



XENICAL®

(orlistat)

CAPSULES

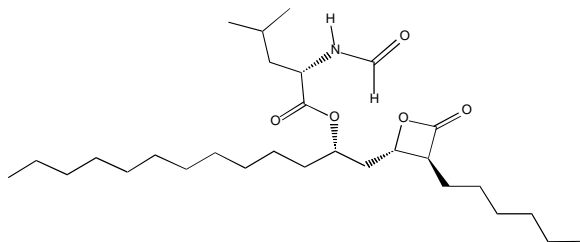
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6 **DESCRIPTION**

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

9 Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[[(2S, 3S)-3-hexyl-4-oxo-2-
10 oxetanyl] methyl]-dodecyl ester. Its empirical formula is C₂₉H₅₃NO₅, and its molecular
11 weight is 495.7. It is a single diastereomeric molecule that contains four chiral centers,
12 with a negative optical rotation in ethanol at 529 nm. The structure is:



13

14 Orlistat is a white to off-white crystalline powder. Orlistat is practically insoluble in
15 water, freely soluble in chloroform, and very soluble in methanol and ethanol. Orlistat
16 has no pK_a within the physiological pH range.

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

23 **CLINICAL PHARMACOLOGY**

24 **Mechanism of Action**

25 Orlistat is a reversible inhibitor of lipases. It exerts its therapeutic activity in the lumen of
26 the stomach and small intestine by forming a covalent bond with the active serine residue
27 site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to
28 hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and
29 monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit
30 may have a positive effect on weight control. Systemic absorption of the drug is therefore
31 not needed for activity. At the recommended therapeutic dose of 120 mg three times a
32 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 ¹⁴C-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 ¹⁴C-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 ¹⁴C-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 ¹⁴C-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.

Pediatric Info

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.

Pediatric Info

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 μ mole/24 hours and
101 40.4 μ mole/24 hours in orlistat and placebo treatment groups, respectively.

102 **Dose-response Relationship**

103 A simple maximum effect (E_{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 [†]								
Study No.	$\geq 5\%$ Weight Loss				$\geq 10\%$ Weight Loss			
	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.

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

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic:		
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
Cardiovascular:		
Systolic Blood Pressure, mm Hg	-1.01	+0.58
Diastolic Blood Pressure, mm Hg	-1.19	+0.46
Anthropometric:		
Waist Circumference, cm	-6.45	-4.04
Hip Circumference, cm	-5.31	-2.96

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

† Intent-to-treat population at week 52, observed data based on pooled data from 5 studies

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Population With Abnormal Risk Factors at Randomization

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

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Effect on Weight Regain

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Three studies were designed to evaluate the effects of XENICAL compared to placebo in reducing weight regain after a previous weight loss achieved following either diet alone (one study, 14302) or prior treatment with XENICAL (two studies, 14119C and 14185). 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 randomization.
214 Pooled data from four clinical studies indicate that the relative weight loss advantage
215 between XENICAL 120 mg three times a day and placebo treatment groups was the same
216 after 2 years as for 1 year, indicating that the pharmacologic advantage of XENICAL was
217 maintained over 2 years. In the same studies cited in the **One-year Results** (see Table 1),
218 the percentages of patients achieving a $\geq 5\%$ and $\geq 10\%$ weight loss after 2 years are
219 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**

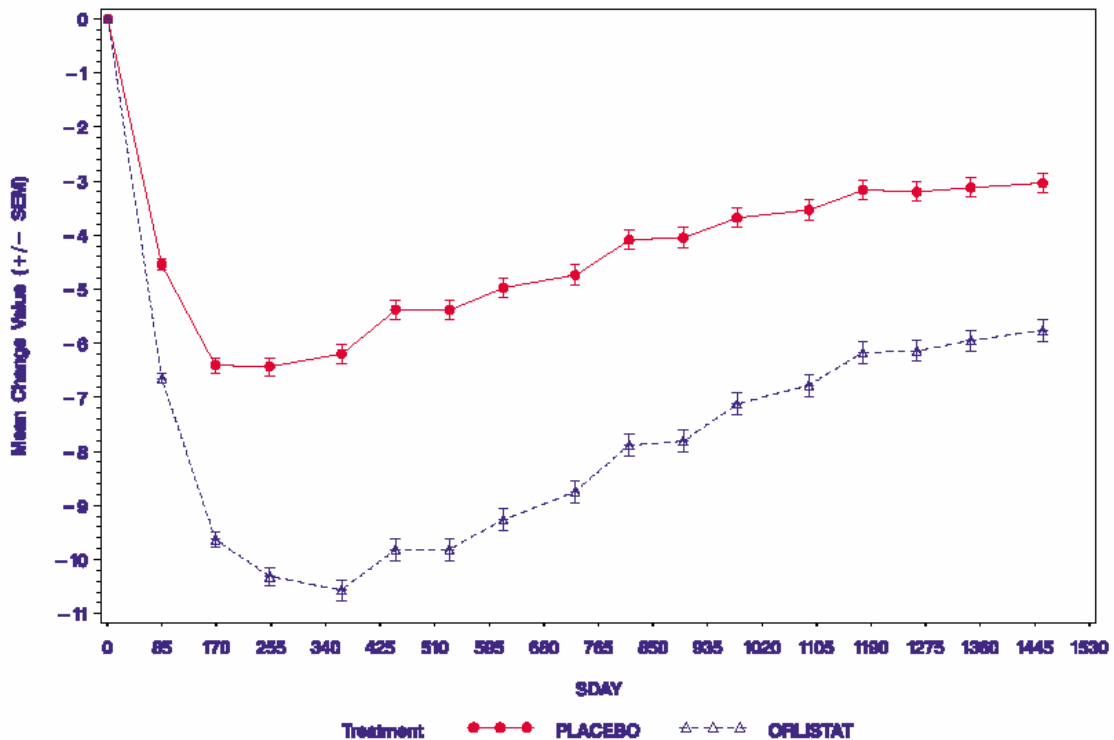
241 The relative differences in risk factors between treatment with XENICAL and placebo
 242 were similar to the results following 1 year of therapy for LDL- and HDL-cholesterol,
 243 triglycerides, fasting insulin, diastolic blood pressure, and waist circumference. The
 244 relative differences between 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**



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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***

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic:		
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
Cardiovascular:		
Systolic Blood Pressure, mm Hg	-4.12	-2.60
Diastolic Blood Pressure, mm Hg	-1.93	-0.87
Anthropometric:		
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**

	XENICAL 120 mg* (n=162)	Placebo* (n=159)	Statistical Significance
% 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	

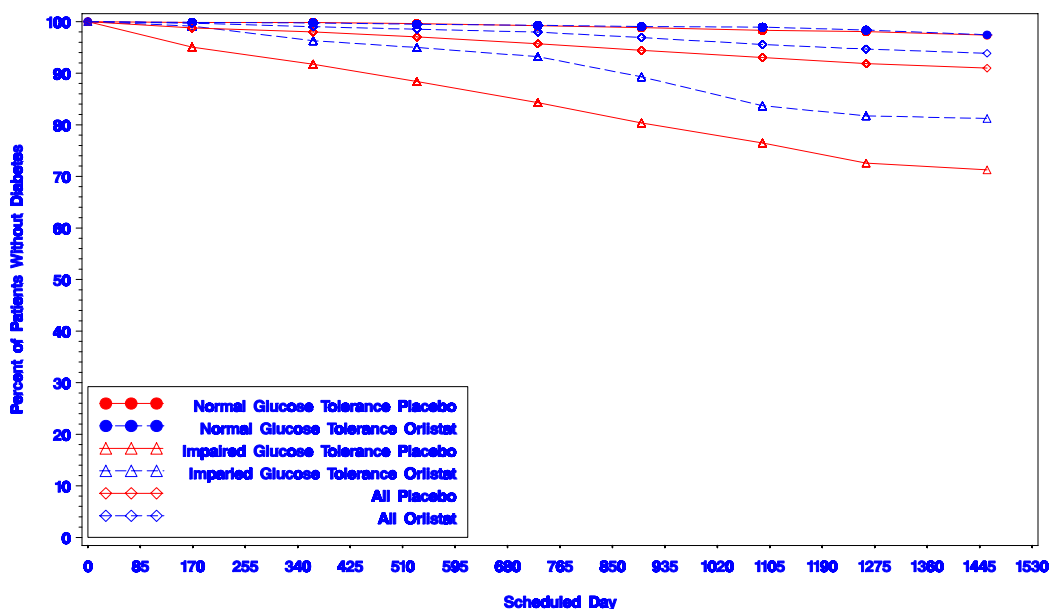
330 *Based on patients with a baseline and at least one follow-up OGTT measurement

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**

Pediatric Info

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 95th 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/m² in the
 351 XENICAL-treated patients and increased by an average of 0.31 kg/m² in the placebo-
 352 treated patients (p=0.001).

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

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

	Intent-to-Treat Population†			
	$\geq 5\%$ 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

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

360 † Last observation carried forward

361

362 **INDICATIONS AND USAGE**

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

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

371 **Table 8 Body Mass Index (BMI), kg/m^2 ***

		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	

372 * Conversion Factors:

373 Weight in lbs \div 2.2 = weight in kilograms (kg)

374 Height in inches \times 0.0254 = height in meters (m)

375 1 foot = 12 inches

376

377 **CONTRAINDICATIONS**

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

381 **WARNINGS**

382 **Miscellaneous**

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

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

392 **PRECAUTIONS**

393 **General**

394 Patients should be advised to adhere to dietary guidelines (see DOSAGE AND
395 ADMINISTRATION). Gastrointestinal events (see ADVERSE REACTIONS) may
396 increase when XENICAL is taken with a diet high in fat (>30% total daily calories from
397 fat). The daily intake of fat should be distributed over three main meals. If XENICAL is
398 taken with any one meal very high in fat, the possibility of gastrointestinal effects
399 increases.

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

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

411 **Table 9** **Incidence of Low Vitamin Values on Two or More**
 412 **Consecutive Visits (Nonsupplemented Adult Patients With**
 413 **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%

414 * Treatment designates placebo plus diet or XENICAL plus diet

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

417 **Table 10** **Incidence of Low Vitamin Values on Two or More**
 418 **Consecutive Visits (Pediatric Patients With Normal Baseline**
 419 **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%

420 * All patients were treated with vitamin supplementation throughout the course of the
 421 study

422 † Treatment designates placebo plus diet or XENICAL plus diet

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

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

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

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436 **Misuse Potential**

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

440 **Information for Patients**

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

443 **Drug Interactions**

444 **Alcohol**

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

449 **Cyclosporine**

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

453 **Digoxin**

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

456 **Fat-soluble Vitamin Supplements and Analogues**

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

462 **Glyburide**

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

466 **Nifedipine (extended-release tablets)**

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

469 **Oral Contraceptives**

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

473 **Phenytoin**

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

476 **Pravastatin**

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

480 **Warfarin**

481 In 12 normal-weight subjects, administration of XENICAL 120 mg three times a day for
482 16 days did not result in any change in either warfarin pharmacokinetics (both R- and S-
483 enantiomers) or pharmacodynamics (prothrombin time and serum Factor VII). Although
484 undercarboxylated osteocalcin, a marker of vitamin K nutritional status, was unaltered
485 with XENICAL administration, vitamin K levels tended to decline in subjects taking
486 XENICAL. Therefore, as vitamin K absorption may be decreased with XENICAL,
487 patients on chronic stable doses of warfarin who are prescribed XENICAL should be
488 monitored closely for changes in coagulation parameters.

489 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

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

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

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

501 **Pregnancy**

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

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

507 The incidence of dilated cerebral ventricles was increased in the mid- and high-dose
508 groups of the rat teratology study. These doses were 6 and 23 times the daily human dose
509 calculated on a body surface area (mg/m²) basis for the mid- and high-dose levels,
510 respectively. This finding was not reproduced in two additional rat teratology studies at
511 similar doses.

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

515 **Nursing Mothers**

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

518 **Pediatric Use**

519 The safety and efficacy of XENICAL have been evaluated in obese adolescent patients
520 aged 12 to 16 years. Use of XENICAL in this age group is supported by evidence from
521 adequate and well-controlled studies of XENICAL in adults with additional data from a
522 54-week efficacy and safety study and a 21-day mineral balance study in obese
523 adolescent patients aged 12 to 16 years. Patients treated with XENICAL had a mean
524 reduction in BMI of 0.55 kg/m² compared with an average increase of 0.31 kg/m² in
525 placebo-treated patients (p=0.001). In both adolescent studies, adverse effects were
526 generally similar to those described in adults and included fatty/oily stool, oily spotting,
527 and oily evacuation. In a subgroup of 152 orlistat and 77 placebo patients from the 54-
528 week study, changes in body composition measured by DEXA were similar in both
529 treatment groups with the exception of fat mass, which was significantly reduced in
530 patients treated with XENICAL compared to patients treated with placebo (-2.5 kg vs -
531 0.6 kg, p=0.033). Because XENICAL can interfere with the absorption of fat-soluble
532 vitamins, all patients should take a daily multivitamin that contains vitamins A, D, E, K,
533 and beta-carotene. The supplement should be taken at least 2 hours before or after
534 XENICAL (see CLINICAL PHARMACOLOGY: Other Short-term Studies; CLINICAL
535 STUDIES: Pediatric Clinical Studies; ADVERSE REACTIONS: Pediatric Patients).
536 XENICAL has not been studied in pediatric patients below the age of 12 years.

537 **Geriatric Use**

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

540 **ADVERSE REACTIONS**

541 **Commonly Observed (based on first year and second year data - XENICAL** 542 **120 mg three times a day versus placebo):**

543 Gastrointestinal (GI) symptoms were the most commonly observed treatment-emergent
544 adverse events associated with the use of XENICAL in the seven double-blind, placebo-
545 controlled clinical trials and are primarily a manifestation of the mechanism of action.

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546 (Commonly observed is defined as an incidence of $\geq 5\%$ and an incidence in the
 547 XENICAL 120 mg group that is at least twice that of placebo.)

548 **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

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

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

556 **Discontinuation of Treatment**

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

561 **Incidence in Controlled Clinical Trials**

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

567
568

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 & 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 & Vestibular Disorders</i>				
Otitis	4.3	3.4	2.9	2.5
<i>Cardiovascular Disorders</i>				
Pedal Edema	–	–	2.8	1.9

569 * Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus
570 diet
571 – None reported at a frequency $\geq 2\%$ and greater than placebo
572

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

576 **Other Clinical Studies or Postmarketing Surveillance**

577 Rare cases of hypersensitivity have been reported with the use of XENICAL. Signs and
578 symptoms have included pruritus, rash, urticaria, angioedema, bronchospasm and
579 anaphylaxis. Very rare cases of bullous eruption, increase in transaminases and in
580 alkaline phosphatase, and exceptional cases of hepatitis that may be serious have been
581 reported. No causal relationship or physiopathological mechanism between hepatitis and
582 orlistat therapy has been established. Reports of decreased prothrombin, increased INR
583 and unbalanced anticoagulant treatment resulting in change of hemostatic parameters
584 have been reported in patients treated concomitantly with orlistat and anticoagulants.
585 Pancreatitis has been reported with the use of XENICAL in postmarketing surveillance.
586 No causal relationship or physiopathological mechanism between pancreatitis and obesity
587 therapy has been definitively established.

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

590 Preliminary data from a XENICAL and cyclosporine drug interaction study indicate a
591 reduction in cyclosporine plasma levels when XENICAL was coadministered with
592 cyclosporine (see WARNINGS).

593 **Pediatric Patients**

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

596 **OVERDOSAGE**

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

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

603 **DOSAGE AND ADMINISTRATION**

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

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

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

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

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

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

621 **HOW SUPPLIED**

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

623 XENICAL 120 mg Capsules: Dark-blue, two-piece, No. 1 opaque hard-gelatin capsule
624 imprinted with Roche and XENICAL 120 in light-blue ink — bottle of 90 (NDC 0004-
625 0256-52).

626 **Storage Conditions**

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

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

630 Distributed by:



Pharmaceuticals

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Nutley, New Jersey 07110-1199

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632 xxxxxxxx

633 Revised: Month Year

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