		0	0		0	0		0
ABORTION	1	(0.2)	1	0		0	0		0	0		0
ABORTION SPONTANEOUS	1	(0.2)	1	0		0	0		0	0		0
GASTRO-INTESTINAL SYSTEM DISORDERS	4	(0.6)	4	1	(0.6)	1	7	(1.1)	7	5	(0.8)	5
ABDOMINAL PAIN	0		0	0		0	1	(0.2)	1	1	(0.2)	1
HERNIA UMBILICAL	0		0	0		0	1	(0.2)	1	1	(0.2)	1
ABDOMINAL PAIN LOWER	0		0	0		0	0		0	1	(0.2)	1
APPENDICITIS	0		0	0		0	0		0	1	(0.2)	1
GI HEMORRHAGE	0		0	0		0	0		0	1	(0.2)	1
HERNIA INGUINAL	0		0	0		0	2	(0.3)	2	0		0
COLON CARCINOMA	0		0	0		0	1	(0.2)	1	0		0
DIVERTICULITIS	0		0	0		0	1	(0.2)	1	0		0
ESOPHAGUS OBSTRUCTION	0		0	0		0	1	(0.2)	1	0		0
HEMORRHAGE RECTUM	1	(0.2)	1	1	(0.6)	1	0		0	0		0
ABDOMINAL MASS	1	(0.2)	1	0		0	0		0	0		0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: M:\Gemini(ISS\Programming_xfinal\t_ae.sas Source: ae.xpt, profile.xpt

Serious Adverse Events in Year 1 of Treatment
Safety Population

Studies: XN14148, XN14161, XN14302

Body System/ Preferred Term	Placebo (N=654) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=823) n	(%)	NAE	Orlistat 120 mg tid (N=832) n	(%)	NAE
(...Body System Continues)												
HEMORRHOIDS	1	(0.2)	1	0		0	0		0	0		0
ILEITIS	1	(0.2)	1	0		0	0		0	0		0
BODY AS A WHOLE - GENERAL DISORDERS	10	(1.6)	10	5	(2.7)	5	5	(0.6)	5	4	(0.5)	4
SURGICAL PROCEDURE	7	(1.1)	7	5	(2.7)	5	5	(0.6)	5	4	(0.5)	4
TRAUMA	2	(0.3)	2	0		0	0		0	0		0
PAIN BODY	1	(0.2)	1	0		0	0		0	0		0
LIVER AND BILIARY SYSTEM DISORDERS	7	(1.1)	7	2	(1.1)	2	4	(0.5)	4	4	(0.5)	4
CHOLELITHIASIS	1	(0.2)	1	2	(1.1)	2	1	(0.1)	1	3	(0.4)	3
CHOLECYSTITIS	6	(0.9)	6	0		0	3	(0.4)	3	1	(0.1)	1
BILIARY COLIC	1	(0.2)	1	0		0	0		0	0		0
MUSCULO-SKELETAL SYSTEM DISORDERS	6	(0.9)	6	1	(0.5)	1	4	(0.5)	4	3	(0.4)	3
BONE FRACTURE	1	(0.2)	1	0		0	1	(0.1)	1	1	(0.1)	1
PAIN KNEE	0		0	1	(0.5)	1	0		0	1	(0.1)	1
SPRAINS AND STRAINS	0		0	0		0	0		0	1	(0.1)	1
INTERVERTEBRAL DISC DISORDER	1	(0.2)	1	0		0	1	(0.1)	1	0		0
JOINT DISLOCATION	0		0	0		0	1	(0.1)	1	0		0
PAIN NAPE	0		0	0		0	1	(0.1)	1	0		0
ARTHRITIS	1	(0.2)	1	0		0	0		0	0		0
HALLUX VALGUS	1	(0.2)	1	0		0	0		0	0		0
PAIN SHOULDER	1	(0.2)	1	0		0	0		0	0		0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\I99\Programming_xfinal\t_ae.sas Source: ae.xpt, profile.xpt

Serious Adverse Events in Year 1 of Treatment
Safety Population

Studies: XN14148, XN14161, XN14302

Body System/ Preferred Term	Placebo (N=654) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=823) n	(%)	NAE	Orlistat 120 mg tid (N=832) n	(%)	NAE
URINARY SYSTEM DISORDERS	1	(0.2)	1	0		0	2	(0.3)	2	3	(0.4)	4
URINARY INCONTINENCE	0		0	0		0	1	(0.1)	1	2	(0.2)	2
BLADDER PROLAPSE	0		0	0		0	0		0	1	(0.1)	1
URETERAL CALCULUS	0		0	0		0	0		0	1	(0.1)	1
URINARY TRACT INFECTION	0		0	0		0	1	(0.1)	1	0		0
RENAL CALCULUS	1	(0.2)	1	0		0	0		0	0		0
MYO-, ENDO-, PERICARDIAL & VALVE DISORD.	1	(0.2)	1	0		0	1	(0.1)	1	3	(0.4)	3
ANGINA PECTORIS	1	(0.2)	1	0		0	0		0	1	(0.1)	1
CORONARY INFARCTION	0		0	0		0	0		0	1	(0.1)	1
MALF. OF PROSTHESES AND HOMEOGRAPHS	0		0	0		0	0		0	1	(0.1)	1
PERIMYOCARDITIS	0		0	0		0	1	(0.1)	1	0		0
PSYCHIATRIC DISORDERS	1	(0.2)	1	0		0	0		0	3	(0.4)	3
DEPRESSION	1	(0.2)	1	0		0	0		0	2	(0.2)	2
SUICIDE ATTEMPT	0		0	0		0	0		0	1	(0.1)	1
CENTRAL & PERIPH. NERVOUS SYST. DISORD.	1	(0.2)	1	0		0	1	(0.1)	1	2	(0.2)	2
EPILEPSY	0		0	0		0	0		0	1	(0.1)	1
HEADACHE	0		0	0		0	0		0	1	(0.1)	1
NEURALGIA SCIATIC	0		0	0		0	1	(0.1)	1	0		0
CARPAL TUNNEL SYNDROME	1	(0.2)	1	0		0	0		0	0		0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\I99\Programming_xfinal\t_ae.sas Source: ae.xpt, profile.xpt

Serious Adverse Events in Year 1 of Treatment
Safety Population

Studies: EM14148, EM14181, EM14302

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=188) n	(%)	NAE	Orlistat 60 mg tid (N=623) n	(%)	NAE	Orlistat 120 mg tid (N=632) n	(%)	NAE
RESPIRATORY SYSTEM DISORDER	1	(0.2)	1	1	(0.5)	1	6	(1.0)	7	1	(0.2)	1
CHRONIC OBSTRUCTIVE LUNG DISEASE	0		0	0		0	0		0	1	(0.2)	1
ANGINA TONSILLARIS	0		0	0		0	1	(0.2)	1	0		0
APNEA	0		0	0		0	1	(0.2)	1	0		0
BRONCHOPNEUMONIA	0		0	0		0	1	(0.2)	1	0		0
COUGHING	0		0	0		0	1	(0.2)	1	0		0
DYSPNEA	0		0	0		0	1	(0.2)	1	0		0
RESPIRATORY INSUFFICIENCY	0		0	0		0	1	(0.2)	1	0		0
SINUSITIS	0		0	0		0	1	(0.2)	1	0		0
INFECTION LUNG	0		0	1	(0.5)	1	0		0	0		0
ASTHMA BRONCHIAL	1	(0.2)	1	0		0	0		0	0		0
HEART RATE AND RHYTHM	0		0	0		0	1	(0.2)	1	1	(0.2)	1
FIBRILLATION ATRIAL	0		0	0		0	0		0	1	(0.2)	1
PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA	0		0	0		0	1	(0.2)	1	0		0
VASCULAR (EXTRACARDIAC) DISORDERS	0		0	0		0	1	(0.2)	1	1	(0.2)	1
VARICOSE VEINS	0		0	0		0	1	(0.2)	1	1	(0.2)	1
ENDOCRINE DISORDERS	0		0	0		0	0		0	1	(0.2)	1
TUMOR THYROID	0		0	0		0	0		0	1	(0.2)	1
SKIN AND APPENDAGES DISORDERS	0		0	0		0	2	(0.3)	3	0		0
PRURITUS	0		0	0		0	1	(0.2)	1	0		0
TUMOR SKIN	0		0	0		0	1	(0.2)	1	0		0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_rfinal\t_ae.sas Source: ae.xpt, profile.xpt

Serious Adverse Events in Year 1 of Treatment
Safety Population

Studies: EM14148, EM14181, EM14302

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=188) n	(%)	NAE	Orlistat 60 mg tid (N=623) n	(%)	NAE	Orlistat 120 mg tid (N=632) n	(%)	NAE
(...Body System Continues)												
URTICARIA	0		0	0		0	1	(0.2)	1	0		0
AUTONOMIC NERVOUS SYSTEM DISORDER	0		0	1	(0.5)	1	1	(0.2)	1	0		0
SYNCOPE	0		0	1	(0.5)	1	1	(0.2)	1	0		0
CARDIOVASCULAR DISORDERS	0		0	0		0	1	(0.2)	1	0		0
CARDIAC FAILURE	0		0	0		0	1	(0.2)	1	0		0
HEARING AND VESTIBULAR DISORDERS	0		0	0		0	1	(0.2)	1	0		0
OTITIS MEDIA	0		0	0		0	1	(0.2)	1	0		0
NEOPLASM, URINARY SYSTEM	0		0	1	(0.5)	1	0		0	0		0
CARCINOMA RENAL	0		0	1	(0.5)	1	0		0	0		0
RESISTANCE MECHANISM DISORDERS	2	(0.3)	2	0		0	0		0	0		0
ABSCESS LEGAL	1	(0.2)	1	0		0	0		0	0		0
WOUND INFECTION	1	(0.2)	1	0		0	0		0	0		0
NEOPLASM, RESPIRATORY SYSTEM	1	(0.2)	1	0		0	0		0	0		0
NEOPLASM PHARYNX MALIGNANT	1	(0.2)	1	0		0	0		0	0		0

(Last Page)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first year of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_rfinal\t_ae.sas Source: ae.xpt, profile.xpt

10.3.2 Adverse Events Leading to Discontinuation; Pooled Studies: First Year

Adverse Events that Led to Discontinuation in Year 1 of Treatment
Safety Population

Studies: 8M14148, 8M14161, 8M14202

Body System/ Preferred Term	Placebo (N=634) n (%)	Orlistat 30 mg tid (N=155) n (%)	Orlistat 60 mg tid (N=622) n (%)	Orlistat 120 mg tid (N=632) n (%)
SUBJECTS WITH AT LEAST 1 ADVERSE EVENT THAT LED TO DISCONTINUATION	20 (3.2)	17 (9.7)	41 (6.6)	66 (5.7)
GASTRO-INTESTINAL SYSTEM DISORDERS	6 (0.9)	10 (6.4)	27 (4.3)	39 (6.2)
FECAL INCONTINENCE	0	1 (0.6)	8 (1.3)	10 (1.6)
OILY SPOTTING	0	0	1 (0.2)	7 (1.1)
LIQUID STOOLS	0	2 (1.3)	2 (0.3)	5 (0.8)
FLATUS WITH DISCHARGE	0	1 (0.6)	1 (0.2)	5 (0.8)
FECAL URGENCY	1 (0.2)	2 (1.3)	6 (1.0)	3 (0.5)
ABDOMINAL PAIN	0	1 (0.6)	4 (0.6)	2 (0.3)
FLATULENCE	2 (0.3)	1 (0.6)	1 (0.2)	1 (0.2)
INCREASED DEFECATION	0	0	1 (0.2)	1 (0.2)
FECES BLOODSTAINED	0	1 (0.6)	0	1 (0.2)
STOMACH ULCER	0	0	0	1 (0.2)
STOOLS SOFT	0	0	0	1 (0.2)
TENDERNESS HYPOCHONDRIUM	0	0	0	1 (0.2)
DECREASED DEFECATION	0	0	2 (0.3)	0
OILY EVACUATION	0	0	1 (0.2)	0
PELLETS	0	1 (0.6)	0	0
GASTROESOPHAGEAL REFLUX	1 (0.2)	0	0	0
ILEITIS	1 (0.2)	0	0	0
PYROSIS	1 (0.2)	0	0	0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event.
Treatment-emergent adverse events that occurred and led to discontinuation in first year of study medication use are tabulated.
Program: X:\Gemini\ISS\Programming_sfinal\t_ae_disc.sas Source: ae.xpt, profile.xpt

Adverse Events that Led to Discontinuation in Year 1 of Treatment
Safety Population

Studies: 8M14148, 8M14161, 8M14202

Body System/ Preferred Term	Placebo (N=634) n (%)	Orlistat 30 mg tid (N=155) n (%)	Orlistat 60 mg tid (N=622) n (%)	Orlistat 120 mg tid (N=632) n (%)
REPRODUCTIVE DISORDERS, FEMALE	0	0	2 (0.3)	3 (0.5)
NEOPLASM BREAST FEMALE	0	0	1 (0.2)	3 (0.5)
CARCINOMA CERVIX	0	0	1 (0.2)	0
CENTRAL & PERIPH. NERVOUS SYST. DISORD.	0	0	4 (0.6)	2 (0.3)
DIZZINESS	0	0	1 (0.2)	1 (0.2)
CONFUSION	0	0	0	1 (0.2)
VERTIGO	0	0	2 (0.3)	0
HEADACHE	0	0	1 (0.2)	0
LIVER AND BILIARY SYSTEM DISORDERS	0	1 (0.6)	2 (0.3)	2 (0.3)
CHOLECYSTITIS	0	0	2 (0.3)	1 (0.2)
CHOLELITHIASIS	0	0	0	1 (0.2)
HEPATITIS	0	1 (0.6)	0	0
SKIN AND APPENDAGES DISORDERS	4 (0.6)	1 (0.6)	1 (0.2)	2 (0.3)
ECZEMA	0	0	0	1 (0.2)
XERODERMA	0	0	0	1 (0.2)
RASH	0	1 (0.6)	1 (0.2)	0
URTICARIA	2 (0.3)	0	0	0
HAIR TEXTURE ABNORMAL	1 (0.2)	0	0	0
PRURITUS	1 (0.2)	0	0	0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event.
Treatment-emergent adverse events that occurred and led to discontinuation in first year of study medication use are tabulated.
Program: X:\Gemini\ISS\Programming_sfinal\t_ae_disc.sas Source: ae.xpt, profile.xpt

Adverse Events that Led to Discontinuation in Year 1 of Treatment
Safety Population

Studies: SM14149, NM14161, NM14302

Body System/ Preferred Term	Placebo (N=634) n (%)	Orlistat 30 mg tid (N=655) n (%)	Orlistat 60 mg tid (N=623) n (%)	Orlistat 120 mg tid (N=632) n (%)
MYO-, ENDO-, PERICARDIAL & VALVE DISORD.	0	1 (0.2)	0	2 (0.3)
ANGINA PECTORIS	0	0	0	1 (0.2)
MALF. OF PROSTHESES AND HOMOGRAFTS	0	0	0	1 (0.2)
CARDIOMYOPATHY HYPERTROPHIC OBSTR	0	1 (0.2)	0	0
PSYCHIATRIC DISORDERS	1 (0.2)	0	3 (0.5)	1 (0.2)
SUICIDE ATTEMPT	0	0	0	1 (0.2)
ANXIETY	0	0	2 (0.3)	0
DEPRESSION	1 (0.2)	0	1 (0.2)	0
RESPIRATORY SYSTEM DISORDER	0	2 (0.3)	1 (0.2)	1 (0.2)
CHRONIC OBSTRUCTIVE LUNG DISEASE	0	0	0	1 (0.2)
DYSPNEA	0	0	1 (0.2)	0
ASTHMATIC ATTACK	0	1 (0.2)	0	0
INFECTION LUNG	0	1 (0.2)	0	0
BODY AS A WHOLE - GENERAL DISORDERS	2 (0.3)	1 (0.2)	0	1 (0.2)
TRAUMA	1 (0.2)	0	0	1 (0.2)
FATIGUE	0	1 (0.2)	0	0
SURGICAL PROCEDURE	1 (0.2)	0	0	0
ENDOCRINE DISORDERS	1 (0.2)	0	0	1 (0.2)
THYROIDITIS	0	0	0	1 (0.2)
HYPERTHYROIDISM	1 (0.2)	0	0	0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event.
Treatment-emergent adverse events that occurred and led to discontinuation in first year of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_xfinal\t_ae_disc.sas Source: ae.xpt, profile.xpt

Adverse Events that Led to Discontinuation in Year 1 of Treatment
Safety Population

Studies: SM14149, NM14161, NM14302

Body System/ Preferred Term	Placebo (N=634) n (%)	Orlistat 30 mg tid (N=655) n (%)	Orlistat 60 mg tid (N=623) n (%)	Orlistat 120 mg tid (N=632) n (%)
URINARY SYSTEM DISORDERS	1 (0.2)	0	0	1 (0.2)
CYSTITIS HEMORRHAGIC	0	0	0	1 (0.2)
RENAL CALCULUS	1 (0.2)	0	0	0
RESISTANCE MECHANISM DISORDERS	0	0	1 (0.2)	0
INFECTION VIRAL	0	0	1 (0.2)	0
NEOPLASM, URINARY SYSTEM	0	1 (0.2)	0	0
CARCINOMA RENAL	0	1 (0.2)	0	0
MUSCULO-SKELETAL SYSTEM DISORDERS	3 (0.5)	0	0	0
ARTHRITIS	1 (0.2)	0	0	0
PAIN ANKLE	1 (0.2)	0	0	0
PAIN ARM	1 (0.2)	0	0	0
METABOLIC AND NUTRITIONAL DISORDERS	1 (0.2)	0	0	0
APPETITE INCREASED	1 (0.2)	0	0	0
NEOPLASM, RESPIRATORY SYSTEM	1 (0.2)	0	0	0
NEOPLASM PHARYNX MALIGNANT	1 (0.2)	0	0	0

(Last Page)

n (%) is the number (percentage) of subjects who experienced the event.
Treatment-emergent adverse events that occurred and led to discontinuation in first year of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_xfinal\t_ae_disc.sas Source: ae.xpt, profile.xpt

10.3.3 All Adverse Events; Pooled Safety Studies: First Six Months

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14349, NN14161, NN14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=525) n	(%)	NAE	Orlistat 120 mg tid (N=652) n	(%)	NAE
SUBJECTS WITH AT LEAST 1 ADVERSE EVENT	586	(84.5)	2488	179	(96.2)	1119	555	(89.3)	3189	583	(91.9)	8451
SUBJECTS WITH NO ADVERSE EVENTS	98	(15.5)		7	(3.8)		68	(10.9)		53	(8.1)	
GASTRO-INTESTINAL SYSTEM DISORDERS	326	(51.4)	814	148	(79.5)	574	429	(68.7)	1512	472	(74.7)	1713
FECAL URGENCY	50	(7.9)	61	55	(29.5)	70	117	(18.6)	166	148	(23.4)	193
OILY SPOTTING	7	(1.1)	8	31	(16.7)	61	110	(17.7)	145	137	(21.7)	207
FATTY/OILY STOOL	17	(2.7)	17	11	(5.9)	15	107	(17.2)	132	137	(21.7)	174
ABDOMINAL PAIN	89	(19.1)	125	47	(25.9)	62	125	(20.1)	160	132	(20.9)	168
FLATUS WITH DISCHARGE	12	(1.9)	14	40	(21.5)	58	109	(17.5)	145	126	(19.9)	166
FLATULENCE	114	(18.0)	135	78	(41.9)	95	116	(18.6)	147	114	(18.0)	132
LIQUID STOOLS	47	(7.4)	59	26	(14.0)	33	74	(11.9)	101	90	(14.2)	112
OILY EVACUATION	4	(0.6)	4	26	(18.4)	45	72	(11.6)	101	85	(13.4)	102
INCREASED DEFECATION	17	(2.7)	17	9	(4.8)	12	44	(7.1)	50	52	(8.2)	57
STOOLS SOFT	37	(5.8)	52	13	(7.0)	13	68	(10.8)	96	49	(7.8)	61
FECAL INCONTINENCE	5	(0.8)	10	6	(4.3)	10	29	(4.7)	82	49	(7.8)	61
NAUSEA	41	(6.5)	47	17	(9.1)	19	23	(4.7)	84	47	(7.4)	61
ENTERITIS	23	(3.6)	25	2	(1.1)	2	18	(2.9)	18	24	(3.8)	25
DECREASED DEFECATION	59	(9.4)	64	16	(8.5)	17	27	(4.8)	33	28	(3.5)	24
TOOTHACHE	12	(1.9)	12	6	(3.2)	6	14	(2.2)	16	15	(2.4)	17
HEMORRHOIDS	11	(1.7)	11	4	(2.2)	4	7	(1.1)	8	15	(2.4)	15
VOMITING	17	(2.7)	18	8	(4.3)	9	11	(1.8)	11	14	(2.2)	14
DYSPEPSIA	15	(2.4)	15	5	(2.7)	5	14	(2.2)	19	13	(2.1)	14
INFECTIOUS DIARRHEA	20	(3.2)	21	3	(1.6)	4	18	(2.9)	19	12	(1.9)	12
PERIODONTAL BREAKDOWN	4	(0.6)	4	2	(1.1)	2	5	(0.8)	5	9	(1.4)	10
ABDOMINAL DISCOMFORT	9	(1.8)	9	1	(0.5)	1	5	(0.8)	6	6	(1.3)	8

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_zfinal\t_ae.sas Source: ae.xpt, prefile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14349, NN14161, NN14802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=652) n	(%)	NAE
(...Body System Continues)												
PYROSIS	12	(1.9)	16	6	(3.2)	6	5	(0.8)	5	5	(0.8)	5
ABDOMINAL PAIN LOWER	1	(0.2)	1	0		0	0		0	5	(0.8)	5
FECES DISCOLORED	3	(0.5)	4	1	(0.5)	1	3	(0.6)	3	4	(0.6)	5
BORBORYGMUS	1	(0.2)	1	0		0	3	(0.6)	3	4	(0.6)	4
RECTAL PAIN	1	(0.2)	1	0		0	2	(0.4)	3	4	(0.6)	5
GASTRITIS	4	(0.6)	4	4	(2.2)	4	1	(0.2)	1	4	(0.6)	4
HEMORRHAGE RECTUM	1	(0.2)	1	0		0	1	(0.2)	1	4	(0.6)	4
FECES BLOODSTAINED	1	(0.2)	2	5	(2.7)	5	0		0	4	(0.6)	4
FLANK PAIN	1	(0.2)	1	1	(0.5)	1	0		0	4	(0.6)	4
FULLNESS ABDOMINAL	5	(0.8)	6	1	(0.5)	1	6	(1.0)	7	3	(0.5)	4
ERUCTATION	1	(0.2)	1	2	(1.1)	2	3	(0.6)	3	3	(0.5)	3
BUCCAL MUCOSA ULCERATION	0		0	1	(0.5)	1	0		0	3	(0.5)	3
ESOPHAGITIS	1	(0.2)	1	0		0	0		0	3	(0.5)	3
GINGIVITIS	1	(0.2)	1	0		0	0		0	3	(0.5)	3
IRRITATION ANAL	0		0	0		0	0		0	3	(0.5)	3
COLIC	0		0	0		0	2	(0.4)	2	2	(0.3)	2
PAIN PELVIC	1	(0.2)	1	0		0	0		0	2	(0.3)	2
STOMACH UPSET	2	(0.3)	2	2	(1.1)	2	4	(0.8)	4	1	(0.2)	1
ABDOMINAL DISTENTION	1	(0.2)	1	1	(0.5)	1	4	(0.8)	4	1	(0.2)	2
STOOLS HARD	3	(0.5)	7	0		0	3	(0.6)	3	1	(0.2)	1
MOUTH DRY	2	(0.3)	2	2	(1.1)	2	2	(0.4)	2	1	(0.2)	1
CANKER SORES ORAL	1	(0.2)	1	1	(0.5)	1	2	(0.4)	2	1	(0.2)	1
BURNING ANAL	2	(0.3)	2	2	(1.1)	2	1	(0.2)	1	1	(0.2)	1

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_zfinal\t_ae.sas Source: ae.xpt, prefile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: EM14349, EM14361, EM14302

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=523) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
TOOTH DISORDER	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	1	(0.2)	1
COLONIC POLYPOSIS	0		0	0		0	1	(0.2)	1	1	(0.2)	1
DIVERTICULUM CECUM	0		0	0		0	1	(0.2)	1	1	(0.2)	1
FECES UNPLEASANT SMELL	0		0	0		0	1	(0.2)	1	1	(0.2)	1
MELENA	0		0	0		0	1	(0.2)	1	1	(0.2)	1
PAIN ILIACFOSSA	0		0	0		0	1	(0.2)	2	1	(0.2)	1
TOOTH CARIES	0		0	0		0	1	(0.2)	1	1	(0.2)	2
REFLUX ESOPHAGITIS	2	(0.4)	2	1	(0.5)	1	0		0	1	(0.2)	1
PAIN INGUINAL	1	(0.2)	1	1	(0.5)	1	0		0	1	(0.2)	1
EPIGASTRIC PAIN NOT FOOD-RELATED	1	(0.2)	1	0		0	0		0	1	(0.2)	1
ANAL SPHINCTER DISORDER	0		0	0		0	0		0	1	(0.2)	1
APPENDICITIS	0		0	0		0	0		0	1	(0.2)	1
GI HEMORRHAGE	0		0	0		0	0		0	1	(0.2)	1
PAROTITIS	0		0	0		0	0		0	1	(0.2)	1
PROCTALGIA	0		0	0		0	0		0	1	(0.2)	1
STOMACH ULCER	0		0	0		0	0		0	1	(0.2)	1
STOOLS SOLID	0		0	0		0	0		0	1	(0.2)	1
PELLETS	8	(1.5)	8	1	(0.5)	2	4	(0.8)	4	0		0
FOOD POISONING	1	(0.2)	1	3	(1.6)	3	2	(0.4)	2	0		0
FECAL FISTULA	0		0	0		0	2	(0.4)	2	0		0
HERNIA INGUINAL	0		0	0		0	2	(0.4)	2	0		0
GASTROESOPHAGEAL REFLUX	2	(0.4)	2	0		0	1	(0.2)	1	0		0
REFLUX DUODENO-GASTRIC	2	(0.4)	2	0		0	1	(0.2)	1	0		0

(Continued)

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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: EM14349, EM14361, EM14302

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=523) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
GASTROINTESTINAL DISORDER NOS	1	(0.2)	1	0		0	1	(0.2)	1	0		0
BLISTERS MOUTH	0		0	0		0	1	(0.2)	1	0		0
COLITIS	0		0	0		0	1	(0.2)	2	0		0
COLON CARCINOMA	0		0	0		0	1	(0.2)	1	0		0
DIVERTICULITIS	0		0	0		0	1	(0.2)	1	0		0
HERNIA UMBILICAL	0		0	0		0	1	(0.2)	1	0		0
HICCUP	0		0	0		0	1	(0.2)	1	0		0
ULCER	0		0	0		0	1	(0.2)	1	0		0
PAINFUL DEFECATION	1	(0.2)	1	2	(1.1)	2	0		0	0		0
HERNIA HIATAL	2	(0.4)	2	1	(0.5)	1	0		0	0		0
ABDOMINAL MASS	1	(0.2)	1	0		0	0		0	0		0
ANGULUS INFECTIOSUS ORIS	1	(0.2)	1	0		0	0		0	0		0
BAD BREATH	1	(0.2)	1	0		0	0		0	0		0
BURNING TONGUE	1	(0.2)	1	0		0	0		0	0		0
COLON SPASTIC	1	(0.2)	2	0		0	0		0	0		0
ESOPHAGEAL COMPLAINTS	1	(0.2)	1	0		0	0		0	0		0
ILEITIS	1	(0.2)	1	0		0	0		0	0		0
SALIVARY GLAND ENLARGEMENT	1	(0.2)	1	0		0	0		0	0		0
RESPIRATORY SYSTEM DISORDER	203	(32.0)	302	72	(36.7)	105	203	(32.6)	312	220	(24.8)	338
SINUSITIS	54	(8.5)	61	29	(15.6)	34	66	(10.6)	86	63	(10.0)	72
UPPER RESP TRACT INFECTION	57	(9.0)	70	14	(7.5)	14	51	(8.2)	68	56	(8.9)	65
PHARYNGITIS	32	(5.0)	36	12	(6.5)	12	23	(3.7)	24	44	(7.0)	49

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\IBS\Programming_tfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14149, BM14161, BM14202

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 30 mg tid (N=166) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
BRONCHITIS	25	(4.1)	27	8	(4.8)	10	24	(3.5)	26	37	(5.9)	41
RHINITIS ALLERGIC ATOPIC	25	(3.9)	28	12	(6.5)	14	27	(4.0)	30	29	(4.5)	30
COUGHING	19	(3.0)	20	6	(3.2)	6	15	(2.4)	16	13	(2.1)	15
RHINITIS	17	(2.7)	18	3	(1.6)	3	13	(2.0)	16	9	(1.4)	13
ANGINA TONSILLARIS	7	(1.1)	10	1	(0.5)	1	5	(0.8)	5	9	(1.4)	9
NASAL CONGESTION	9	(1.4)	9	2	(1.1)	2	11	(1.8)	12	6	(0.9)	6
LARYNGITIS	2	(0.2)	2	1	(0.5)	1	3	(0.5)	3	6	(0.9)	6
PNEUMONIA	3	(0.5)	3	1	(0.5)	1	8	(1.2)	8	5	(0.8)	5
ASTHMA BRONCHIAL	1	(0.2)	1	1	(0.5)	1	3	(0.5)	3	4	(0.6)	5
NOSEBLEED	3	(0.5)	5	1	(0.5)	1	1	(0.2)	1	4	(0.6)	5
ASTHMATIC ATTACK	1	(0.2)	2	1	(0.5)	3	2	(0.5)	3	1	(0.2)	1
TRACHEOBRONCHITIS	2	(0.3)	2	0		0	1	(0.2)	1	1	(0.2)	1
SINUSITIS MAXILLARY	1	(0.2)	1	0		0	0		0	1	(0.2)	1
BRONCHIAL SECRETION EXCESSIVE	0		0	0		0	0		0	1	(0.2)	1
BRONCHOPNEUMONIA	0		0	0		0	0		0	1	(0.2)	1
CHRONIC OBSTRUCTIVE LUNG DISEASE	0		0	0		0	0		0	1	(0.2)	1
HOARSENESS	0		0	0		0	0		0	1	(0.2)	1
NASAL MUCOSA SWOLLEN	0		0	0		0	0		0	1	(0.2)	3
VOCAL CORD THICKENING	0		0	0		0	0		0	1	(0.2)	1
DYSPNEA	4	(0.6)	4	0		0	2	(0.3)	2	0		0
ASTHMA-LIKE REACTION	0		0	0		0	1	(0.2)	1	0		0
LARYNGOPHARYNGITIS	0		0	0		0	1	(0.2)	2	0		0
PHLEGM	0		0	0		0	1	(0.2)	1	0		0

(Continued)

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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14149, BM14161, BM14202

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 30 mg tid (N=166) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
SARCOIDOSIS	0		0	0		0	1	(0.2)	1	0		0
SINUS CONGESTION	0		0	0		0	1	(0.2)	1	0		0
SNEEZING EXCESSIVE	0		0	0		0	1	(0.2)	1	0		0
SUBGLOTTIC EDEMA	0		0	1	(0.5)	2	0		0	0		0
IRRITATION PHARYNX	2	(0.3)	2	0		0	0		0	0		0
NASAL SEPTUM DEVIATION	1	(0.2)	1	0		0	0		0	0		0
RESISTANCE MECHANISM DISORDERS	204	(32.2)	286	56	(30.1)	68	191	(30.7)	265	210	(33.2)	286
INFLUENZA SYNDROME	185	(29.2)	251	52	(28.0)	62	168	(27.0)	226	188	(29.7)	255
INFLUENZA	11	(1.7)	13	2	(1.1)	2	11	(1.8)	12	7	(1.1)	9
INFECTION MYCOTIC	7	(1.1)	7	3	(1.6)	3	5	(1.0)	6	6	(0.9)	6
INFECTION VIRAL	1	(0.2)	1	0		0	2	(0.3)	2	6	(0.9)	5
HERPES SIMPLEX	4	(0.6)	5	1	(0.5)	1	5	(1.0)	6	4	(0.5)	5
HERPES ZOSTER	2	(0.3)	2	0		0	1	(0.2)	1	2	(0.3)	2
WHITLOW	1	(0.2)	1	0		0	0		0	2	(0.3)	2
MONILIASIS	0		0	0		0	2	(0.3)	3	1	(0.2)	1
ABSCESS LOCAL	0		0	0		0	1	(0.2)	1	1	(0.2)	1
INFECTION STAPHYLOCOCCAL	0		0	0		0	0		0	1	(0.2)	1
INFECTIOUS MONONUCLEOSIS	0		0	0		0	0		0	1	(0.2)	1
INFECTION	2	(0.3)	2	0		0	2	(0.3)	2	0		0
HERPES LABIALIS	2	(0.3)	2	0		0	1	(0.2)	1	0		0
SCABIES	0		0	0		0	1	(0.2)	1	0		0
ABSCESS	1	(0.2)	1	0		0	0		0	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BN14149, BN14161, BN14302

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=165) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
HERPES	1	(0.2)	1	0		0	0		0	0		0
INFECTION SALMONELLA	1	(0.2)	1	0		0	0		0	0		0
WOUND INFECTION	1	(0.2)	1	0		0	0		0	0		0
CENTRAL & PERIPH. NERVOUS SYST. DISORD.	150	(25.2)	279	56	(29.6)	101	170	(27.6)	330	185	(25.3)	331
HEADACHE	119	(19.8)	159	42	(22.6)	81	116	(18.6)	239	146	(28.1)	259
DIZZINESS	18	(2.1)	18	5	(2.7)	5	17	(2.7)	18	18	(2.8)	20
MIGRAINE	20	(3.2)	39	9	(4.8)	13	15	(2.4)	22	12	(1.9)	15
VERTIGO	9	(1.4)	11	0		0	12	(1.9)	16	6	(0.9)	7
PARESTHESIA	1	(0.2)	1	0		0	7	(1.1)	10	6	(0.9)	6
NEURALGIA SCIATIC	5	(0.8)	5	0		0	6	(1.0)	6	3	(0.5)	3
GANGLION	0		0	0		0	1	(0.2)	1	3	(0.5)	3
APPETITE LOST	1	(0.2)	1	0		0	2	(0.3)	2	2	(0.3)	2
CARPAL TUNNEL SYNDROME	1	(0.2)	1	0		0	3	(0.6)	3	1	(0.2)	1
PAIN PARAVERTEBRAL	0		0	0		0	1	(0.2)	1	1	(0.2)	1
TWITCHING	0		0	0		0	1	(0.2)	1	1	(0.2)	1
NEURALGIA	1	(0.2)	1	0		0	0		0	1	(0.2)	1
BURNING EXTREMITIES	0		0	0		0	0		0	1	(0.2)	1
CONFUSION	0		0	0		0	0		0	1	(0.2)	1
HEAD FULLNESS	0		0	0		0	0		0	1	(0.2)	1
HEADACHE FRONTAL	0		0	0		0	0		0	1	(0.2)	1
NEUROMA	0		0	0		0	0		0	1	(0.2)	1
PARESTHESIA FINGERS	0		0	0		0	0		0	1	(0.2)	1

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BN14149, BN14161, BN14302

Body System/ Preferred Term	Placebo (N=534) n	(%)	NAE	Orlistat 30 mg tid (N=165) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
PARESTHESIA FOOT	0		0	0		0	0		0	1	(0.2)	1
PERIPHERAL COLDNESS	0		0	0		0	0		0	1	(0.2)	1
PTOSIS	0		0	0		0	0		0	1	(0.2)	1
SPASMS	0		0	0		0	0		0	1	(0.2)	1
TRIGEMINAL NEURALGIA	0		0	0		0	0		0	1	(0.2)	1
RESTLESS LEGS	1	(0.2)	1	0		0	1	(0.2)	2	0		0
BURNING LEGS	0		0	0		0	1	(0.2)	1	0		0
CRANIAL INJURY NOS	0		0	0		0	1	(0.2)	1	0		0
NUMBNESS EXTREMITIES	0		0	0		0	1	(0.2)	1	0		0
NUMBNESS FINGERS	0		0	0		0	1	(0.2)	1	0		0
NUMBNESS HAND	0		0	0		0	1	(0.2)	1	0		0
PAIN FACIAL	0		0	0		0	1	(0.2)	1	0		0
PARESTHESIA DISTAL	0		0	0		0	1	(0.2)	1	0		0
PRE-SYNCOPE	0		0	0		0	1	(0.2)	1	0		0
RADICULITIS	0		0	0		0	1	(0.2)	1	0		0
TREMOR HAND	0		0	0		0	1	(0.2)	1	0		0
HYPERTONIA	1	(0.2)	1	1	(0.5)	1	0		0	0		0
HYPOESTHESIA	0		0	1	(0.5)	1	0		0	0		0
NEUROPATHY SENSORY	1	(0.2)	1	0		0	0		0	0		0
NUMBNESS TOES	1	(0.2)	1	0		0	0		0	0		0
PRICKLY SENSATION	1	(0.2)	1	0		0	0		0	0		0
TREMOR	1	(0.2)	1	0		0	0		0	0		0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_tfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14349, BM14361, BM14302

Body System/ Preferred Term	Placebo (N=594) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=622) n	(%)	NAE	Orlistat 120 mg tid (N=582) n	(%)	NAE
MUSCULO-SKELETAL SYSTEM DISORDERS	188	(29.7)	251	58	(31.2)	80	153	(24.6)	250	178	(27.4)	266
BACK PAIN	37	(5.8)	41	13	(7.0)	15	45	(7.2)	65	53	(8.1)	69
PAIN KNEE	12	(1.9)	12	8	(4.3)	9	12	(1.9)	15	16	(2.5)	16
MYALGIA	19	(3.0)	19	9	(4.9)	9	9	(1.4)	11	15	(2.4)	17
SPRAINS AND STRAINS	6	(0.9)	7	3	(1.6)	3	9	(1.4)	10	15	(2.4)	15
ARTHRALGIA	14	(2.2)	21	7	(3.8)	7	11	(1.8)	12	13	(2.1)	14
PAIN LIMBS	10	(1.6)	10	2	(1.1)	2	9	(1.4)	12	11	(1.7)	11
PAIN SHOULDER	8	(1.3)	8	3	(1.6)	3	12	(1.9)	13	10	(1.6)	11
PAIN NAPE	15	(2.4)	17	1	(0.5)	1	6	(1.0)	13	10	(1.6)	11
PAIN FEET	10	(1.6)	12	6	(3.2)	6	9	(1.4)	10	9	(1.4)	13
LUMBAGO	5	(0.8)	6	0		0	10	(1.6)	10	7	(1.1)	7
ARTHRITIS	7	(1.1)	9	1	(0.5)	1	7	(1.1)	7	7	(1.1)	7
TENDINITIS	9	(1.4)	9	1	(0.5)	1	4	(0.6)	4	7	(1.1)	10
PAIN LEG	12	(1.9)	15	1	(0.5)	2	7	(1.1)	8	6	(0.9)	9
CRAMPS LEG	5	(0.9)	6	1	(0.5)	1	5	(0.8)	5	6	(0.9)	6
PAIN ARM	10	(1.6)	11	0		0	4	(0.6)	4	6	(0.9)	6
PAIN HIP	8	(1.3)	8	2	(1.1)	2	3	(0.5)	5	5	(0.8)	5
ARTHROSIS	1	(0.2)	1	1	(0.5)	1	2	(0.3)	2	5	(0.8)	5
PAIN ANKLE	5	(0.8)	5	2	(1.1)	2	1	(0.2)	1	5	(0.9)	5
PAIN WRIST	2	(0.3)	2	1	(0.5)	1	4	(0.6)	4	4	(0.6)	4
STIFF NECK	2	(0.3)	2	2	(1.1)	2	2	(0.3)	2	4	(0.6)	4
SYMPTOMS REFERABLE TO LIMBS	0		0	0		0	0		0	3	(0.5)	3
BONE FRACTURE	7	(1.1)	7	3	(1.6)	3	6	(1.0)	6	2	(0.3)	2
BURSITIS	4	(0.6)	4	2	(1.1)	2	3	(0.5)	3	2	(0.3)	2
MUSCULO-SKELETAL BRUISING	2	(0.3)	2	0		0	3	(0.5)	3	2	(0.3)	2

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\I88\Programming_zfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14349, BM14361, BM14302

Body System/ Preferred Term	Placebo (N=594) n	(%)	NAE	Orlistat 30 mg tid (N=186) n	(%)	NAE	Orlistat 60 mg tid (N=623) n	(%)	NAE	Orlistat 120 mg tid (N=582) n	(%)	NAE
(...Body System Continues)												
PAIN HAND	2	(0.3)	2	0		0	2	(0.3)	2	2	(0.3)	3
JOINT DISLOCATION	0		0	0		0	1	(0.2)	1	2	(0.3)	2
CRAMPS MUSCLE	3	(0.5)	3	0		0	2	(0.3)	3	1	(0.2)	1
PAIN RIBS	3	(0.5)	3	1	(0.5)	1	1	(0.2)	1	1	(0.2)	1
INJURY LEG	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	1	(0.2)	1
CRAMPS EXTREMITIES	1	(0.2)	1	0		0	0		0	1	(0.2)	1
EDEMA HAND	0		0	0		0	0		0	1	(0.2)	1
STIFFNESS SHOULDER	0		0	0		0	0		0	1	(0.2)	1
TENDOVAGINITIS	0		0	0		0	0		0	1	(0.2)	1
WEAKNESS KNEE	0		0	0		0	0		0	1	(0.2)	1
BONE SPUR	3	(0.5)	3	0		0	3	(0.5)	3	0		0
TMJ DISORDER	2	(0.3)	2	0		0	2	(0.3)	2	0		0
FASCIITIS	0		0	0		0	2	(0.3)	2	0		0
INTERVERTEBRAL DISC DISORDER	3	(0.5)	4	1	(0.5)	1	1	(0.2)	1	0		0
PAIN JAW	0		0	1	(0.5)	1	1	(0.2)	1	0		0
INJURY UPPER LIMB	2	(0.3)	2	0		0	1	(0.2)	1	0		0
STIFFNESS EXTREMITIES	2	(0.3)	2	0		0	1	(0.2)	1	0		0
ARTHROPATHY	1	(0.2)	1	0		0	1	(0.2)	1	0		0
LEG DISCOMFORT	0		0	0		0	1	(0.2)	1	0		0
OSTEOCHONDROPATHY	0		0	0		0	1	(0.2)	1	0		0
POLYMYALGIA RHEUMATICA	0		0	0		0	1	(0.2)	1	0		0
ROTATOR CUFF SYNDROME OF SHOULDER	0		0	0		0	1	(0.2)	1	0		0
STIFFNESS	0		0	0		0	1	(0.2)	1	0		0

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BNI4349, BNI4161, BNI4802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=652) n	(%)	NAE
(...Body System Continues)												
FRACTURE PATHOLOGICAL	0		0	1	(0.5)	1	0		0	0		0
JOINT STIFFNESS	0		0	1	(0.5)	1	0		0	0		0
TEAR OF MENISCUS	0		0	1	(0.5)	1	0		0	0		0
BURSITIS OLECRANON	1	(0.2)	1	0		0	0		0	0		0
CHONDROMALACIA	1	(0.2)	1	0		0	0		0	0		0
HALLUX VALGUS	1	(0.2)	1	0		0	0		0	0		0
MUSCLE DISORDER	1	(0.2)	1	0		0	0		0	0		0
MYOSITIS	1	(0.2)	2	0		0	0		0	0		0
PAIN POLYARTICULAR	1	(0.2)	1	0		0	0		0	0		0
PAIN STERNUM	1	(0.2)	1	0		0	0		0	0		0
TENDON DISORDER	1	(0.2)	1	0		0	0		0	0		0
BODY AS A WHOLE - GENERAL DISORDERS	93	(14.7)	116	32	(17.2)	45	109	(16.5)	129	98	(14.7)	117
SURGICAL PROCEDURE	17	(2.7)	19	9	(4.8)	11	19	(3.0)	23	17	(2.7)	19
ASTHENIA	16	(2.5)	18	1	(0.5)	1	19	(3.0)	20	16	(2.5)	19
FATIGUE	4	(0.6)	4	12	(6.5)	13	11	(1.8)	13	16	(2.5)	15
INSOMNIA	17	(2.7)	21	2	(1.1)	2	18	(2.8)	17	14	(2.2)	14
FEVER	5	(0.8)	5	2	(1.1)	2	9	(1.4)	9	9	(1.4)	9
EDEMA	11	(1.7)	11	3	(1.6)	3	11	(1.8)	13	8	(1.3)	9
PAIN POST TRAUMATIC	9	(1.4)	11	2	(1.1)	2	8	(1.8)	8	7	(1.1)	7
NERVOUSNESS	1	(0.2)	2	3	(1.6)	4	5	(0.8)	6	5	(0.8)	5
ALLERGIC REACTION	5	(0.8)	5	1	(0.5)	1	5	(0.8)	5	4	(0.6)	4
TRAUMA	9	(1.4)	9	1	(0.5)	1	7	(1.1)	7	3	(0.5)	3

(Continued)

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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BNI4349, BNI4161, BNI4802

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 30 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=652) n	(%)	NAE
(...Body System Continues)												
PAIN BODY	3	(0.5)	3	1	(0.5)	1	2	(0.4)	2	2	(0.3)	2
MALAISE	2	(0.3)	2	0		0	3	(0.6)	3	1	(0.2)	1
LETHARGY	0		0	0		0	2	(0.4)	2	1	(0.2)	1
ANIMAL BITE	0		0	1	(0.5)	1	1	(0.2)	1	1	(0.2)	1
IRRITABILITY	1	(0.2)	1	0		0	1	(0.2)	1	1	(0.2)	1
PAIN	0		0	0		0	1	(0.2)	1	1	(0.2)	1
WEAKNESS GENERALIZED	0		0	1	(0.5)	1	0		0	1	(0.2)	2
SHIVERING	2	(0.3)	2	0		0	0		0	1	(0.2)	1
POSTMENOPAUSAL SYNDROME	0		0	0		0	0		0	1	(0.2)	1
WOUND	0		0	0		0	0		0	1	(0.2)	1
ABRASIONS	0		0	0		0	2	(0.4)	2	0		0
SLEEP DISORDER	0		0	0		0	2	(0.4)	2	0		0
AGITATION	0		0	1	(0.5)	2	1	(0.2)	1	0		0
CHEST PRESSURE SENSATION	1	(0.2)	1	0		0	0		0	0		0
EARLY MORNING WAKENING	1	(0.2)	1	0		0	0		0	0		0
STAB WOUND	1	(0.2)	1	0		0	0		0	0		0
REPRODUCTIVE DISORDERS, FEMALE	62	(9.8)	84	19	(10.2)	29	48	(7.7)	66	78	(12.3)	107
DYSMENORRHEA	22	(3.5)	31	10	(5.4)	14	23	(3.7)	33	25	(4.0)	35
COLPITIS	12	(1.9)	13	3	(1.6)	4	7	(1.1)	9	14	(2.2)	17
MENOPAUSAL SYNDROME	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	5	(0.8)	5
MENSTRUAL IRREGULARITY	3	(0.5)	3	0		0	4	(0.8)	4	4	(0.6)	5
MENSTRUAL DISORDER	0		0	0		0	2	(0.4)	2	4	(0.6)	4

(Continued)

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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: 8M14149, 8M14161, 8M14802

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 30 mg tid (N=685) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
BREAST PAIN FEMALE	3	(0.5)	5	2	(0.1)	2	1	(0.2)	1	4	(0.6)	4
MENORRHAGIA	7	(1.1)	9	0		0	1	(0.2)	1	4	(0.6)	4
VAGINAL ITCHING	3	(0.5)	3	0		0	1	(0.2)	1	4	(0.6)	4
VAGINAL DISCHARGE	0		0	0		0	0		0	4	(0.6)	4
VAGINAL HEMORRHAGE	1	(0.2)	1	0		0	1	(0.2)	1	3	(0.5)	3
INTERMENSTRUAL BLEEDING	0		0	0		0	2	(0.3)	2	2	(0.3)	2
AMENORRHEA	0		0	3	(1.5)	3	1	(0.2)	1	2	(0.3)	2
VULVOVAGINITIS	2	(0.3)	2	0		0	1	(0.2)	1	2	(0.3)	2
NEOPLASM BREAST FEMALE	0		0	0		0	1	(0.2)	1	2	(0.3)	2
VAGINAL DISORDER	0		0	1	(0.5)	1	0		0	2	(0.3)	2
PERIMENOPAUSAL SYNDROME	3	(0.5)	3	2	(0.1)	2	0		0	1	(0.2)	1
VAGINAL WALL PROLAPSE	0		0	1	(0.5)	1	0		0	1	(0.2)	1
UTERINE HEMORRHAGE	2	(0.3)	2	0		0	0		0	1	(0.2)	1
CERVICITIS	0		0	0		0	0		0	1	(0.2)	1
MASTOPATHY	0		0	0		0	0		0	1	(0.2)	1
OVARIAN DISORDER	0		0	0		0	0		0	1	(0.2)	1
SPOTTING BETWEEN MENSES	0		0	0		0	0		0	1	(0.2)	1
SPOTTING VAGINAL	0		0	0		0	0		0	1	(0.2)	1
TUMOR BREAST	0		0	0		0	0		0	1	(0.2)	1
UTEROVAGINAL PROLAPSE	0		0	0		0	0		0	1	(0.2)	1
VAGINAL PROLAPSE	0		0	0		0	0		0	1	(0.2)	1
ABORTION	1	(0.2)	1	0		0	1	(0.2)	1	0		0
FIBROADENOSIS BREAST	1	(0.2)	1	0		0	1	(0.2)	1	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: 8M14149, 8M14161, 8M14802

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 30 mg tid (N=685) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
CARCINOMA CERVIX	0		0	0		0	1	(0.2)	1	0		0
CERVICAL DYSPLASIA	0		0	0		0	1	(0.2)	1	0		0
OLIGOMENORRHEA	0		0	0		0	1	(0.2)	1	0		0
TUMOR UTERUS	0		0	0		0	1	(0.2)	1	0		0
UTERINE INFLAMMATION	0		0	0		0	1	(0.2)	1	0		0
VAGINAL DRYNESS	1	(0.2)	1	1	(0.5)	1	0		0	0		0
CYST OVARIAN BENIGN	2	(0.3)	2	0		0	0		0	0		0
ABORTION SPONTANEOUS	1	(0.2)	1	0		0	0		0	0		0
BREAST TENSION	1	(0.2)	1	0		0	0		0	0		0
CYST BREAST	1	(0.2)	1	0		0	0		0	0		0
GENITALIA SORE	1	(0.2)	1	0		0	0		0	0		0
MASTITIS	1	(0.2)	1	0		0	0		0	0		0
MENSES ONSET DELAYED	1	(0.2)	1	0		0	0		0	0		0
SKIN AND APPENDAGES DISORDERS	94	(14.6)	122	29	(15.5)	34	70	(11.2)	90	74	(11.7)	86
XERODERMA	4	(0.6)	4	8	(1.5)	8	3	(0.5)	5	13	(1.7)	12
RASH	19	(3.0)	22	9	(4.8)	10	9	(1.4)	12	9	(1.4)	9
ECZEMA	5	(0.8)	7	0		0	5	(0.8)	5	6	(0.9)	6
ACNE NOS	12	(1.9)	13	6	(3.2)	5	6	(1.0)	7	6	(0.9)	5
INSECT BITES	3	(0.5)	3	0		0	4	(0.6)	4	4	(0.6)	4
PRURITUS	1	(0.2)	2	1	(0.5)	1	3	(0.5)	4	4	(0.6)	4
URTICARIA	7	(1.1)	7	0		0	3	(0.5)	3	4	(0.6)	4
ERYTHEMA	0		0	1	(0.5)	1	0		0	4	(0.6)	5

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14349, BM14361, BM14302

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 60 mg tid (N=165) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
ALOPECIA	9	(1.3)	8	2	(1.2)	3	4	(0.6)	4	3	(0.5)	3
HAIR TEXTURE ABNORMAL	2	(0.3)	2	0		0	3	(0.5)	3	3	(0.5)	3
ONYCHOMYCOSIS	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	3	(0.5)	3
CELLULITIS	1	(0.2)	2	0		0	1	(0.2)	1	3	(0.5)	3
INFECTION SKIN	1	(0.2)	1	1	(0.5)	1	0		0	2	(0.3)	2
CYST SEBACEOUS	3	(0.6)	4	0		0	0		0	2	(0.3)	2
DERMATITIS	5	(0.9)	6	1	(0.5)	1	3	(0.5)	3	1	(0.2)	1
NAIL DISORDER	0		0	1	(0.5)	1	3	(0.5)	3	1	(0.2)	1
NAILS BRITTLE	2	(0.3)	2	0		0	3	(0.5)	3	1	(0.2)	1
EDEMA LEGS	1	(0.2)	1	0		0	3	(0.5)	3	1	(0.2)	1
ANKLE EDEMA	4	(0.6)	5	0		0	2	(0.3)	3	1	(0.2)	1
DERMATITIS CONTACT	3	(0.5)	3	0		0	2	(0.3)	2	1	(0.2)	1
PRURITUS ANI	1	(0.2)	1	0		0	2	(0.3)	2	1	(0.2)	1
PSORIASIS	2	(0.3)	2	0		0	1	(0.2)	1	1	(0.2)	1
PUSTULAR REACTION	2	(0.3)	2	0		0	1	(0.2)	1	1	(0.2)	1
TUMOR-LIKE SKIN CONDITION NOS	2	(0.3)	2	0		0	1	(0.2)	1	1	(0.2)	1
DERMATITIS FUNGAL	1	(0.2)	1	0		0	1	(0.2)	1	1	(0.2)	1
HAIR CHANGES	0		0	0		0	1	(0.2)	1	1	(0.2)	1
SKIN DISORDER	1	(0.2)	1	1	(0.5)	1	0		0	1	(0.2)	1
BURNING FEET	0		0	0		0	0		0	1	(0.2)	1
ECZEMA PRURITIC	0		0	0		0	0		0	1	(0.2)	1
EDEMA JOINT	0		0	0		0	0		0	1	(0.2)	1
EXANTHEMA PURPURIC	0		0	0		0	0		0	1	(0.2)	1

(Continued)

n (%) is the number (percentage) of subjects who experienced the event; NAE is the number of occurrences of the event.
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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14349, BM14361, BM14302

Body System/ Preferred Term	Placebo (N=634) n	(%)	NAE	Orlistat 60 mg tid (N=166) n	(%)	NAE	Orlistat 60 mg tid (N=628) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
FURUNCULOSIS	0		0	0		0	0		0	1	(0.2)	1
MYCOSIS MUCOSAL	0		0	0		0	0		0	1	(0.2)	1
NIPPLES TENDER	0		0	0		0	0		0	1	(0.2)	1
PHOTOSENSITIVITY REACTION	0		0	0		0	0		0	1	(0.2)	1
SKIN BURNS	0		0	0		0	3	(0.5)	4	0		0
DERMATITIS SEBORRHEIC	1	(0.2)	1	0		0	2	(0.3)	2	0		0
LIP DRYNESS	1	(0.2)	1	1	(0.5)	1	1	(0.2)	1	0		0
ALLERGY CONTACT	2	(0.3)	2	0		0	1	(0.2)	1	0		0
BULLOUS REACTION	1	(0.2)	1	0		0	1	(0.2)	1	0		0
ACNE PUSTULAR	0		0	0		0	1	(0.2)	1	0		0
FACE EDEMA	0		0	0		0	1	(0.2)	1	0		0
FOLLICULITIS	0		0	0		0	1	(0.2)	1	0		0
HYPERKERATOSIS	0		0	0		0	1	(0.2)	1	0		0
NEVUS	0		0	0		0	1	(0.2)	1	0		0
RASH IMPETIGINOUS	0		0	0		0	1	(0.2)	1	0		0
SEBORRHEA	0		0	0		0	1	(0.2)	1	0		0
SKIN EXCORIATION	0		0	0		0	1	(0.2)	1	0		0
SKIN NODULE	0		0	0		0	1	(0.2)	1	0		0
TINEA CORPORIS	0		0	0		0	1	(0.2)	1	0		0
SWELLING KNEE	0		0	2	(1.2)	2	0		0	0		0
NEVI PIGMENTED	0		0	1	(0.5)	1	0		0	0		0
TUMOR SKIN	0		0	1	(0.5)	1	0		0	0		0
VERRUCA	3	(0.5)	3	0		0	0		0	0		0

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\I88\Programming_tfinal\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14449, BM14461, BM14802

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 30 mg tid (N=166) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
EDEMA PERIORBITAL	2	(0.3)	2	0		0	0		0	0		0
HYPERTRICHOSIS	1	(0.2)	1	0		0	0		0	0		0
INTERTRIGO	1	(0.2)	1	0		0	0		0	0		0
LIPOMA	1	(0.2)	1	0		0	0		0	0		0
NAILGROWTH INHIBITION	1	(0.2)	1	0		0	0		0	0		0
NAILS THICKENING	1	(0.2)	1	0		0	0		0	0		0
PAPULAR RASH	1	(0.2)	1	0		0	0		0	0		0
PITYRIASIS	1	(0.2)	1	0		0	0		0	0		0
PSORIASIFORM LESIONS	1	(0.2)	1	0		0	0		0	0		0
RASH PRURITIC	1	(0.2)	1	0		0	0		0	0		0
RHAGADES	1	(0.2)	1	0		0	0		0	0		0
SKIN WRINKLED	1	(0.2)	1	0		0	0		0	0		0
URINARY SYSTEM DISORDERS	47	(7.4)	62	19	(10.2)	22	41	(5.6)	46	50	(7.9)	62
URINARY TRACT INFECTION	33	(5.2)	48	11	(5.9)	13	27	(4.8)	32	32	(5.1)	37
CYSTITIS	4	(0.6)	4	0		0	2	(0.3)	2	4	(0.6)	4
URINARY INCONTINENCE	2	(0.3)	2	1	(0.5)	1	4	(0.6)	4	3	(0.5)	4
DYSURIA	1	(0.2)	1	1	(0.5)	1	0		0	3	(0.5)	3
MICTURITION FREQUENCY	4	(0.6)	4	2	(1.1)	2	4	(0.8)	4	2	(0.3)	2
POLYURIA	3	(0.6)	3	2	(1.1)	2	2	(0.3)	2	2	(0.3)	2
URINARY TRACT BLEEDING	0		0	0		0	2	(0.3)	2	1	(0.2)	1
RENAL CALCULUS	0		0	1	(0.5)	1	0		0	1	(0.2)	1
PYELONEPHRITIS	1	(0.2)	2	0		0	0		0	1	(0.2)	1

(Continued)

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Treatment-emergent adverse events that occurred in first 6 months of study medication use are tabulated.
Program: K:\Gemini\ISS\Programming_final\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: BM14449, BM14461, BM14802

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 30 mg tid (N=166) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
BLADDER PROLAPSE	0		0	0		0	0		0	1	(0.2)	1
CYSTITIS HEMORRHAGIC	0		0	0		0	0		0	1	(0.2)	1
MOONFACE (CUSHING)	0		0	0		0	0		0	1	(0.2)	1
PYELITIS	0		0	0		0	0		0	1	(0.2)	1
URETERAL CALCULUS	0		0	0		0	0		0	1	(0.2)	1
URINARY RETENTION	0		0	0		0	0		0	1	(0.2)	1
URINE DISCOLORATION	0		0	0		0	0		0	1	(0.2)	1
URETHRITIS	0		0	1	(0.5)	1	1	(0.2)	1	0		0
OLIGURIA	0		0	0		0	1	(0.2)	1	0		0
URINE UNPLEASANT SMELL	0		0	1	(0.5)	1	0		0	0		0
BACTERIURIA	1	(0.2)	1	0		0	0		0	0		0
EDEMA ORBITAL	1	(0.2)	1	0		0	0		0	0		0
RENAL COLIC	1	(0.2)	1	0		0	0		0	0		0
PSYCHIATRIC DISORDERS	30	(4.7)	35	7	(5.8)	8	32	(5.1)	37	38	(6.0)	42
ANXIETY	7	(1.8)	9	1	(0.5)	1	16	(2.6)	17	19	(3.0)	21
DEPRESSION	28	(3.6)	35	4	(3.2)	5	14	(2.2)	17	17	(2.7)	17
SUICIDE ATTEMPT	0		0	1	(0.5)	1	0		0	1	(0.2)	1
PSYCHIC DISORDER	1	(0.2)	1	0		0	0		0	1	(0.2)	1
ANXIETY STATE	0		0	0		0	0		0	1	(0.2)	1
CRAVING FOR MILK	0		0	0		0	0		0	1	(0.2)	1
HUNGER ABNORMAL	0		0	1	(0.5)	1	1	(0.2)	1	0		0
EMOTIONAL LABILITY	1	(0.2)	1	0		0	1	(0.2)	1	0		0

(Continued)

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Program: K:\Gemini\ISS\Programming_final\t_ae.sas Source: ae.xpt, profile.xpt

Adverse Events in First 6 Months of Treatment
Safety Population

Studies: EM14149, EM14161, EM14802

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 60 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
FORGETFULNESS	0		0	0		0	1	(0.2)	1	0		0
ANXIETY ATTACK	1	(0.2)	1	0		0	0		0	0		0
ANXIETY NEUROSIS	1	(0.2)	1	0		0	0		0	0		0
CARDIOVASCULAR DISORDERS	18	(2.6)	22	4	(2.2)	5	17	(2.7)	16	20	(2.9)	22
CHEST PAIN	9	(1.4)	10	2	(1.1)	2	5	(0.8)	5	18	(2.1)	14
HYPERTENSION	3	(0.5)	3	0		0	9	(1.5)	8	6	(0.5)	3
CHEST CONGESTION	2	(0.3)	2	0		0	0		0	2	(0.3)	3
EDEMA OF EXTREMITIES	3	(0.5)	3	1	(0.5)	1	1	(0.2)	1	1	(0.2)	1
CONGESTION	2	(0.3)	2	1	(0.5)	2	0		0	1	(0.2)	1
CARDIAC FAILURE	0		0	0		0	1	(0.2)	1	0		0
ECG ABNORMAL	0		0	0		0	1	(0.2)	1	0		0
EDEMA FOOT	0		0	0		0	1	(0.2)	1	0		0
HEART MURMUR	0		0	0		0	1	(0.2)	1	0		0
CHEST DISCOMFORT	2	(0.3)	2	0		0	0		0	0		0
HEARING AND VESTIBULAR DISORDERS	21	(3.1)	25	12	(6.5)	19	16	(2.6)	17	19	(2.8)	24
EARACHE	8	(1.2)	10	3	(1.6)	3	3	(0.6)	3	6	(0.9)	7
OTITIS	7	(1.1)	7	6	(3.2)	5	7	(1.1)	7	4	(0.6)	5
OTITIS MEDIA	3	(0.5)	3	0		0	1	(0.2)	1	4	(0.6)	4
EAR BUZZING	1	(0.2)	1	1	(0.5)	1	3	(0.6)	3	2	(0.3)	3
OTITIS EXTERNA	2	(0.3)	2	0		0	1	(0.2)	1	2	(0.3)	2
HEARING DECREASED	0		0	0		0	0		0	2	(0.3)	2

(Continued)

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Adverse Events in First 6 Months of Treatment
Safety Population

Studies: EM14149, EM14161, EM14802

Body System/ Preferred Term	Placebo (N=684) n	(%)	NAE	Orlistat 60 mg tid (N=185) n	(%)	NAE	Orlistat 60 mg tid (N=528) n	(%)	NAE	Orlistat 120 mg tid (N=682) n	(%)	NAE
(...Body System Continues)												
ATAXIA VESTIBULAR	0		0	0		0	0		0	1	(0.2)	1
MOTION SICKNESS	0		0	2	(1.1)	3	1	(0.2)	1	0		0
FULLNESS EARS	2	(0.3)	2	0		0	1	(0.2)	1	0		0
AUTONOMIC NERVOUS SYSTEM DISORDER	5	(0.8)	6	6	(3.2)	6	9	(1.4)	9	16	(2.4)	16
SYNCOPE	1	(0.2)	1	0		0	1	(0.2)	1	5	(0.8)	5
HOT FLUSHES	3	(0.5)	3	4	(2.2)	4	3	(0.6)	3	4	(0.6)	4
SWEATING INCREASED	1	(0.2)	1	2	(1.1)	2	2	(0.3)	2	3	(0.5)	3
FLUSHING	0		0	0		0	1	(0.2)	1	2	(0.3)	2
MYDRIASIS	1	(0.2)	1	0		0	0		0	1	(0.2)	1
NIGHT SWEATS	0		0	0		0	0		0	1	(0.2)	1
ALGONEURODYSTROPHY	0		0	0		0	1	(0.2)	1	0		0
EJACULATION CHANGES	0		0	0		0	1	(0.2)	1	0		0
METABOLIC AND NUTRITIONAL DISORDERS	14	(2.0)	14	10	(5.4)	10	15	(2.4)	15	14	(2.0)	14
APPETITE INCREASED	8	(1.2)	8	3	(1.6)	3	5	(0.8)	5	5	(0.8)	5
THIRST	1	(0.2)	1	3	(1.6)	3	2	(0.3)	2	2	(0.3)	2
APPETITE DECREASED	2	(0.3)	2	2	(1.1)	2	2	(0.3)	2	2	(0.3)	2
DIABETES MELLITUS	1	(0.2)	1	0		0	0		0	1	(0.2)	1
GOUT	1	(0.2)	1	0		0	0		0	1	(0.2)	1
EDEMA PERIPHERAL	0		0	0		0	0		0	1	(0.2)	1
HYPERCHOLESTEROLEMIA	0		0	0		0	0		0	1	(0.2)	1
HYPOGLYCEMIA	0		0	0		0	0		0	1	(0.2)	1

(Continued)

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