



**XENICAL**

**(orlistat)**

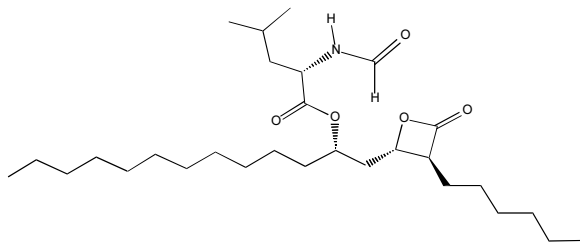
**CAPSULES**

**R<sub>x</sub> only**

## **DESCRIPTION**

XENICAL (orlistat) is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats.

Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. Its empirical formula is C<sub>29</sub>H<sub>53</sub>NO<sub>5</sub>, and its molecular weight is 495.7. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529 nm. The structure is:



Orlistat is a white to off-white crystalline powder. Orlistat is practically insoluble in water, freely soluble in chloroform, and very soluble in methanol and ethanol. Orlistat has no pK<sub>a</sub> within the physiological pH range.

XENICAL is available for oral administration in dark-blue, hard-gelatin capsules, with light-blue imprinting. Each capsule contains 120 mg of the active ingredient, orlistat. The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc. Each capsule shell contains gelatin, titanium dioxide, and FD&C Blue No. 1, with printing of pharmaceutical glaze NF, titanium dioxide, and FD&C Blue No. 1 aluminum lake.

## **CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

Orlistat is a reversible inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control. Systemic absorption of the drug is therefore not needed for activity. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by approximately 30%.

### 33 **Pharmacokinetics**

#### 34 **Absorption**

35 Systemic exposure to orlistat is minimal. Following oral dosing with 360 mg <sup>14</sup>C-orlistat,  
36 plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact  
37 orlistat were near the limits of detection (<5 ng/mL). In therapeutic studies involving  
38 monitoring of plasma samples, detection of intact orlistat in plasma was sporadic and  
39 concentrations were low (<10 ng/mL or 0.02 μM), without evidence of accumulation, and  
40 consistent with minimal absorption.

41 The average absolute bioavailability of intact orlistat was assessed in studies with male  
42 rats at oral doses of 150 and 1000 mg/kg/day and in male dogs at oral doses of 100 and  
43 1000 mg/kg/day and found to be 0.12%, 0.59% in rats and 0.7%, 1.9% in dogs,  
44 respectively.

#### 45 **Distribution**

46 In vitro orlistat was >99% bound to plasma proteins (lipoproteins and albumin were  
47 major binding proteins). Orlistat minimally partitioned into erythrocytes.

#### 48 **Metabolism**

49 Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the  
50 gastrointestinal wall. Based on an oral <sup>14</sup>C-orlistat mass balance study in obese patients,  
51 two metabolites, M1 (4-member lactone ring hydrolyzed) and M3 (M1 with N-formyl  
52 leucine moiety cleaved), accounted for approximately 42% of total radioactivity in  
53 plasma. M1 and M3 have an open β-lactone ring and extremely weak lipase inhibitory  
54 activity (1000- and 2500-fold less than orlistat, respectively). In view of this low  
55 inhibitory activity and the low plasma levels at the therapeutic dose (average of 26 ng/mL  
56 and 108 ng/mL for M1 and M3, respectively, 2 to 4 hours after a dose), these metabolites  
57 are considered pharmacologically inconsequential. The primary metabolite M1 had a  
58 short half-life (approximately 3 hours) whereas the secondary metabolite M3 disappeared  
59 at a slower rate (half-life approximately 13.5 hours). In obese patients, steady-state  
60 plasma levels of M1, but not M3, increased in proportion to orlistat doses.

#### 61 **Elimination**

62 Following a single oral dose of 360 mg <sup>14</sup>C-orlistat in both normal weight and obese  
63 subjects, fecal excretion of the unabsorbed drug was found to be the major route of  
64 elimination. Orlistat and its M1 and M3 metabolites were also subject to biliary excretion.  
65 Approximately 97% of the administered radioactivity was excreted in feces; 83% of that  
66 was found to be unchanged orlistat. The cumulative renal excretion of total radioactivity  
67 was <2% of the given dose of 360 mg <sup>14</sup>C-orlistat. The time to reach complete excretion  
68 (fecal plus urinary) was 3 to 5 days. The disposition of orlistat appeared to be similar  
69 between normal weight and obese subjects. Based on limited data, the half-life of the  
70 absorbed orlistat is in the range of 1 to 2 hours.

71 **Special Populations**

72 Because the drug is minimally absorbed, studies in special populations (geriatric,  
73 different races, patients with renal and hepatic insufficiency) were not conducted.

74 **Pediatrics**

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

78 **Drug-Drug Interactions**

79 Drug-drug interaction studies indicate that XENICAL had no effect on pharmacokinetics  
80 and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release  
81 tablets), oral contraceptives, phenytoin, pravastatin, or warfarin. Alcohol did not affect  
82 the pharmacodynamics of orlistat.

83 **Other Short-term Studies**

84 **Adults**

85 In several studies of up to 6-weeks duration, the effects of therapeutic doses of  
86 XENICAL on gastrointestinal and systemic physiological processes were assessed in  
87 normal weight and obese subjects. Postprandial cholecystokinin plasma concentrations  
88 were lowered after multiple doses of XENICAL in two studies but not significantly  
89 different from placebo in two other experiments. There were no clinically significant  
90 changes observed in gallbladder motility, bile composition or lithogenicity, or colonic  
91 cell proliferation rate, and no clinically significant reduction of gastric emptying time or  
92 gastric acidity. In addition, no effects on plasma triglyceride levels or systemic lipases  
93 were observed with the administration of XENICAL in these studies. In a 3-week study  
94 of 28 healthy male volunteers, XENICAL (120 mg three times a day) did not  
95 significantly affect the balance of calcium, magnesium, phosphorus, zinc, copper, and  
96 iron.

97 **Pediatrics**

98 In a 3-week study of 32 obese adolescents aged 12 to 16 years, XENICAL (120 mg three  
99 times a day) did not significantly affect the balance of calcium, magnesium, phosphorus,  
100 zinc, or copper. The iron balance was decreased by 64.7  $\mu\text{mole}/24$  hours and  
101 40.4  $\mu\text{mole}/24$  hours in orlistat and placebo treatment groups, respectively.

102 **Dose-response Relationship**

103 A simple maximum effect ( $E_{\text{max}}$ ) model was used to define the dose-response curve of the  
104 relationship between XENICAL daily dose and fecal fat excretion as representative of  
105 gastrointestinal lipase inhibition. The dose-response curve demonstrated a steep portion  
106 for doses up to approximately 400 mg daily, followed by a plateau for higher doses. At  
107 doses greater than 120 mg three times a day, the percentage increase in effect was  
108 minimal.

109 **CLINICAL STUDIES**

110 Observational epidemiologic studies have established a relationship between obesity and  
111 visceral fat and the risks for cardiovascular disease, type 2 diabetes, certain forms of  
112 cancer, gallstones, certain respiratory disorders, and an increase in overall mortality.  
113 These studies suggest that weight loss, if maintained, may produce health benefits for  
114 obese patients who have or are at risk of developing weight-related comorbidities. The  
115 long-term effects of orlistat on morbidity and mortality associated with obesity have not  
116 been established.

117 The effects of XENICAL on weight loss, weight maintenance, and weight regain and on  
118 a number of comorbidities (eg, type 2 diabetes, lipids, blood pressure) were assessed in  
119 the 4-year XENDOS study and in seven long-term (1- to 2-years duration) multicenter,  
120 double-blind, placebo-controlled clinical trials. During the first year of therapy, the  
121 studies of 2-year duration assessed weight loss and weight maintenance. During the  
122 second year of therapy, some studies assessed continued weight loss and weight  
123 maintenance and others assessed the effect of orlistat on weight regain. These studies  
124 included over 2800 patients treated with XENICAL and 1400 patients treated with  
125 placebo. The majority of these patients had obesity-related risk factors and comorbidities.  
126 In the XENDOS study, which included 3304 patients, the time to onset of type 2 diabetes  
127 was assessed in addition to weight management. In all these studies, treatment with  
128 XENICAL and placebo designates treatment with XENICAL plus diet and placebo plus  
129 diet, respectively.

130 During the weight loss and weight maintenance period, a well-balanced, reduced-calorie  
131 diet that was intended to result in an approximate 20% decrease in caloric intake and  
132 provide 30% of calories from fat was recommended to all patients. In addition, all  
133 patients were offered nutritional counseling.

134 **One-year Results: Weight Loss, Weight Maintenance, and Risk Factors**

135 Weight loss was observed within 2 weeks of initiation of therapy and continued for 6 to  
136 12 months.

137 Pooled data from five clinical trials indicated that the overall mean weight loss from  
138 randomization to the end of 6 months and 1 year of treatment in the intent-to-treat  
139 population were 12.4 lbs and 13.4 lbs in the patients treated with XENICAL and 6.2 lbs  
140 and 5.8 lbs in the placebo-treated patients, respectively. During the 4-week placebo lead-  
141 in period of the studies, an additional 5 to 6 lb weight loss was also observed in the same  
142 patients. Of the patients who completed 1 year of treatment, 57% of the patients treated  
143 with XENICAL (120 mg three times a day) and 31% of the placebo-treated patients lost  
144 at least 5% of their baseline body weight.

145 The percentages of patients achieving  $\geq 5\%$  and  $\geq 10\%$  weight loss after 1 year in five  
146 large multicenter studies for the intent-to-treat populations are presented in Table 1.

147 **Table 1 Percentage of Patients Losing  $\geq 5\%$  and  $\geq 10\%$  of Body**  
 148 **Weight From Randomization After 1-Year Treatment\***

Intent-to-Treat Population <sup>†</sup>									
Study No.	$\geq 5\%$ Weight Loss					$\geq 10\%$ Weight Loss			
	XENICAL n	Placebo n	p-value	XENICAL n	Placebo n	p-value	XENICAL n	Placebo n	p-value
14119B	35.5% 110	21.3% 108	0.021	16.4% 110	6.5% 108	0.022			
14119C	54.8% 343	27.4% 340	<0.001	24.8% 343	8.2% 340	<0.001			
14149	50.6% 241	26.3% 236	<0.001	22.8% 241	11.9% 236	0.02			
14161‡	37.1% 210	16.0% 212	<0.001	19.5% 210	3.8% 212	<0.001			
14185	42.6% 657	22.4% 223	<0.001	17.7% 657	9.9% 223	0.006			

149 The diet utilized during year 1 was a reduced-calorie diet.

150 \* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus  
 151 diet

152 † Last observation carried forward

153 ‡ All studies, with the exception of 14161, were conducted at centers specialized in  
 154 treating obesity and complications of obesity. Study 14161 was conducted with  
 155 primary care physicians.

156

157 The relative changes in risk factors associated with obesity following 1 year of therapy  
 158 with XENICAL and placebo are presented for the population as a whole and for the  
 159 population with abnormal values at randomization.

## 160 **Population as a Whole**

161 The changes in metabolic, cardiovascular and anthropometric risk factors associated with  
 162 obesity based on pooled data for five clinical studies, regardless of the patient's risk  
 163 factor status at randomization, are presented in Table 2. One year of therapy with  
 164 XENICAL resulted in relative improvement in several risk factors.

165  
166

**Table 2 Mean Change in Risk Factors From Randomization Following 1-Year Treatment\* Population as a Whole**

<b>Risk Factor</b>	<b>XENICAL 120 mg†</b>	<b>Placebo†</b>
<b>Metabolic:</b>		
Total Cholesterol	-2.0%	+5.0%
LDL-Cholesterol	-4.0%	+5.0%
HDL-Cholesterol	+9.3%	+12.8%
LDL/HDL	-0.37	-0.20
Triglycerides	+1.34%	+2.9%
Fasting Glucose, mmol/L	-0.04	+0.0
Fasting Insulin, pmol/L	-6.7	+5.2
<b>Cardiovascular:</b>		
Systolic Blood Pressure, mm Hg	-1.01	+0.58
Diastolic Blood Pressure, mm Hg	-1.19	+0.46
<b>Anthropometric:</b>		
Waist Circumference, cm	-6.45	-4.04
Hip Circumference, cm	-5.31	-2.96

167 \* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus  
168 diet  
169 † Intent-to-treat population at week 52, observed data based on pooled data from 5  
170 studies  
171

172 **Population With Abnormal Risk Factors at Randomization**

173 The changes from randomization following 1-year treatment in the population with  
174 abnormal lipid levels (LDL  $\geq$  130 mg/dL, LDL/HDL  $\geq$  3.5, HDL  $<$  35 mg/dL) were greater  
175 for XENICAL compared to placebo with respect to LDL-cholesterol (-7.83% vs +1.14%)  
176 and the LDL/HDL ratio (-0.64 vs -0.46). HDL increased in the placebo group by 20.1%  
177 and in the XENICAL group by 18.8%. In the population with abnormal blood pressure at  
178 baseline (systolic BP  $\geq$  140 mm Hg), the change in SBP from randomization to 1 year  
179 was greater for XENICAL (-10.89 mm Hg) than placebo (-5.07 mm Hg). For patients  
180 with a diastolic blood pressure  $\geq$  90 mm Hg, XENICAL patients decreased by -  
181 7.9 mm Hg while the placebo patients decreased by -5.5 mm Hg. Fasting insulin  
182 decreased more for XENICAL than placebo (-39 vs -16 pmol/L) from randomization to 1  
183 year in the population with abnormal baseline values ( $\geq$  120 pmol/L). A greater reduction  
184 in waist circumference for XENICAL vs placebo (-7.29 vs -4.53 cm) was observed in the  
185 population with abnormal baseline values ( $\geq$  100 cm).

186 **Effect on Weight Regain**

187 Three studies were designed to evaluate the effects of XENICAL compared to placebo in  
188 reducing weight regain after a previous weight loss achieved following either diet alone  
189 (one study, 14302) or prior treatment with XENICAL (two studies, 14119C and 14185).  
190 The diet utilized during the 1-year weight regain portion of the studies was a weight-

191 maintenance diet, rather than a weight-loss diet, and patients received less nutritional  
192 counseling than patients in weight-loss studies. For studies 14119C and 14185, patients'  
193 previous weight loss was due to 1 year of treatment with XENICAL in conjunction with a  
194 mildly hypocaloric diet. Study 14302 was conducted to evaluate the effects of 1 year of  
195 treatment with XENICAL on weight regain in patients who had lost 8% or more of their  
196 body weight in the previous 6 months on diet alone.

197 In study 14119C, patients treated with placebo regained 52% of the weight they had  
198 previously lost while the patients treated with XENICAL regained 26% of the weight  
199 they had previously lost ( $p < 0.001$ ). In study 14185, patients treated with placebo regained  
200 63% of the weight they had previously lost while the patients treated with XENICAL  
201 regained 35% of the weight they had lost ( $p < 0.001$ ). In study 14302, patients treated with  
202 placebo regained 53% of the weight they had previously lost while the patients treated  
203 with XENICAL regained 32% of the weight that they had lost ( $p < 0.001$ ).

#### 204 **Two-year Results: Long-term Weight Control and Risk Factors**

205 The treatment effects of XENICAL were examined for 2 years in four of the five 1-year  
206 weight management clinical studies previously discussed (see Table 1). At the end of  
207 year 1, the patients' diets were reviewed and changed where necessary. The diet  
208 prescribed in the second year was designed to maintain patient's current weight.  
209 XENICAL was shown to be more effective than placebo in long-term weight control in  
210 four large, multicenter, 2-year double-blind, placebo-controlled studies.

211 Pooled data from four clinical studies indicate that 40% of all patients treated with  
212 120 mg three times a day of XENICAL and 24% of patients treated with placebo who  
213 completed 2 years of the same therapy had  $\geq 5\%$  loss of body weight from  
214 randomization. Pooled data from four clinical studies indicate that the relative weight loss  
215 advantage between XENICAL 120 mg three times a day and placebo treatment groups  
216 was the same after 2 years as for 1 year, indicating that the pharmacologic advantage of  
217 XENICAL was maintained over 2 years. In the same studies cited in the **One-year**  
218 **Results** (see Table 1), the percentages of patients achieving a  $\geq 5\%$  and  $\geq 10\%$  weight  
219 loss after 2 years are shown in Table 3.

220 **Table 3 Percentage of Patients Losing  $\geq 5\%$  and  $\geq 10\%$  of Body**  
 221 **Weight From Randomization After 2-Year Treatment\***

Study No.	Intent-to-Treat Population†					
	$\geq 5\%$ Weight Loss			$\geq 10\%$ Weight Loss		
	XENICAL n	Placebo n	p-value	XENICAL n	Placebo n	p-value
14119C	45.1% 133	23.6% 123	<0.001	24.8% 133	6.5% 123	<0.001
14149	43.3% 178	27.2% 158	0.002	18.0% 178	9.5% 158	0.025
14161‡	25.0% 148	15.0% 113	0.049	16.9% 148	3.5% 113	0.001
14185	34.0% 147	27.9% 122	0.279	17.7% 147	11.5% 122	0.154

222 The diet utilized during year 2 was designed for weight maintenance and not weight loss.

223 \* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus  
 224 diet

225 † Last observation carried forward

226 ‡ All studies, with the exception of 14161 were conducted at centers specializing in  
 227 treating obesity or complications of obesity. Study 14161 was conducted with primary  
 228 care physicians.  
 229

230 The relative changes in risk factors associated with obesity following 2 years of therapy  
 231 were also assessed in the population as a whole and the population with abnormal risk  
 232 factors at randomization.

### 233 **Population as a Whole**

234 The relative differences in risk factors between treatment with XENICAL and placebo  
 235 were similar to the results following 1 year of therapy for total cholesterol, LDL-  
 236 cholesterol, LDL/HDL ratio, triglycerides, fasting glucose, fasting insulin, diastolic blood  
 237 pressure, waist circumference, and hip circumference. The relative differences between  
 238 treatment groups for HDL cholesterol and systolic blood pressure were less than that  
 239 observed in the year one results.

### 240 **Population With Abnormal Risk Factors at Randomization**

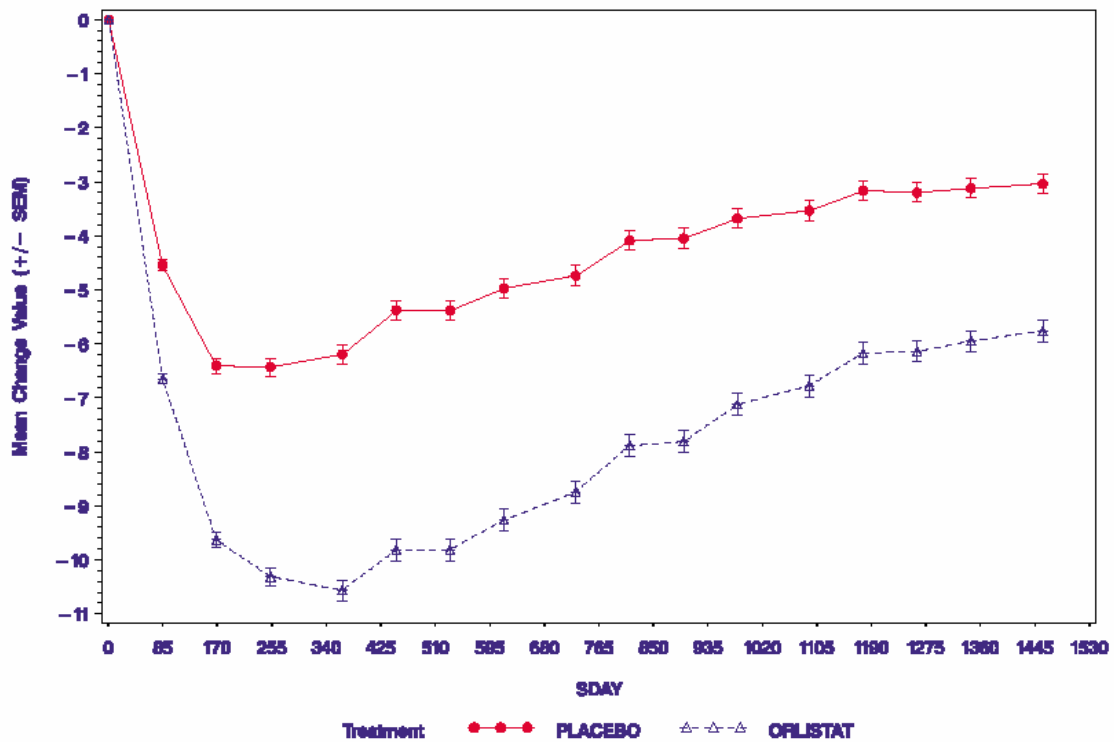
241 The relative differences in risk factors between treatment with XENICAL and placebo  
 242 were similar to the results following 1 year of therapy for LDL- and HDL-cholesterol,  
 243 triglycerides, fasting insulin, diastolic blood pressure, and waist circumference. The  
 244 relative differences between treatment groups for LDL/HDL ratio and isolated systolic  
 245 blood pressure were less than that observed in the year one results.

### 246 **Four-year Results: Long-term Weight Control and Risk Factors**

247 In the 4-year double-blind, placebo-controlled XENDOS study, the effects of orlistat in  
 248 delaying the onset of type 2 diabetes and on body weight were compared to placebo in  
 249 3304 obese patients who had either normal or impaired glucose tolerance at baseline.  
 250 Thirty-four percent of the 1655 patients who were randomized to the placebo group and  
 251 52% of the 1649 patients who were randomized to the orlistat group completed the 4-year  
 252 study.

253 At the end of the study, the mean percent weight loss in the placebo group was -2.75%  
 254 compared with -5.17% in the orlistat group ( $p < 0.001$ ) (see Figure 1). Forty-five percent  
 255 of the placebo patients and 73% of the orlistat patients lost  $\geq 5\%$  of their baseline body  
 256 weight, and 21% of the placebo patients and 41% of the orlistat patients lost  $\geq 10\%$  of  
 257 their baseline body weight following the first year of treatment. Following 4 years of  
 258 treatment, 28% of the placebo patients and 45% of the orlistat patients lost  $\geq 5\%$  of their  
 259 baseline body weight and 10% of the placebo patients and 21% of the orlistat patients lost  
 260  $\geq 10\%$  of their baseline body weight.

261 **Figure 1 Mean Change from Baseline Body Weight (Kgs) Over Time**



262

263

264 The relative changes from baseline in risk factors associated with obesity following 4  
 265 years of therapy were assessed in the XENDOS study population (see Table 4).

266 **Table 4** **Mean Change in Risk Factors From Randomization**  
 267 **Following 4-Years Treatment\***

<b>Risk Factor</b>	<b>XENICAL 120 mg†</b>	<b>Placebo†</b>
<b>Metabolic:</b>		
Total Cholesterol	-7.02%	-2.03%
LDL-Cholesterol	-11.66%	-3.85%
HDL-Cholesterol	+5.92%	+7.01%
LDL/HDL	-0.53	-0.33
Triglycerides	+3.64%	+1.30
Fasting Glucose, mmol/L	+0.12	+0.23
Fasting Insulin, pmol/L	-24.93	-15.71
<b>Cardiovascular:</b>		
Systolic Blood Pressure, mm Hg	-4.12	-2.60
Diastolic Blood Pressure, mm Hg	-1.93	-0.87
<b>Anthropometric:</b>		
Waist Circumference, cm	-5.78	-3.99

268 \*Treatment designates XENICAL 120 mg three times a day plus  
 269 diet or placebo plus diet  
 270 †Intent-to-treat population

271 **Study of Patients With Type 2 Diabetes**

272 A 1-year double-blind, placebo-controlled study in type 2 diabetics (N=321) stabilized on  
 273 sulfonylureas was conducted. Thirty percent of patients treated with XENICAL achieved  
 274 at least a 5% or greater reduction in body weight from randomization compared to 13%  
 275 of the placebo-treated patients (p<0.001). Table 5 describes the changes over 1 year of  
 276 treatment with XENICAL compared to placebo, in sulfonylurea usage and dose reduction  
 277 as well as in hemoglobin HbA1c, fasting glucose, and insulin.

278 **Table 5** **Mean Changes in Body Weight and Glycemic Control From**  
 279 **Randomization Following 1-Year Treatment in Patients With**  
 280 **Type 2 Diabetes**

	<b>XENICAL 120 mg* (n=162)</b>	<b>Placebo* (n=159)</b>	<b>Statistical Significance</b>
% patients who discontinued dose of oral sulfonylurea	11.7%	7.5%	†
% patients who decreased dose of oral sulfonylurea	31.5%	21.4%	
Average reduction in sulfonylurea medication dose	-22.8%	-9.1%	†
Body weight change (lbs)	-8.9	-4.2	†
HbA1c	-0.18%	+0.28%	†
Fasting glucose, mmol/L	-0.02	+0.54	†
Fasting insulin, pmol/L	-19.68	-18.02	ns

281 Statistical significance based on intent-to-treat population, last observation carried  
 282 forward.

283 \* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus  
 284 diet

285 † Statistically significant ( $p \leq 0.05$ ) based on intent-to-treat, last observation carried  
 286 forward

287 ns nonsignificant,  $p > 0.05$

288

289 In addition, XENICAL (n=162) compared to placebo (n=159) was associated with  
 290 significant lowering for total cholesterol (-1.0% vs +9.0%,  $p \leq 0.05$ ), LDL-cholesterol (-  
 291 3.0% vs +10.0%,  $p \leq 0.05$ ), LDL/HDL ratio (-0.26 vs -0.02,  $p \leq 0.05$ ) and triglycerides  
 292 (+2.54% vs +16.2%,  $p \leq 0.05$ ), respectively. For HDL cholesterol, there was a +6.49%  
 293 increase on XENICAL and +8.6% increase on placebo,  $p > 0.05$ . Systolic blood pressure  
 294 increased by +0.61 mm Hg on XENICAL and increased by +4.33 mm Hg on placebo,  
 295  $p > 0.05$ . Diastolic blood pressure decreased by -0.47 mm Hg for XENICAL and by  
 296 -0.5 mm Hg for placebo,  $p > 0.05$ .

### 297 **Glucose Tolerance in Obese Patients**

298 Two-year studies that included oral glucose tolerance tests were conducted in obese  
 299 patients not previously diagnosed or treated for type 2 diabetes and whose baseline oral  
 300 glucose tolerance test (OGTT) status at randomization was either normal, impaired, or  
 301 diabetic.

302 The progression from a normal OGTT at randomization to a diabetic or impaired OGTT  
 303 following 2 years of treatment with XENICAL (n=251) or placebo (n=207) were  
 304 compared. Following treatment with XENICAL, 0.0% and 7.2% of the patients

305 progressed from normal to diabetic and normal to impaired, respectively, compared to  
 306 1.9% and 12.6% of the placebo treatment group, respectively.

307 In patients found to have an impaired OGTT at randomization, the percent of patients  
 308 improving to normal or deteriorating to diabetic status following 1 and 2 years of  
 309 treatment with XENICAL compared to placebo are presented. After 1 year of treatment,  
 310 45.8% of the placebo patients and 73% of the XENICAL patients had a normal oral  
 311 glucose tolerance test while 10.4% of the placebo patients and 2.6% of the XENICAL  
 312 patients became diabetic. After 2 years of treatment, 50% of the placebo patients and  
 313 71.7% of the XENICAL patients had a normal oral glucose tolerance test while 7.5% of  
 314 placebo patients were found to be diabetic and 1.7% of XENICAL patients were found to  
 315 be diabetic after treatment.

### 316 **Onset of Type 2 Diabetes in Obese Patients**

317 In the XENDOS trial, in the overall population, orlistat delayed the onset of type 2  
 318 diabetes such that at the end of four years of treatment the cumulative incidence rate of  
 319 diabetes was 8.3% for the placebo group compared to 5.5% for the orlistat group, p=0.01  
 320 (see Table 6). This finding was driven by a statistically-significant reduction in the  
 321 incidence of developing type 2 diabetes in those patients who had impaired glucose  
 322 tolerance at baseline (Table 6 and Figure 2). Orlistat did not reduce the risk for the  
 323 development of diabetes in patients with normal glucose tolerance at baseline.

324 The effect of XENICAL to delay the onset of type 2 diabetes in obese patients with IGT  
 325 is presumably due to weight loss, and not to any independent effects of the drug on  
 326 glucose or insulin metabolism. The effect of orlistat on weight loss is adjunctive to diet  
 327 and exercise.

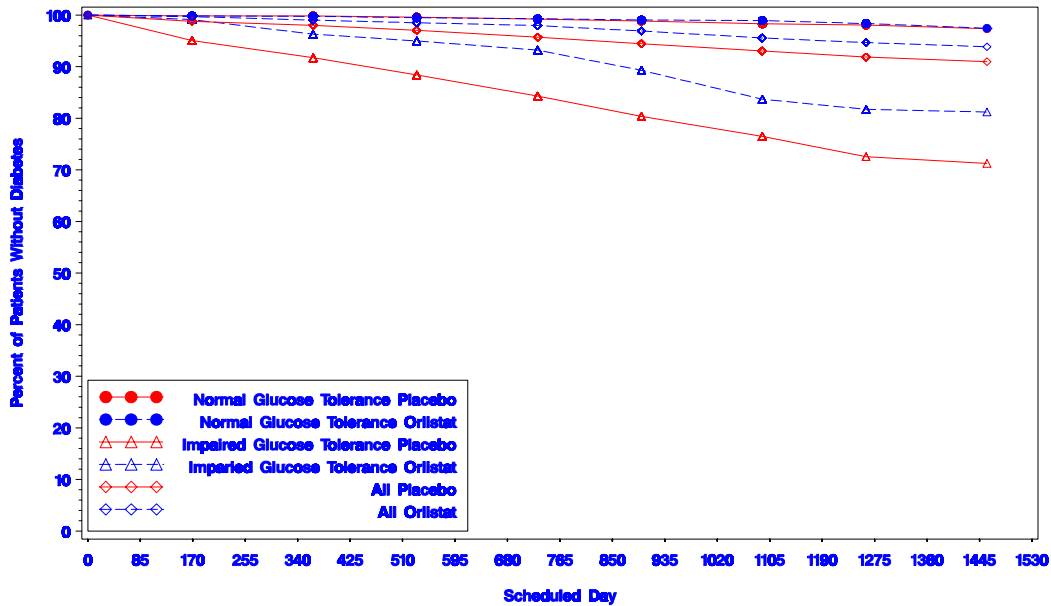
328 **Table 6 Incidence Rate of Diabetes at Year 4 by OGTT Status at**  
 329 **Baseline\***

OGTT at baseline	Normal		Impaired		All	
	Placebo	Orlistat	Placebo	Orlistat	Placebo	Orlistat
Treatment						
Number of patients*	1148	1235	324	337	1472	1572
# pts developing diabetes	16	21	62	48	78	69
Life table rate†	2.1%	1.7%	27.2%	18.7%	8.3%	5.5%
Observed percent	1.4%	1.7%	19.1%	14.2%	5.3%	4.4%
Absolute risk reduction						
Life table	0.4%		8.5%		2.8%	
Observed	-0.3%		4.9%		0.9%	
Relative risk reduction††	8%		42%		34%	
p-value	0.79		<0.01		0.01	

330 \*Based on patients with a baseline and at least one follow-up OGTT measurement

331 †Rate adjusted for dropouts  
 332 †† Computed as (1- hazard ratio)  
 333

334 **Figure 2 Percentage of Patients Without Diabetes Over Time**



335

336 **Pediatric Clinical Studies**

337 The effects of XENICAL on body mass index (BMI) and weight loss were assessed in a  
 338 54-week multicenter, double-blind, placebo-controlled study in 539 obese adolescents  
 339 (357 receiving XENICAL 120 mg three times a day, 182 receiving placebo), aged 12 to  
 340 16 years. All study participants had a baseline BMI that was 2 units greater than the US  
 341 weighted mean for the 95<sup>th</sup> percentile based on age and gender. Body mass index was the  
 342 primary efficacy parameter because it takes into account changes in height and body  
 343 weight, which occur in growing children.

344 During the study, all patients were instructed to take a multivitamin containing fat-  
 345 soluble vitamins at least 2 hours before or after ingestion of XENICAL. Patients were  
 346 also maintained on a well-balanced, reduced-calorie diet that was intended to provide  
 347 30% of calories from fat. In addition, all patients were placed on a behavior modification  
 348 program and offered exercise counseling.

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

350 Following one year of treatment, BMI decreased by an average of 0.55 kg/m<sup>2</sup> in the  
 351 XENICAL-treated patients and increased by an average of 0.31 kg/m<sup>2</sup> in the placebo-  
 352 treated patients (p=0.001).

353 The percentages of patients achieving  $\geq 5\%$  and  $\geq 10\%$  reduction in BMI and body  
 354 weight after 52 weeks of treatment for the intent-to-treat population are presented in  
 355 Table 7.

356 **Table 7 Percentages of Patients with  $\geq 5\%$  and  $\geq 10\%$  Decrease in**  
 357 **Body Mass Index and Body Weight After 1-Year Treatment\***  
 358 **(Protocol NM16189)**

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

359 \* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus  
 360 diet

361 † Last observation carried forward

362

### 363 INDICATIONS AND USAGE

364 XENICAL is indicated for obesity management including weight loss and weight  
 365 maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also  
 366 indicated to reduce the risk for weight regain after prior weight loss. XENICAL is  
 367 indicated for obese patients with an initial body mass index (BMI)  $\geq 30 \text{ kg/m}^2$  or  
 368  $\geq 27 \text{ kg/m}^2$  in the presence of other risk factors (eg, hypertension, diabetes,  
 369 dyslipidemia).

370 Table 8 illustrates body mass index (BMI) according to a variety of weights and heights.  
 371 The BMI is calculated by dividing weight in kilograms by height in meters squared. For  
 372 example, a person who weighs 180 lbs and is 5'5" would have a BMI of 30.

373 **Table 8 Body Mass Index (BMI), kg/m<sup>2</sup>\***

		WEIGHT (lb)																				
		120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300	310	320
HEIGHT (ft/in)	4'10"	25	27	29	31	34	36	38	40	42	44	46	48	50	52	54	57	59	61	63	65	67
	4'11"	24	26	28	30	32	34	36	38	40	43	45	47	49	51	53	55	57	59	61	63	65
	5'0"	23	25	27	29	31	33	35	37	39	41	43	45	47	49	51	53	55	57	59	61	63
	5'1"	23	25	27	28	30	32	34	36	38	40	42	44	45	47	49	51	53	55	57	59	61
	5'2"	22	24	26	27	29	31	33	35	37	38	40	42	44	46	48	49	51	53	55	57	59
	5'3"	21	23	25	27	28	30	32	34	36	37	39	41	43	44	46	48	50	51	53	55	57
	5'4"	21	22	24	26	28	29	31	33	34	36	38	40	41	43	45	46	48	50	52	53	55
	5'5"	20	22	23	25	27	28	30	32	33	35	37	38	40	42	43	45	47	48	50	52	53
	5'6"	19	21	23	24	26	27	29	31	32	34	36	37	39	40	42	44	45	47	49	50	52
	5'7"	19	20	22	24	25	27	28	30	31	33	35	36	38	39	41	42	44	46	47	49	50
	5'8"	18	20	21	23	24	26	27	29	30	32	34	35	37	38	40	41	43	44	46	47	49
	5'9"	18	19	21	22	24	25	27	28	30	31	33	34	36	37	38	40	41	43	44	46	47
	5'10"	17	19	20	22	23	24	26	27	29	30	32	33	35	36	37	39	40	42	43	45	46
	5'11"	17	18	20	21	22	24	25	27	28	29	31	32	34	35	36	38	39	41	42	43	45
	6'0"	16	18	19	20	22	23	24	26	27	29	30	31	33	34	35	37	38	39	41	42	43
	6'1"	16	17	19	20	21	22	24	25	26	28	29	30	32	33	34	36	37	38	40	41	42
	6'2"	15	17	18	19	21	22	23	24	26	27	28	30	31	32	33	35	36	37	39	40	41

374 \* Conversion Factors:

375 Weight in lbs ÷ 2.2 = weight in kilograms (kg)

376 Height in inches × 0.0254 = height in meters (m)

377 1 foot = 12 inches

378

379 **CONTRAINDICATIONS**

380 XENICAL is contraindicated in patients with chronic malabsorption syndrome or  
 381 cholestasis, and in patients with known hypersensitivity to XENICAL or to any  
 382 component of this product.

383 **WARNINGS**

384 **Miscellaneous**

385 Organic causes of obesity (eg, hypothyroidism) should be excluded before prescribing  
 386 XENICAL.

387 Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a  
 388 reduction in cyclosporine plasma levels when XENICAL was coadministered with  
 389 cyclosporine. Therefore, XENICAL and cyclosporine should not be coadministered. To  
 390 reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 2  
 391 hours before or after XENICAL in patients taking both drugs. In addition, in those  
 392 patients whose cyclosporine levels are being measured, more frequent monitoring should  
 393 be considered.

394 **PRECAUTIONS**

395 **General**

396 Patients should be advised to adhere to dietary guidelines (see **DOSAGE AND**  
 397 **ADMINISTRATION**). Gastrointestinal events (see **ADVERSE REACTIONS**) may  
 398 increase when XENICAL is taken with a diet high in fat (>30% total daily calories from  
 399 fat). The daily intake of fat should be distributed over three main meals. If XENICAL is

400 taken with any one meal very high in fat, the possibility of gastrointestinal effects  
401 increases.

402 Patients should be strongly encouraged to take a multivitamin supplement that contains  
403 fat-soluble vitamins to ensure adequate nutrition because XENICAL has been shown to  
404 reduce the absorption of some fat-soluble vitamins and beta-carotene (see **DOSAGE**  
405 **AND ADMINISTRATION**). In addition, the levels of vitamin D and beta-carotene may  
406 be low in obese patients compared with non-obese subjects. The supplement should be  
407 taken once a day at least 2 hours before or after the administration of XENICAL, such as  
408 at bedtime.

409 Table 9 illustrates the percentage of adult patients on XENICAL and placebo who  
410 developed a low vitamin level on two or more consecutive visits during 1 and 2 years of  
411 therapy in studies in which patients were not previously receiving vitamin  
412 supplementation.

413 **Table 9**                    **Incidence of Low Vitamin Values on Two or More**  
414                                    **Consecutive Visits (Nonsupplemented Adult Patients With**  
415                                    **Normal Baseline Values - First and Second Year)**

	Placebo*	XENICAL*
Vitamin A	1.0%	2.2%
Vitamin D	6.6%	12.0%
Vitamin E	1.0%	5.8%
Beta-carotene	1.7%	6.1%

416 \* Treatment designates placebo plus diet or XENICAL plus diet

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

419 **Table 10**      **Incidence of Low Vitamin Values on Two or More**  
 420 **Consecutive Visits (Pediatric Patients With Normal Baseline**  
 421 **Values\*)**

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

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

424 † Treatment designates placebo plus diet or XENICAL plus diet

425 Some patients may develop increased levels of urinary oxalate following treatment with  
 426 XENICAL. Caution should be exercised when prescribing XENICAL to patients with a  
 427 history of hyperoxaluria or calcium oxalate nephrolithiasis.

428 Weight-loss induction by XENICAL may be accompanied by improved metabolic  
 429 control in diabetics, which might require a reduction in dose of oral hypoglycemic  
 430 medication (eg, sulfonylureas, metformin) or insulin (see **CLINICAL STUDIES**).

431 Substantial weight loss can increase the risk of cholelithiasis. In a clinical trial of  
 432 XENICAL for the prevention of type 2 diabetes, the rates of cholelithiasis as an adverse  
 433 event were 2.9% (47/1649) for patients randomized to XENICAL and 1.8% (30/1655) for  
 434 patients randomized to placebo. In this trial, the incidence of cholelithiasis was similar  
 435 for XENICAL and placebo at similar amounts of weight loss. An increase in  
 436 cholelithiasis with XENICAL was not seen in trials that were not evaluating the  
 437 prevention of type 2 diabetes.

#### 438 **Misuse Potential**

439 As with any weight-loss agent, the potential exists for misuse of XENICAL in  
 440 inappropriate patient populations (eg, patients with anorexia nervosa or bulimia). See  
 441 **INDICATIONS AND USAGE** for recommended prescribing guidelines.

#### 442 **Information for Patients**

443 Patients should read the Patient Information before starting treatment with XENICAL  
 444 and each time their prescription is renewed.

#### 445 **Drug Interactions**

##### 446 **Alcohol**

447 In a multiple-dose study in 30 normal-weight subjects, coadministration of XENICAL  
 448 and 40 grams of alcohol (eg, approximately 3 glasses of wine) did not result in alteration  
 449 of alcohol pharmacokinetics, orlistat pharmacodynamics (fecal fat excretion), or systemic  
 450 exposure to orlistat.

451 Cyclosporine

452 Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a  
453 reduction in cyclosporine plasma levels when XENICAL was coadministered with  
454 cyclosporine (see **WARNINGS**).

455 Digoxin

456 In 12 normal-weight subjects receiving XENICAL 120 mg three times a day for 6 days,  
457 XENICAL did not alter the pharmacokinetics of a single dose of digoxin.

458 Fat-soluble Vitamin Supplements and Analogues

459 A pharmacokinetic interaction study showed a 30% reduction in beta-carotene  
460 supplement absorption when concomitantly administered with XENICAL. XENICAL  
461 inhibited absorption of a vitamin E acetate supplement by approximately 60%. The effect  
462 of orlistat on the absorption of supplemental vitamin D, vitamin A, and nutritionally-  
463 derived vitamin K is not known at this time.

464 Glyburide

465 In 12 normal-weight subjects receiving orlistat 80 mg three times a day for 5 days,  
466 orlistat did not alter the pharmacokinetics or pharmacodynamics (blood glucose-  
467 lowering) of glyburide.

468 Levothyroxine

469 Hypothyroidism has been reported in patients treated concomitantly with orlistat and  
470 levothyroxine postmarketing (see **ADVERSE REACTIONS: Other Clinical Studies or**  
471 **Postmarketing Surveillance**). Patients treated concomitantly with orlistat and  
472 levothyroxine should be monitored for changes in thyroid function. Administer  
473 levothyroxine and orlistat at least 4 hours apart.

474 Nifedipine (extended-release tablets)

475 In 17 normal-weight subjects receiving XENICAL 120 mg three times a day for 6 days,  
476 XENICAL did not alter the bioavailability of nifedipine (extended-release tablets).

477 Oral Contraceptives

478 In 20 normal-weight female subjects, the treatment of XENICAL 120 mg three times a  
479 day for 23 days resulted in no changes in the ovulation-suppressing action of oral  
480 contraceptives.

481 Phenytoin

482 In 12 normal-weight subjects receiving XENICAL 120 mg three times a day for 7 days,  
483 XENICAL did not alter the pharmacokinetics of a single 300-mg dose of phenytoin.

484 **Pravastatin**

485 In a 2-way crossover study of 24 normal-weight, mildly hypercholesterolemic patients  
486 receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not affect the  
487 pharmacokinetics of pravastatin.

488 **Warfarin**

489 In 12 normal-weight subjects, administration of XENICAL 120 mg three times a day for  
490 16 days did not result in any change in either warfarin pharmacokinetics (both R- and S-  
491 enantiomers) or pharmacodynamics (prothrombin time and serum Factor VII). Although  
492 undercarboxylated osteocalcin, a marker of vitamin K nutritional status, was unaltered  
493 with XENICAL administration, vitamin K levels tended to decline in subjects taking  
494 XENICAL. Therefore, as vitamin K absorption may be decreased with XENICAL,  
495 patients on chronic stable doses of warfarin who are prescribed XENICAL should be  
496 monitored closely for changes in coagulation parameters.

497 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

498 Carcinogenicity studies in rats and mice did not show a carcinogenic potential for orlistat  
499 at doses up to 1000 mg/kg/day and 1500 mg/kg/day, respectively. For mice and rats, these  
500 doses are 38 and 46 times the daily human dose calculated on an area under concentration vs  
501 time curve basis of total drug-related material.

502 Orlistat had no detectable mutagenic or genotoxic activity as determined by the Ames  
503 test, a mammalian forward mutation assay (V79/HPRT), an in vitro clastogenesis assay in  
504 peripheral human lymphocytes, an unscheduled DNA synthesis assay (UDS) in rat  
505 hepatocytes in culture, and an in vivo mouse micronucleus test.

506 When given to rats at a dose of 400 mg/kg/day in a fertility and reproduction study,  
507 orlistat had no observable adverse effects. This dose is 12 times the daily human dose  
508 calculated on a body surface area ( $\text{mg}/\text{m}^2$ ) basis.

509 **Pregnancy**

510 **Teratogenic Effects: Pregnancy Category B.**

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

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

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

523 **Nursing Mothers**

524 It is not known if orlistat is secreted in human milk. Therefore, XENICAL should not be  
525 taken by nursing women.

526 **Pediatric Use**

527 The safety and efficacy of XENICAL have been evaluated in obese adolescent patients  
528 aged 12 to 16 years. Use of XENICAL in this age group is supported by evidence from  
529 adequate and well-controlled studies of XENICAL in adults with additional data from a  
530 54-week efficacy and safety study and a 21-day mineral balance study in obese  
531 adolescent patients aged 12 to 16 years. Patients treated with XENICAL had a mean  
532 reduction in BMI of 0.55 kg/m<sup>2</sup> compared with an average increase of 0.31 kg/m<sup>2</sup> in  
533 placebo-treated patients (p=0.001). In both adolescent studies, adverse effects were  
534 generally similar to those described in adults and included fatty/oily stool, oily spotting,  
535 and oily evacuation. In a subgroup of 152 orlistat and 77 placebo patients from the 54-  
536 week study, changes in body composition measured by DEXA were similar in both  
537 treatment groups with the exception of fat mass, which was significantly reduced in  
538 patients treated with XENICAL compared to patients treated with placebo (-2.5 kg vs -  
539 0.6 kg, p=0.033). Because XENICAL can interfere with the absorption of fat-soluble  
540 vitamins, all patients should take a daily multivitamin that contains vitamins A, D, E, K,  
541 and beta-carotene. The supplement should be taken at least 2 hours before or after  
542 XENICAL (see **CLINICAL PHARMACOLOGY: Other Short-term Studies;**  
543 **CLINICAL STUDIES: Pediatric Clinical Studies;** **ADVERSE REACTIONS:**  
544 **Pediatric Patients**). XENICAL has not been studied in pediatric patients below the age  
545 of 12 years.

546 **Geriatric Use**

547 Clinical studies of XENICAL did not include sufficient numbers of patients aged 65  
548 years and older to determine whether they respond differently from younger patients.

549 **ADVERSE REACTIONS**

550 **Commonly Observed (based on first year and second year data - XENICAL**  
551 **120 mg three times a day versus placebo):**

552 Gastrointestinal (GI) symptoms were the most commonly observed treatment-emergent  
553 adverse events associated with the use of XENICAL in the seven double-blind, placebo-  
554 controlled clinical trials and are primarily a manifestation of the mechanism of action.  
555 (Commonly observed is defined as an incidence of ≥ 5% and an incidence in the  
556 XENICAL 120 mg group that is at least twice that of placebo.)

557 **Table 11 Commonly Observed Adverse Events**

Adverse Event	Year 1		Year 2	
	XENICAL* % Patients (N=1913)	Placebo* % Patients (N=1466)	XENICAL* % Patients (N=613)	Placebo* % Patients (N=524)
Oily Spotting	26.6	1.3	4.4	0.2
Flatus with Discharge	23.9	1.4	2.1	0.2
Fecal Urgency	22.1	6.7	2.8	1.7
Fatty/Oily Stool	20.0	2.9	5.5	0.6
Oily Evacuation	11.9	0.8	2.3	0.2
Increased Defecation	10.8	4.1	2.6	0.8
Fecal Incontinence	7.7	0.9	1.8	0.2

558 \* Treatment designates XENICAL three times a day plus diet or placebo plus diet

559 These and other commonly observed adverse reactions were generally mild and transient,  
 560 and they decreased during the second year of treatment. In general, the first occurrence of  
 561 these events was within 3 months of starting therapy. Overall, approximately 50% of all  
 562 episodes of GI adverse events associated with orlistat treatment lasted for less than 1  
 563 week, and a majority lasted for no more than 4 weeks. However, GI adverse events may  
 564 occur in some individuals over a period of 6 months or longer.

565 **Discontinuation of Treatment**

566 In controlled clinical trials, 8.8% of patients treated with XENICAL discontinued  
 567 treatment due to adverse events, compared with 5.0% of placebo-treated patients. For  
 568 XENICAL, the most common adverse events resulting in discontinuation of treatment  
 569 were gastrointestinal.

570 **Incidence in Controlled Clinical Trials**

571 The following table lists other treatment-emergent adverse events from seven  
 572 multicenter, double-blind, placebo-controlled clinical trials that occurred at a frequency  
 573 of  $\geq 2\%$  among patients treated with XENICAL 120 mg three times a day and with an  
 574 incidence that was greater than placebo during year 1 and year 2, regardless of  
 575 relationship to study medication.

576  
577

**Table 12 Other Treatment-Emergent Adverse Events From Seven Placebo-Controlled Clinical Trials**

Body System/Adverse Event	Year 1		Year 2	
	XENICAL* % Patients (N=1913)	Placebo* % Patients (N=1466)	XENICAL* % Patients (N=613)	Placebo* % Patients (N=524)
<i>Gastrointestinal System</i>				
Abdominal Pain/Discomfort	25.5	21.4	–	–
Nausea	8.1	7.3	3.6	2.7
Infectious Diarrhea	5.3	4.4	–	–
Rectal Pain/Discomfort	5.2	4.0	3.3	1.9
Tooth Disorder	4.3	3.1	2.9	2.3
Gingival Disorder	4.1	2.9	2.0	1.5
Vomiting	3.8	3.5	–	–
<i>Respiratory System</i>				
Influenza	39.7	36.2	–	–
Upper Respiratory Infection	38.1	32.8	26.1	25.8
Lower Respiratory Infection	7.8	6.6	–	–
Ear, Nose & Throat Symptoms	2.0	1.6	–	–
<i>Musculoskeletal System</i>				
Back Pain	13.9	12.1	–	–
Pain Lower Extremities	–	–	10.8	10.3
Arthritis	5.4	4.8	–	–
Myalgia	4.2	3.3	–	–
Joint Disorder	2.3	2.2	–	–
Tendonitis	–	–	2.0	1.9
<i>Central Nervous System</i>				
Headache	30.6	27.6	–	–
Dizziness	5.2	5.0	–	–
<i>Body as a Whole</i>				
Fatigue	7.2	6.4	3.1	1.7
Sleep Disorder	3.9	3.3	–	–
<i>Skin &amp; Appendages</i>				
Rash	4.3	4.0	–	–
Dry Skin	2.1	1.4	–	–
<i>Reproductive, Female</i>				
Menstrual Irregularity	9.8	7.5	–	–
Vaginitis	3.8	3.6	2.6	1.9
<i>Urinary System</i>				
Urinary Tract Infection	7.5	7.3	5.9	4.8
<i>Psychiatric Disorder</i>				
Psychiatric Anxiety	4.7	2.9	2.8	2.1
Depression	–	–	3.4	2.5
<i>Hearing &amp; Vestibular Disorders</i>				
Otitis	4.3	3.4	2.9	2.5
<i>Cardiovascular Disorders</i>				
Pedal Edema	–	–	2.8	1.9

578 \* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus  
579 diet

580 – None reported at a frequency  $\geq 2\%$  and greater than placebo

581

582 In the 4-year XENDOS study, the general pattern of adverse events was similar to that  
583 reported for the 1- and 2-year studies with the total incidence of gastrointestinal-related  
584 adverse events occurring in year 1 decreasing each year over the 4-year period.

### 585 **Other Clinical Studies or Postmarketing Surveillance**

586 Rare cases of hypersensitivity have been reported with the use of XENICAL. Signs and  
587 symptoms have included pruritus, rash, urticaria, angioedema, bronchospasm and  
588 anaphylaxis. Very rare cases of bullous eruption, increase in transaminases and in  
589 alkaline phosphatase, and exceptional cases of hepatitis that may be serious have been  
590 reported. No causal relationship or physiopathological mechanism between hepatitis and  
591 orlistat therapy has been established. Reports of decreased prothrombin, increased INR  
592 and unbalanced anticoagulant treatment resulting in change of hemostatic parameters  
593 have been reported in patients treated concomitantly with orlistat and anticoagulants.  
594 Hypothyroidism has been reported in patients treated concomitantly with orlistat and  
595 levothyroxine. Pancreatitis has been reported with the use of XENICAL in postmarketing  
596 surveillance. No causal relationship or physiopathological mechanism between  
597 pancreatitis and obesity therapy has been definitively established.

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

600 Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a  
601 reduction in cyclosporine plasma levels when XENICAL was coadministered with  
602 cyclosporine (see **WARNINGS**).

### 603 **Pediatric Patients**

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

### 606 **OVERDOSAGE**

607 Single doses of 800 mg XENICAL and multiple doses of up to 400 mg three times a day  
608 for 15 days have been studied in normal weight and obese subjects without significant  
609 adverse findings.

610 Should a significant overdose of XENICAL occur, it is recommended that the patient be  
611 observed for 24 hours. Based on human and animal studies, systemic effects attributable  
612 to the lipase-inhibiting properties of orlistat should be rapidly reversible.

### 613 **DOSAGE AND ADMINISTRATION**

614 The recommended dose of XENICAL is one 120-mg capsule three times a day with each  
615 main meal containing fat (during or up to 1 hour after the meal).

616 The patient should be on a nutritionally balanced, reduced-calorie diet that contains  
617 approximately 30% of calories from fat. The daily intake of fat, carbohydrate, and protein  
618 should be distributed over three main meals. If a meal is occasionally missed or contains  
619 no fat, the dose of XENICAL can be omitted.

620 Because XENICAL has been shown to reduce the absorption of some fat-soluble  
621 vitamins and beta-carotene, patients should be counseled to take a multivitamin  
622 containing fat-soluble vitamins to ensure adequate nutrition (see **PRECAUTIONS:**  
623 **General**). The supplement should be taken at least 2 hours before or after the  
624 administration of XENICAL, such as at bedtime.

625 For patients receiving both orlistat and levothyroxine therapy, administer levothyroxine  
626 and orlistat at least 4 hours apart.

627 Doses above 120 mg three times a day have not been shown to provide additional benefit.

628 Based on fecal fat measurements, the effect of XENICAL is seen as soon as 24 to 48  
629 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to  
630 pretreatment levels within 48 to 72 hours.

631 The safety and effectiveness of XENICAL beyond 4 years have not been determined at  
632 this time.

### 633 **HOW SUPPLIED**

634 XENICAL is a dark-blue, hard-gelatin capsule containing pellets of powder.

635 XENICAL 120 mg Capsules: Dark-blue, two-piece, No. 1 opaque hard-gelatin capsule  
636 imprinted with Roche and XENICAL 120 in light-blue ink — bottle of 90 (NDC 0004-  
637 0256-52).

### 638 **Storage Conditions**

639 Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP  
640 Controlled Room Temperature]. Keep bottle tightly closed.

641 XENICAL should not be used after the given expiration date.

642 Distributed by:



**Pharmaceuticals**

Roche Laboratories Inc.  
340 Kingsland Street  
Nutley, New Jersey 07110-1199

643

644 27899513

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