

1 **XENICAL®**

2 **(orlistat)**

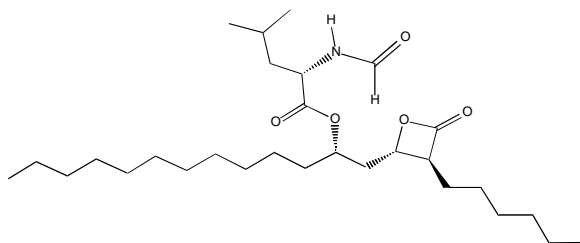
3 **CAPSULES**

4 **R_x only**

5 **DESCRIPTION**

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

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



12

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

16 XENICAL is available for oral administration as a dark-blue or turquoise hard-gelatin
17 capsule. The dark blue capsule is imprinted with light blue and the turquoise capsule is
18 imprinted with black. Each capsule contains a pellet formulation consisting of 120 mg of
19 the active ingredient, orlistat, as well as the inactive ingredients microcrystalline
20 cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc. The dark
21 blue capsule shell contains gelatin, titanium dioxide, and FD&C Blue No. 1, with printing
22 of pharmaceutical glaze NF, titanium dioxide, and FD&C Blue No. 1 aluminum lake. The
23 turquoise capsule shell contains gelatin, titanium dioxide, and FD&C Blue No. 2 with
24 black printing ink containing pharmaceutical grade shellac, dehydrated alcohol, isopropyl
25 alcohol, butyl alcohol, propylene glycol, strong ammonium solution, potassium
26 hydroxide and black iron oxide.

27 **CLINICAL PHARMACOLOGY**

28 **Mechanism of Action**

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

35 not needed for activity. At the recommended therapeutic dose of 120 mg three times a
36 day, orlistat inhibits dietary fat absorption by approximately 30%.

37 **Pharmacokinetics**

38 **Absorption**

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

45 The average absolute bioavailability of intact orlistat was assessed in studies with male
46 rats at oral doses of 150 and 1000 mg/kg/day and in male dogs at oral doses of 100 and
47 1000 mg/kg/day and found to be 0.12%, 0.59% in rats and 0.7%, 1.9% in dogs,
48 respectively.

49 **Distribution**

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

52 **Metabolism**

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

65 **Elimination**

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

75 **Special Populations**

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

78 **Pediatrics**

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

82 **Drug-Drug Interactions**

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

87 **Other Short-term Studies**

88 **Adults**

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

101 **Pediatrics**

102 In a 3-week study of 32 obese adolescents aged 12 to 16 years, XENICAL (120 mg three
103 times a day) did not significantly affect the balance of calcium, magnesium, phosphorus,
104 zinc, or copper. The iron balance was decreased by 64.7 $\mu\text{mole}/24$ hours and
105 40.4 $\mu\text{mole}/24$ hours in orlistat and placebo treatment groups, respectively.

106 **Dose-response Relationship**

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

113 **CLINICAL STUDIES**

114 Observational epidemiologic studies have established a relationship between obesity and
115 visceral fat and the risks for cardiovascular disease, type 2 diabetes, certain forms of

116 cancer, gallstones, certain respiratory disorders, and an increase in overall mortality.
117 These studies suggest that weight loss, if maintained, may produce health benefits for
118 obese patients who have or are at risk of developing weight-related comorbidities. The
119 long-term effects of orlistat on morbidity and mortality associated with obesity have not
120 been established.

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

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

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

139 Weight loss was observed within 2 weeks of initiation of therapy and continued for 6 to
140 12 months.

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

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

151 **Table 1** **Percentage of Patients Losing $\geq 5\%$ and $\geq 10\%$ of Body**
 152 **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		

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

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

156 [†] Last observation carried forward

157 [‡] All studies, with the exception of 14161, were conducted at centers specialized in
 158 treating obesity and complications of obesity. Study 14161 was conducted with
 159 primary care physicians.

160

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

164 **Population as a Whole**

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

169
170

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

171 * Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus
172 diet
173 † Intent-to-treat population at week 52, observed data based on pooled data from 5
174 studies
175

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

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

190 **Effect on Weight Regain**

191 Three studies were designed to evaluate the effects of XENICAL compared to placebo in
192 reducing weight regain after a previous weight loss achieved following either diet alone
193 (one study, 14302) or prior treatment with XENICAL (two studies, 14119C and 14185).
194 The diet utilized during the 1-year weight regain portion of the studies was a weight-
195 maintenance diet, rather than a weight-loss diet, and patients received less nutritional

196 counseling than patients in weight-loss studies. For studies 14119C and 14185, patients'
197 previous weight loss was due to 1 year of treatment with XENICAL in conjunction with a
198 mildly hypocaloric diet. Study 14302 was conducted to evaluate the effects of 1 year of
199 treatment with XENICAL on weight regain in patients who had lost 8% or more of their
200 body weight in the previous 6 months on diet alone.

201 In study 14119C, patients treated with placebo regained 52% of the weight they had
202 previously lost while the patients treated with XENICAL regained 26% of the weight
203 they had previously lost ($p<0.001$). In study 14185, patients treated with placebo regained
204 63% of the weight they had previously lost while the patients treated with XENICAL
205 regained 35% of the weight they had lost ($p<0.001$). In study 14302, patients treated with
206 placebo regained 53% of the weight they had previously lost while the patients treated
207 with XENICAL regained 32% of the weight that they had lost ($p<0.001$).

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

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

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

224 **Table 3** **Percentage of Patients Losing $\geq 5\%$ and $\geq 10\%$ of Body**
 225 **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

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

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

229 [†] Last observation carried forward

230 [‡] All studies, with the exception of 14161 were conducted at centers specializing in
 231 treating obesity or complications of obesity. Study 14161 was conducted with primary
 232 care physicians.
 233

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

237 **Population as a Whole**

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

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

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

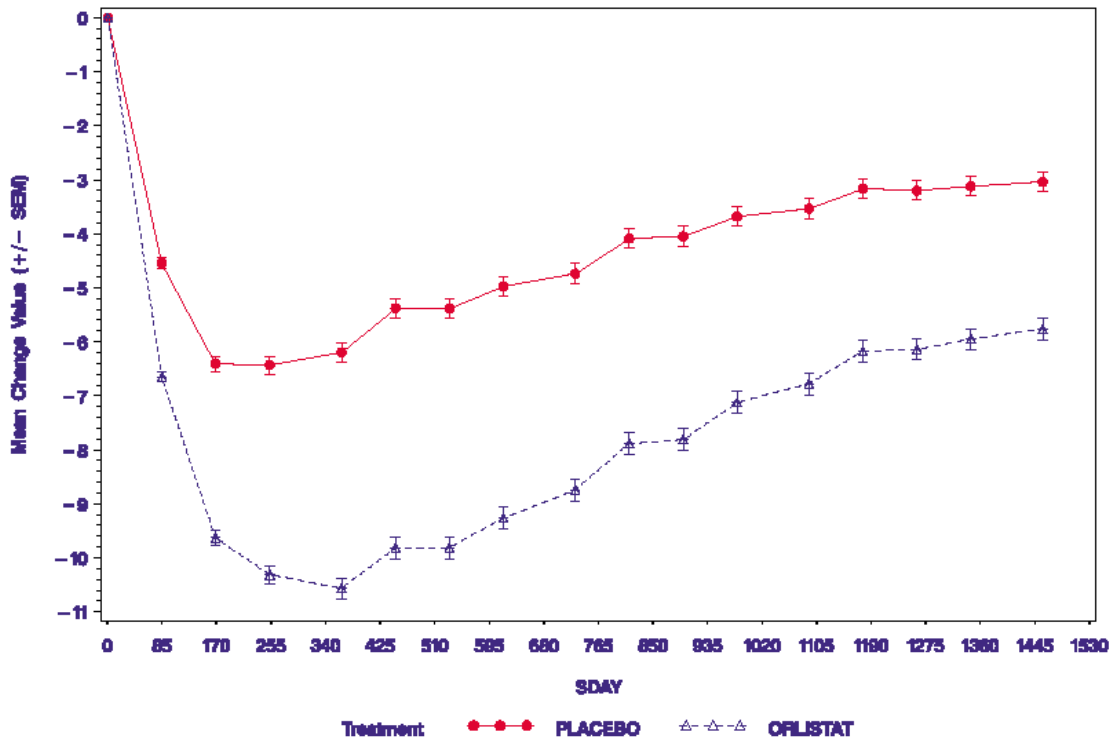
250 **Four-year Results: Long-term Weight Control and Risk Factors**

251 In the 4-year double-blind, placebo-controlled XENDOS study, the effects of orlistat in
 252 delaying the onset of type 2 diabetes and on body weight were compared to placebo in
 253 3304 obese patients who had either normal or impaired glucose tolerance at baseline.
 254 Thirty-four percent of the 1655 patients who were randomized to the placebo group and
 255 52% of the 1649 patients who were randomized to the orlistat group completed the 4-year
 256 study.

257 At the end of the study, the mean percent weight loss in the placebo group was -2.75%
 258 compared with -5.17% in the orlistat group (p<0.001) (see **Figure 1**). Forty-five percent

259 of the placebo patients and 73% of the orlistat patients lost $\geq 5\%$ of their baseline body
 260 weight, and 21% of the placebo patients and 41% of the orlistat patients lost $\geq 10\%$ of
 261 their baseline body weight following the first year of treatment. Following 4 years of
 262 treatment, 28% of the placebo patients and 45% of the orlistat patients lost $\geq 5\%$ of their
 263 baseline body weight and 10% of the placebo patients and 21% of the orlistat patients lost
 264 $\geq 10\%$ of their baseline body weight.

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



266

267

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

270 **Table 4 Mean Change in Risk Factors From Randomization**
 271 **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

272 *Treatment designates XENICAL 120 mg three times a day plus
 273 diet or placebo plus diet
 274 †Intent-to-treat population

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

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

282 **Table 5** **Mean Changes in Body Weight and Glycemic Control From**
 283 **Randomization Following 1-Year Treatment in Patients With**
 284 **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

285 Statistical significance based on intent-to-treat population, last observation carried
 286 forward.

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

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

291 ns nonsignificant, $p > 0.05$

292

293 In addition, XENICAL (n=162) compared to placebo (n=159) was associated with
 294 significant lowering for total cholesterol (-1.0% vs +9.0%, $p \leq 0.05$), LDL-cholesterol (-
 295 3.0% vs +10.0%, $p \leq 0.05$), LDL/HDL ratio (-0.26 vs -0.02, $p \leq 0.05$) and triglycerides
 296 (+2.54% vs +16.2%, $p \leq 0.05$), respectively. For HDL cholesterol, there was a +6.49%
 297 increase on XENICAL and +8.6% increase on placebo, $p > 0.05$. Systolic blood pressure
 298 increased by +0.61 mm Hg on XENICAL and increased by +4.33 mm Hg on placebo,
 299 $p > 0.05$. Diastolic blood pressure decreased by -0.47 mm Hg for XENICAL and by
 300 -0.5 mm Hg for placebo, $p > 0.05$.

301 **Glucose Tolerance in Obese Patients**

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

306 The progression from a normal OGTT at randomization to a diabetic or impaired OGTT
 307 following 2 years of treatment with XENICAL (n=251) or placebo (n=207) were
 308 compared. Following treatment with XENICAL, 0.0% and 7.2% of the patients
 309 progressed from normal to diabetic and normal to impaired, respectively, compared to
 310 1.9% and 12.6% of the placebo treatment group, respectively.

311 In patients found to have an impaired OGTT at randomization, the percent of patients
 312 improving to normal or deteriorating to diabetic status following 1 and 2 years of
 313 treatment with XENICAL compared to placebo are presented. After 1 year of treatment,
 314 45.8% of the placebo patients and 73% of the XENICAL patients had a normal oral
 315 glucose tolerance test while 10.4% of the placebo patients and 2.6% of the XENICAL
 316 patients became diabetic. After 2 years of treatment, 50% of the placebo patients and
 317 71.7% of the XENICAL patients had a normal oral glucose tolerance test while 7.5% of
 318 placebo patients were found to be diabetic and 1.7% of XENICAL patients were found to
 319 be diabetic after treatment.

320 **Onset of Type 2 Diabetes in Obese Patients**

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

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

332 **Table 6 Incidence Rate of Diabetes at Year 4 by OGTT Status at**
 333 **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	

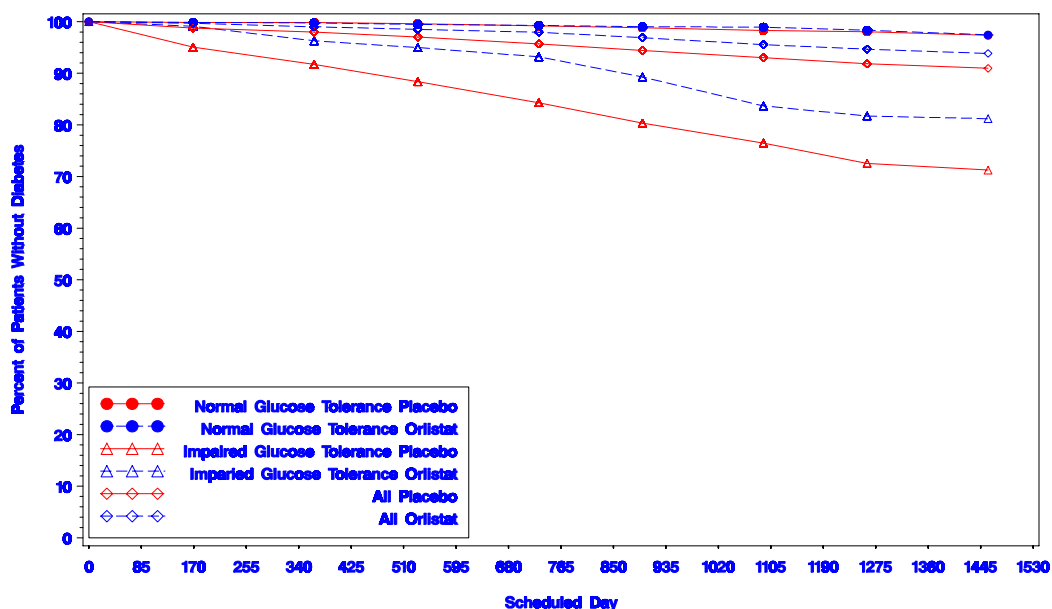
334 *Based on patients with a baseline and at least one follow-up OGTT measurement

335 †Rate adjusted for dropouts

336 †† Computed as (1- hazard ratio)

337

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



339

340 **Pediatric Clinical Studies**

341 The effects of XENICAL on body mass index (BMI) and weight loss were assessed in a
 342 54-week multicenter, double-blind, placebo-controlled study in 539 obese adolescents
 343 (357 receiving XENICAL 120 mg three times a day, 182 receiving placebo), aged 12 to
 344 16 years. All study participants had a baseline BMI that was 2 units greater than the US
 345 weighted mean for the 95th percentile based on age and gender. Body mass index was the
 346 primary efficacy parameter because it takes into account changes in height and body
 347 weight, which occur in growing children.

348 During the study, all patients were instructed to take a multivitamin containing fat-
 349 soluble vitamins at least 2 hours before or after ingestion of XENICAL. Patients were
 350 also maintained on a well-balanced, reduced-calorie diet that was intended to provide
 351 30% of calories from fat. In addition, all patients were placed on a behavior modification
 352 program and offered exercise counseling.

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

354 Following one year of treatment, BMI decreased by an average of 0.55 kg/m² in the
 355 XENICAL-treated patients and increased by an average of 0.31 kg/m² in the placebo-
 356 treated patients (p=0.001).

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

360 **Table 7 Percentages of Patients with $\geq 5\%$ and $\geq 10\%$ Decrease in**
 361 **Body Mass Index and Body Weight After 1-Year Treatment***
 362 **(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

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

365 † Last observation carried forward

366

367 INDICATIONS AND USAGE

368 XENICAL is indicated for obesity management including weight loss and weight
 369 maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also
 370 indicated to reduce the risk for weight regain after prior weight loss. XENICAL is
 371 indicated for obese patients with an initial body mass index (BMI) ≥ 30 kg/m² or
 372 ≥ 27 kg/m² in the presence of other risk factors (eg, hypertension, diabetes,
 373 dyslipidemia).

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

377 **Table 8 Body Mass Index (BMI), kg/m²***

		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

378 * Conversion Factors:

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

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

381 1 foot = 12 inches

382

383 **CONTRAINDICATIONS**

384 XENICAL is contraindicated in patients with chronic malabsorption syndrome or
385 cholestasis, and in patients with known hypersensitivity to XENICAL or to any
386 component of this product.

387 **WARNINGS**

388 **Miscellaneous**

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

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

398 **PRECAUTIONS**

399 **General**

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

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

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

417 **Table 9** **Incidence of Low Vitamin Values on Two or More**
 418 **Consecutive Visits (Nonsupplemented Adult Patients With**
 419 **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%

420 * Treatment designates placebo plus diet or XENICAL plus diet

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

423 **Table 10** **Incidence of Low Vitamin Values on Two or More**
 424 **Consecutive Visits (Pediatric Patients With Normal Baseline**
 425 **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%

426 * All patients were treated with vitamin supplementation throughout the course of the
 427 study

428 † Treatment designates placebo plus diet or XENICAL plus diet

429 There have been rare postmarketing reports of severe liver injury with hepatocellular
 430 necrosis or acute hepatic failure in patients treated with orlistat with some of these cases
 431 resulting in liver transplant or death. Patients should be instructed to report any symptoms
 432 of hepatic dysfunction (anorexia, pruritus, jaundice, dark urine, light colored stools, or
 433 right upper quadrant pain) while taking orlistat. When these symptoms occur, orlistat and
 434 other suspect medications should be discontinued immediately and liver function tests
 435 and ALT and AST levels obtained.

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

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

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

449 **Misuse Potential**

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

453 **Information for Patients**

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

456 **Drug Interactions**

457 Alcohol

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

462 Cyclosporine

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

466 Digoxin

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

469 Fat-soluble Vitamin Supplements and Analogues

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

475 Glyburide

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

479 **Levothyroxine**
480 Hypothyroidism has been reported in patients treated concomitantly with orlistat and
481 levothyroxine postmarketing (see **ADVERSE REACTIONS: Other Clinical Studies or**
482 **Postmarketing Surveillance**). Patients treated concomitantly with orlistat and
483 levothyroxine should be monitored for changes in thyroid function. Administer
484 levothyroxine and orlistat at least 4 hours apart.

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

488 **Oral Contraceptives**
489 In 20 normal-weight female subjects, the treatment of XENICAL 120 mg three times a
490 day for 23 days resulted in no changes in the ovulation-suppressing action of oral
491 contraceptives.

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

495 **Pravastatin**
496 In a 2-way crossover study of 24 normal-weight, mildly hypercholesterolemic patients
497 receiving XENICAL 120 mg three times a day for 6 days, XENICAL did not affect the
498 pharmacokinetics of pravastatin.

499 **Warfarin**
500 In 12 normal-weight subjects, administration of XENICAL 120 mg three times a day for
501 16 days did not result in any change in either warfarin pharmacokinetics (both R- and S-
502 enantiomers) or pharmacodynamics (prothrombin time and serum Factor VII). Although
503 undercarboxylated osteocalcin, a marker of vitamin K nutritional status, was unaltered
504 with XENICAL administration, vitamin K levels tended to decline in subjects taking
505 XENICAL. Therefore, as vitamin K absorption may be decreased with XENICAL,
506 patients on chronic stable doses of warfarin who are prescribed XENICAL should be
507 monitored closely for changes in coagulation parameters.

508 **Carcinogenesis, Mutagenesis, Impairment of Fertility**
509 Carcinogenicity studies in rats and mice did not show a carcinogenic potential for orlistat
510 at doses up to 1000 mg/kg/day and 1500 mg/kg/day, respectively. For mice and rats, these
511 doses are 38 and 46 times the daily human dose calculated on an area under concentration vs
512 time curve basis of total drug-related material.

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

517 When given to rats at a dose of 400 mg/kg/day in a fertility and reproduction study,
518 orlistat had no observable adverse effects. This dose is 12 times the daily human dose
519 calculated on a body surface area (mg/m²) basis.

520 **Pregnancy**

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

522 Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day.
523 Neither study showed embryotoxicity or teratogenicity. This dose is 23 and 47 times the
524 daily human dose calculated on a body surface area (mg/m²) basis for rats and rabbits,
525 respectively.

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

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

534 **Nursing Mothers**

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

537 **Pediatric Use**

538 The safety and efficacy of XENICAL have been evaluated in obese adolescent patients
539 aged 12 to 16 years. Use of XENICAL in this age group is supported by evidence from
540 adequate and well-controlled studies of XENICAL in adults with additional data from a
541 54-week efficacy and safety study and a 21-day mineral balance study in obese
542 adolescent patients aged 12 to 16 years. Patients treated with XENICAL had a mean
543 reduction in BMI of 0.55 kg/m² compared with an average increase of 0.31 kg/m² in
544 placebo-treated patients (p=0.001). In both adolescent studies, adverse effects were
545 generally similar to those described in adults and included fatty/oily stool, oily spotting,
546 and oily evacuation. In a subgroup of 152 orlistat and 77 placebo patients from the 54-
547 week study, changes in body composition measured by DEXA were similar in both
548 treatment groups with the exception of fat mass, which was significantly reduced in
549 patients treated with XENICAL compared to patients treated with placebo (-2.5 kg vs -
550 0.6 kg, p=0.033). Because XENICAL can interfere with the absorption of fat-soluble
551 vitamins, all patients should take a daily multivitamin that contains vitamins A, D, E, K,
552 and beta-carotene. The supplement should be taken at least 2 hours before or after
553 XENICAL (see **CLINICAL PHARMACOLOGY: Other Short-term Studies;**
554 **CLINICAL STUDIES: Pediatric Clinical Studies; ADVERSE REACTIONS:**
555 **Pediatric Patients**). XENICAL has not been studied in pediatric patients below the age
556 of 12 years.

557 **Geriatric Use**

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

560 **ADVERSE REACTIONS**

561 **Commonly Observed (based on first year and second year data - XENICAL**
562 **120 mg three times a day versus placebo):**

563 Gastrointestinal (GI) symptoms were the most commonly observed treatment-emergent
564 adverse events associated with the use of XENICAL in the seven double-blind, placebo-
565 controlled clinical trials and are primarily a manifestation of the mechanism of action.
566 (Commonly observed is defined as an incidence of $\geq 5\%$ and an incidence in the
567 XENICAL 120 mg group that is at least twice that of placebo.)

568 **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

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

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

576 **Discontinuation of Treatment**

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

581 **Incidence in Controlled Clinical Trials**

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

587
588

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

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

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

592

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

596 **Other Clinical Studies or Postmarketing Surveillance**

597 Rare cases of increase in transaminases and in alkaline phosphatase and hepatitis that
598 may be serious have been reported. There have been reports of hepatic failure observed
599 with the use of XENICAL in postmarketing surveillance with some of these cases
600 resulting in liver transplant or death. Rare cases of hypersensitivity have been reported
601 with the use of XENICAL. Signs and symptoms have included pruritus, rash, urticaria,
602 angioedema, bronchospasm and anaphylaxis. Very rare cases of bullous eruption have
603 been reported. Reports of decreased prothrombin, increased INR and unbalanced
604 anticoagulant treatment resulting in change of hemostatic parameters have been reported
605 in patients treated concomitantly with orlistat and anticoagulants. Hypothyroidism has
606 been reported in patients treated concomitantly with orlistat and levothyroxine.
607 Pancreatitis has been reported with the use of XENICAL in postmarketing surveillance.
608 No causal relationship or physiopathological mechanism between pancreatitis and obesity
609 therapy has been definitively established.

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

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

615 **Pediatric Patients**

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

618 **OVERDOSAGE**

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

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

625 **DOSAGE AND ADMINISTRATION**

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

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

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

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

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

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

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

645 **HOW SUPPLIED**

646 XENICAL is a dark-blue or turquoise, hard-gelatin capsule containing pellets of powder.

647 XENICAL 120 mg Capsules: Dark-blue, two-piece, No. 1 opaque hard-gelatin capsule
648 imprinted with Roche and XENICAL 120 in light-blue ink — bottle of 90 (NDC 0004-
649 0256-52).

650 XENICAL 120 mg Capsules: Turquoise, two-piece, No. 1 opaque hard-gelatin capsule
651 imprinted with ROCHE and XENICAL 120 in black ink — bottle of 90 (NDC 0004-
652 0257-52).

653 **Storage Conditions**

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

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

657 XENICAL is a registered trademark of Roche Laboratories Inc.

Distributed by:

Genentech USA, Inc.

A Member of the Roche Group

1 DNA Way

658 South San Francisco, CA 94080-4990

659

660 XLT_180647_PI_MMYYYY_N

661

662 Revised: Month Year

663 © 20XX Genentech, Inc. All rights reserved.

TO PHARMACIST: PLEASE PROVIDE THIS INFORMATION TO THE PATIENT.

Important Patient Information

Patient Information about XENICAL® (orlistat) Capsules

XENICAL (zen' i-cal)

Generic Name: orlistat

R_x only

Please read this information before you start taking XENICAL and each time you renew your prescription. This important information may help you successfully lose weight and maintain your weight loss while taking XENICAL. This patient information is a summary and is not intended to take the place of discussions with your doctor. It does not list all benefits and risks of XENICAL. The medication described here can only be prescribed and dispensed by a licensed health care professional, who has information about your medical condition and more information about the drug, including how to take it, what to expect, and potential side effects. If you have any questions about XENICAL, talk with your doctor.

What is XENICAL?

XENICAL is an oral prescription weight loss medication used to help obese people lose weight and keep this weight off. XENICAL works in your intestines, where it blocks some of the fat you eat from being absorbed. This undigested fat is then eliminated in your bowel movements. XENICAL should be used together with a reduced-calorie diet that your doctor will recommend.

Excess weight has been proven to contribute to an increased risk of developing many medical problems, including high blood pressure, high cholesterol, heart disease, and diabetes. The consumption of excess fatty food and calories plays a significant role in the development of excess weight. While fat is an important component of a balanced diet, the consumption of excess fat contributes to excess body weight, since fat provides twice the number of calories per gram of weight as carbohydrates and protein. Reduction of dietary fat intake is one potential way of losing weight.

How does XENICAL work?

If you eat an excess amount of fat or calories, the excess is stored as fat by the body resulting in weight gain. When you eat fat, your body breaks it down into its simplest components so that it can be absorbed. Enzymes in your intestinal tract, called lipases, help digest (or break down) fat. When you take XENICAL with meals, XENICAL attaches to the lipases and blocks them from breaking down some of the fat you have eaten. The undigested fat cannot be absorbed and is eliminated in your bowel movements. By working this way, XENICAL helps block about 30% of the fat eaten in food from being absorbed by your body.

Information for adult obese patients

Following one year of treatment, XENICAL in combination with diet was shown to be more effective in reducing weight than diet alone. In most cases, weight loss was gradual. Patients treated with XENICAL and a reduced-calorie diet for one year lost an average of 13.4 pounds while those on a reduced-calorie diet alone lost 5.8 pounds.

Information for adolescent obese patients

Following one year of treatment, XENICAL in combination with diet was shown to be more effective in reducing Body Mass Index (BMI) than diet alone. A reduction in Body Mass Index is a better indicator of weight loss in children because it takes into account changes in weight related to growing children.

Who should use XENICAL?

A weight loss program that includes a reduced-calorie diet and appropriate physical activity may be adequate in some patients. You should discuss with your doctor or other health care provider whether XENICAL should be added to such a program.

XENICAL may be right for you if you are considerably overweight (at least 30% above ideal weight or a body mass index of 30 or greater). XENICAL may also be right for you if you are overweight (at least 20% above ideal weight or a body mass index of 27 or greater) and also have other risk factors such as high blood pressure, high cholesterol, heart disease, or diabetes.

How to determine your body mass index (BMI):

The chart below illustrates BMI according to a variety of weights and heights. The BMI is calculated by dividing your weight in kilograms by your height in meters squared. To use this chart:

- Find the height closest to your height in the left-hand column.
- Then move across the top row to find the weight closest to your weight.
- The number where these two meet is your BMI. (For example, a person who weighs 180 lbs and is 5'5" would have a BMI of 30.)

		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

Who should not use XENICAL?

Those who:

- consistently have problems absorbing food (chronic malabsorption); or
- have gallbladder problems; or
- are pregnant or are breastfeeding a child; or
- have ever had an allergic reaction to orlistat or any of the inactive ingredients in XENICAL.

What should I tell my doctor before taking XENICAL?

Before beginning treatment with XENICAL, make sure your doctor knows if you are:

- allergic to any medicines, foods, or dyes;
- taking any other weight-loss medication;
- taking cyclosporine;
- taking thyroid medicine;
- taking any other medicines (including those not prescribed by your doctor);
- taking any dietary supplements, including herbal products;
- planning to become pregnant; or
- anorexic or bulimic.

This information will help you and your physician decide if the expected advantages of XENICAL are greater than any possible disadvantages.

How should I take XENICAL?

The recommended dose is one 120 mg capsule by mouth with liquid at each main meal that contains fat. You can take XENICAL in conjunction with a mildly reduced-calorie diet up to 3 times a day. Each time you take XENICAL, your meal should contain no more than about 30% of calories from fat. Take XENICAL during meals or up to one hour after a meal. If you occasionally miss a meal or have a meal without fat, you can omit your dose of XENICAL. Doses greater than 120 mg three times a day have not been shown to provide an additional weight loss benefit.

You should use XENICAL together with a nutritionally balanced, mildly reduced-calorie diet that contains no more than about 30% of calories from fat. You should evenly divide your daily intake of fat, carbohydrates, and protein over 3 main meals.

You should try to follow a healthy eating plan such as the one developed by the American Heart Association. Following this eating plan will help you lose weight while decreasing some of the possible gastrointestinal effects you may experience while taking XENICAL.

IF YOUR DAILY CALORIE LEVEL IS:	THE RECOMMENDED DAILY GRAMS OF FAT (in a 30% fat diet) ARE:
1500	50
1600	53
1800	60
2000	67

What are the possible risks of XENICAL?

- XENICAL has been shown to reduce the absorption of certain vitamins. You should take a multivitamin containing vitamins D, E, K, and beta-carotene once a day at least 2 hours before or after the administration of XENICAL, such as at bedtime.
- Some patients taking XENICAL may develop an increased risk for the development of kidney stones. Promptly report any symptoms of back pain or blood in the urine.
- Some patients prescribed XENICAL may already be at increased risk for the formation of gall stones. Weight loss with XENICAL can increase the risk of gall stones. Promptly report any symptoms of pain in the upper right portion of the abdomen. The pain may be accompanied by nausea and vomiting.
- There have been rare reports of severe liver injury in patients taking XENICAL. Promptly discontinue XENICAL and contact your healthcare provider if you develop symptoms suggestive of liver impairment, such as loss of appetite, itching, yellowing of the skin, dark urine, light colored stools, or right upper quadrant pain.

Can I take XENICAL while taking other medications?

Be sure to discuss with your doctor all medications (including herbal products) you are currently taking, including medicines you can get without a prescription (over-the-

counter), to determine if XENICAL can be taken in addition to these medications. If you are taking cyclosporine, XENICAL and cyclosporine should be taken at least 2 hours apart. If your cyclosporine levels are being measured, more frequent monitoring may be necessary. If you are taking levothyroxine, XENICAL and levothyroxine should be taken at least 4 hours apart.

How long should I use XENICAL?

The use of XENICAL for more than 4 years has not been studied. You and your doctor should discuss how long you should use XENICAL.

What are the most common side effects of XENICAL?

Because XENICAL works by blocking the absorption of dietary fat, it is likely that you will experience some changes in bowel habits. These generally occur during the first weeks of treatment; however, they may continue throughout your use of XENICAL. These changes may include oily spotting, gas with discharge, urgent need to go to the bathroom, oily or fatty stools, an oily discharge, increased number of bowel movements, and inability to control bowel movements. Due to the presence of undigested fat, the oil seen in a bowel movement may be clear or have a coloration such as orange or brown.

These bowel changes are a natural effect of blocking the fat from being absorbed and indicate that XENICAL is working. They generally occur early in treatment, particularly after meals containing higher amounts of fat than are recommended. These symptoms are often temporary and may lessen or disappear as you continue treatment and keep to your recommended diet of meals containing no more than about 30% fat. However, these side effects may occur in some individuals over a period of 6 months or longer.

In obese adolescent patients treated with XENICAL, the side effects reported were similar to those observed in adults.

If you are concerned about these or any other side effects you experience while taking XENICAL, talk to your doctor or pharmacist.

What lifestyle changes should I consider when taking XENICAL?

You must use XENICAL with a recommended mildly reduced-calorie diet. You should also follow a program of regular physical activity, such as walking. **However, before you undertake any activity or exercise program, be sure to speak with your doctor or health care professional.**

How can I reduce dietary fat?

To help you get started on reducing the fat in your diet to around 30%, read the labels on all the foods you buy. You should avoid foods that contain more than 30% fat while you are taking XENICAL.

- When eating meat, poultry or fish, limit your portion to 2 or 3 ounces (roughly the size of a deck of cards). Choose lean cuts of meat and remove the skin from poultry. Fill up your meal plate by including more grains, fruits, and vegetables.
- Replace whole-milk products with nonfat or 1% milk and nonfat, reduced-fat, or low-fat dairy items.

- Cook with less fat. Use vegetable oil spray when cooking. Salad dressings, many baked items, and prepackaged, processed, and fast foods are usually high in fat. Use the low- or non-fat versions and/or cut back on serving sizes.
- When dining out, ask how foods are prepared and request that they be prepared with little or no added fat.

Please visit www.xenical.com to help you succeed with your weight loss goals.

XENICAL is a registered trademark of Roche Laboratories Inc.

Distributed by:

Genentech USA, Inc.

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

XLT_180647_PPI_032010_N

Revised: Month Year

© 2010 Genentech, Inc. All rights reserved.