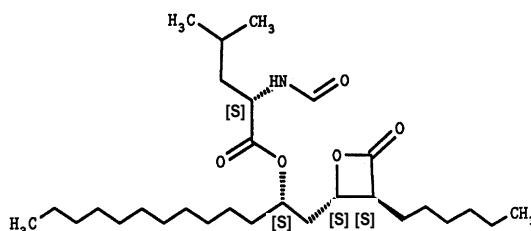


NAME OF THE MEDICINE

XENICAL®

orlistat

CAS: 96829-58-2



The chemical name for orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. The molecular formula is C₂₉H₅₃NO₅. Orlistat has a molecular weight of 495.7.

DESCRIPTION

Orlistat is a white to off-white crystalline powder. Orlistat is practically insoluble in water, freely soluble in chloroform and very soluble in methanol and ethanol. Orlistat is not capable of ionising within the physiological pH range.

XENICAL is available as hard gelatin capsules containing 120 mg of orlistat. Each capsule also contains the inactive ingredients: microcrystalline cellulose, sodium starch glycolate, povidone, sodium lauryl sulfate and talc. Each capsule shell contains gelatin, indigo carmine (CI 73015) and titanium dioxide. The printing ink contains shellac, lecithin, dimethicone 1510 and iron oxide black (CI 77499).

PHARMACOLOGY

Pharmacodynamics

XENICAL (orlistat) is the first of a new class of anti-obesity agents with a unique mode of action. XENICAL is a potent, specific and reversible long acting inhibitor of gastrointestinal lipases, which are required for the systemic absorption of dietary triglycerides.

XENICAL selectively inhibits gastrointestinal (GI) lipase activity within the GI tract and prevents the absorption of 30% of dietary fat, thus producing a weight-loss effect. XENICAL acts by forming a covalent bond with the active serine site of gastric and pancreatic lipases in the lumen of the stomach and small intestine. The inactivated enzyme is thus unable to hydrolyse dietary fat, in the form of triglycerides, into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit has a positive effect on weight control. No systemic absorption is required to exert its therapeutic effect.

XENICAL had no significant effects on the physiological function of the GI tract, nor did it significantly influence systemic lipase activity.

Based on faecal fat measurements, the effect of XENICAL is seen as soon as 24 to 48 hours after dosing. Upon discontinuation of therapy, faecal fat content usually returns to pre-treatment levels, within 48 to 72 hours.

Pharmacokinetics

Absorption and Bioavailability

Studies in normal weight and obese volunteers have shown that the extent of absorption of orlistat was minimal. Plasma concentrations of intact orlistat were non-measurable (< 5 ng/mL) eight hours following oral administration of a single-dose of 360 mg orlistat.

In general, after treatment for up to two years at therapeutic doses, detection of intact orlistat in plasma was sporadic and concentrations were extremely low (<10 ng/mL or 0.02 µM), without evidence of accumulation, and consistent with negligible absorption.

Distribution

The volume of distribution cannot be determined because the drug is minimally absorbed. *In vitro* orlistat is > 99% bound to plasma proteins (lipoproteins and albumin were the major binding proteins). Orlistat minimally partitions into erythrocytes.

Metabolism

Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on a study in obese patients, of the minute fraction of the dose that was absorbed systemically, two major metabolites, M1 (4-member lactone ring hydrolysed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of the total plasma concentration. Concentrations of these metabolites were low, averaging 26 ng/mL and 108 ng/mL respectively. In view of the extremely weak inhibitory effect on systemic lipases (1000 and 2500-fold lower than orlistat respectively) and low plasma concentrations, these metabolites are considered to be pharmacologically inconsequential.

Elimination

Studies in normal weight and obese subjects have shown that faecal excretion of the unabsorbed drug was the major route of elimination. This is consistent with the minimal absorption and gastrointestinal site of action of orlistat. Approximately 97% of the administered dose was excreted in faeces and 83% of the total dose excreted was unchanged orlistat.

The cumulative renal excretion of total orlistat-related materials was < 2% of the given dose. The time to reach complete excretion (faecal plus urinary) was 3 to 5 days. The disposition of orlistat appeared to be similar between normal weight and obese volunteers. Orlistat and the metabolites M1 and M3 are subject to biliary excretion.

Long Term Administration

Evidence from 5 phase III studies demonstrated an extremely low degree of systemic exposure to orlistat and a lack of accumulation in plasma after long-term treatment for up to 2 years.

Special Populations

As XENICAL is minimally absorbed and has a non-systemic mode of action, studies in special populations (geriatric, paediatric, different races, and patients with renal and hepatic insufficiency) were not conducted.

Clinical Trials

Observational epidemiologic studies have established a relationship between obesity, visceral fat and the risks for cardiovascular disease, type II diabetes, certain forms of cancer, gallstones, certain respiratory disorders and an increase in overall mortality. These studies suggest that weight loss, if maintained, may produce health benefits for obese patients who have or are at risk of developing weight-related comorbidities. Since fat provides twice the number of calories per gram as carbohydrates and protein, a selective reduction of calories from the dietary fat intake is a more efficient way of producing weight loss. The long term effects of XENICAL on morbidity and mortality have not been established.

The effects of XENICAL on weight loss, weight maintenance, weight regain and on a number of comorbidities were assessed in the 4-year XENDOS study and in seven multicentre phase III double-blind, placebo-controlled, parallel group studies of 1- to 2-years duration. During the first year of therapy, the studies of 2-year duration assessed weight loss and weight maintenance. During the second year of therapy, some studies assessed continued weight loss and weight maintenance and others assessed the prevention of weight regain. These studies included over 2800 patients treated with XENICAL and 1400 patients treated with placebo. The majority of studies had inclusion criteria of a body mass index (BMI) of 28 - 43 and age greater than 18 years. XENICAL also demonstrated beneficial effects in those patients who were diet-resistant. In the XENDOS study, which included 3304 patients, the time to onset of non-insulin dependent diabetes mellitus was assessed in addition to long-term weight management.

During the weight loss and weight maintenance period, a well-balanced, mildly hypocaloric diet that provided 30% of calories from fat was recommended to all patients.

XENICAL has been shown to be safe and efficacious for long-term treatment for up to 4 years. Possible weight regain and/or attenuation of weight loss may occur after 1 year (Figure 2). Patients who participated in the 4 year XENDOS trial were aged between 30-60 years at enrolment.

The weight loss achieved with XENICAL was associated with significant improvement of risk factors i.e. improved lipid profile (LDL/HDL ratio), reduced total cholesterol, reduced LDL-cholesterol, reduced systolic and diastolic blood pressure, reduced fasting glucose and insulin levels and a reduction in waist circumference, which is associated with reduced visceral adiposity. Improved cardiovascular risk status and improvements in glycaemic control, as shown by reductions in the number of diabetic or impaired patients upon glucose tolerance testing, were determined and are in accordance with the reduction in these risk factors.

XENICAL produced weight loss greater than diet alone only when used in conjunction with a hypocaloric diet.

One-year Results: Weight Loss, Weight Maintenance, Risk Factors and Quality of Life

Weight loss was observed within 2 weeks of initiation of therapy and continued for 6 to 12 months. Weight loss was evident even in those patients where diet alone had failed to induce a significant weight loss. The weight loss was maintained with continued therapy.

During the weight loss and weight maintenance period, a well-balanced mildly hypocaloric diet that provided 30% calories from fat was recommended. The diet was calculated using initial body weight to provide a caloric deficit of 2.1 to 3.3 kilojoules (500 to 800 calories) per day, which represents an average caloric decrease of 20%. In addition, all patients were offered nutritional counselling.

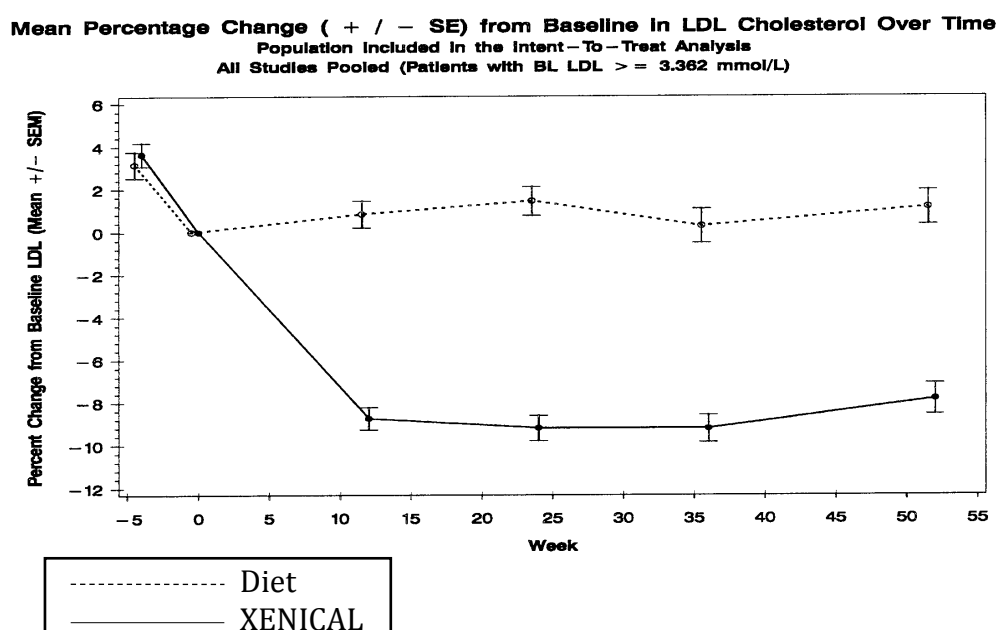
The percentages of patients achieving a > 5% and > 10% weight loss after 1 year in the largest multicentre study (Protocol BM 14119C) for the intent-to-treat population are shown in Table 1.

Table 1. Weight Loss at One Year of Treatment - XENICAL 120 mg three times daily

	Percentage of Patients Losing Weight Intent-to-Treat Population	
	> 5% of Initial Body Weight	> 10% of Initial Body Weight
XENICAL (<i>n</i> = 339)	68.5 %	39.0 %
Diet Alone (<i>n</i> = 337)	49.1 %	17.6 %

One year of therapy with XENICAL also resulted in clinically and statistically significant improvements in many risk factors associated with obesity compared to placebo treatment. The rapid improvement of risk factors included total cholesterol, LDL-cholesterol (see Figure 1), LDL/HDL ratio, systolic and diastolic blood pressure, fasting glucose and fasting insulin. Subpopulations with fasting insulin \geq 120 pmol/L or LDL-cholesterol \geq 3.362 mmol/L had clinically and statistically significant improvements in these risk factors compared to placebo at the end of 1 year of treatment.

Figure 1. Reduction of Elevated LDL-cholesterol ≥ 3.362 mmol/L with XENICAL 120 mg three times daily



The reduction in total cholesterol and LDL cholesterol and the rapid improvement in LDL/HDL ratio produced by XENICAL is independent of weight loss as was demonstrated in an 8-week study in normal weight hyperlipidaemic patients (see *Short-term Studies*).

In addition, anthropometric measurements, including waist circumference and measurements of body composition, showed significant decreases in body fat including a decrease of up to 30% in visceral adipose tissue (Protocols NM 14161, NM 14185, BM 14119B, BM 14119C, BM 14149). A statistically significant difference in the satisfaction with treatment aspect of the Quality of Life questionnaire was observed over 1 year in favour of XENICAL compared to placebo, although both groups showed worsening.

Two-year Results: Long-term Weight Control, Risk Factors and Quality of Life

XENICAL was shown to be more effective than placebo in long-term weight control in four large, multicentre, 2-year double-blind, placebo-controlled studies (Protocols BM 14119C, NM 14161, BM 14149, NM 14185). At the end of year one the patients' diets were reviewed and changed where necessary. The diet prescribed in the second year was designed for weight maintenance rather than to produce additional weight loss.

Fifty-two percent (52%) of all patients who were treated with 120 mg three times daily of XENICAL and completed 2 years of the same therapy had $> 5\%$ weight loss. The weight loss advantage between XENICAL 120 mg three times daily and diet-alone treatment groups was the same after 2 years as for 1 year, indicating that the pharmacologic advantage of XENICAL was maintained over 2 years. In the same study cited in the *One-year Results* (Protocol BM 14119C), the percentages of patients achieving a $> 5\%$ and $> 10\%$ weight loss after 2 years are shown in Table 2.

Table 2. Weight Loss after Two Full Years of Treatment - XENICAL 120 mg three times daily

	Percentage of Patients Losing Weight Intent-to-Treat Population	
	> 5% of Initial Body Weight	> 10% of Initial Body Weight
XENICAL (<i>n</i> = 135)	57.1 %	33.8 %
Diet Alone (<i>n</i> = 126)	37.6 %	14.6 %

Compared to placebo, 2 years of therapy with XENICAL also resulted in clinically and statistically significant improvements in many risk factors associated with obesity. A sustained improvement in total cholesterol, LDL-cholesterol, LDL/HDL ratio, fasting glucose and fasting insulin was observed. Subpopulations with fasting insulin ≥ 120 pmol/L or LDL-cholesterol ≥ 3.362 mmol/L who were treated with XENICAL had clinically and statistically significant improvements in these risk factors compared to placebo at the end of 2 years of treatment.

In addition, in patients treated with XENICAL, anthropometric measurements, including waist circumference and measurements of body composition, showed significant decreases in body fat. A statistically significant difference in quality of life (overweight distress and satisfaction with treatment) was observed over 2 years in favour of XENICAL compared to diet alone.

Ancillary studies conducted during BM 14119C and BM 14149 showed that the majority of weight loss was loss in fat mass, which consistently accounted for more than 75% of total weight lost.

Prevention of Weight Regain

Three separate studies (Protocols NM 14302, NM 14185, BM 14119C) evaluated the effect of XENICAL on the prevention of weight regain in patients who previously lost at least 5% of their initial body weight.

In two of the studies (Protocols NM 14185, BM 14119C), by the end of the second year the patients receiving dietary and counselling treatment alone regained a mean of 56% of their lost weight after 1 year, while patients treated with XENICAL regained a mean of 31%. The third study (Protocol NM 14302) was conducted to evaluate the effect of XENICAL on prevention of weight regain in patients who lost 8% or more of their initial body weight with diet alone. There was significantly less weight regain in patients treated with XENICAL than with diet alone. Patients receiving dietary and counselling treatment alone regained a mean of 59% of their lost weight, while patients treated with XENICAL regained a mean of 33%.

For all three studies, approximately one-half of the patients treated with XENICAL regained no more than 25% of their lost weight. For all three studies, approximately one-quarter of patients either did not regain any weight at all or continued to lose weight.

Four-Year Results: Long-term Weight Control and Risk Factors

In the XENDOS study (a 4-year multicentre, randomised, double-blind, parallel group, placebo-controlled trial), the effects of XENICAL treatment on long-term weight management and progression to non-insulin dependent diabetes mellitus (type 2 diabetes) in obese patients (BMI ≥ 30 kg/m² in males and females) were compared to placebo in 3304 obese patients who had either normal or impaired glucose tolerance at baseline. Thirty-four percent of the 1655 patients who were randomised to the placebo group and 52% of the 1649 patients who were randomised to the XENICAL group completed the 4-year study. Patients were aged between 30 - 60 years at the time of enrolment.

XENICAL was shown to be more effective than placebo in long-term weight control. Results showed that 73% of the XENICAL-treated patients lost $\geq 5\%$ of baseline body weight after 1 year of treatment compared with 45% of the placebo-treated patients ($p < 0.001$). In addition, 41% of the XENICAL-treated patients lost $\geq 10\%$ of body weight after 1 year compared with 21% of the placebo-treated patients ($p < 0.001$). Mean change in body weight was -10.56 kg for the XENICAL treatment group compared to -6.19 kg for the placebo treatment group at the end of the first year of treatment ($p < 0.001$). After 4 years of treatment, 44.8% and 21% of the XENICAL-treated patients lost $\geq 5\%$ and $\geq 10\%$ of body weight compared to 28.0% and 10% of the placebo treated patients, respectively ($p < 0.001$). Mean change in body weight after 4 years of treatment was -5.75 kg for the XENICAL treatment group compared to -3.03 kg for the placebo treatment group ($p < 0.001$).

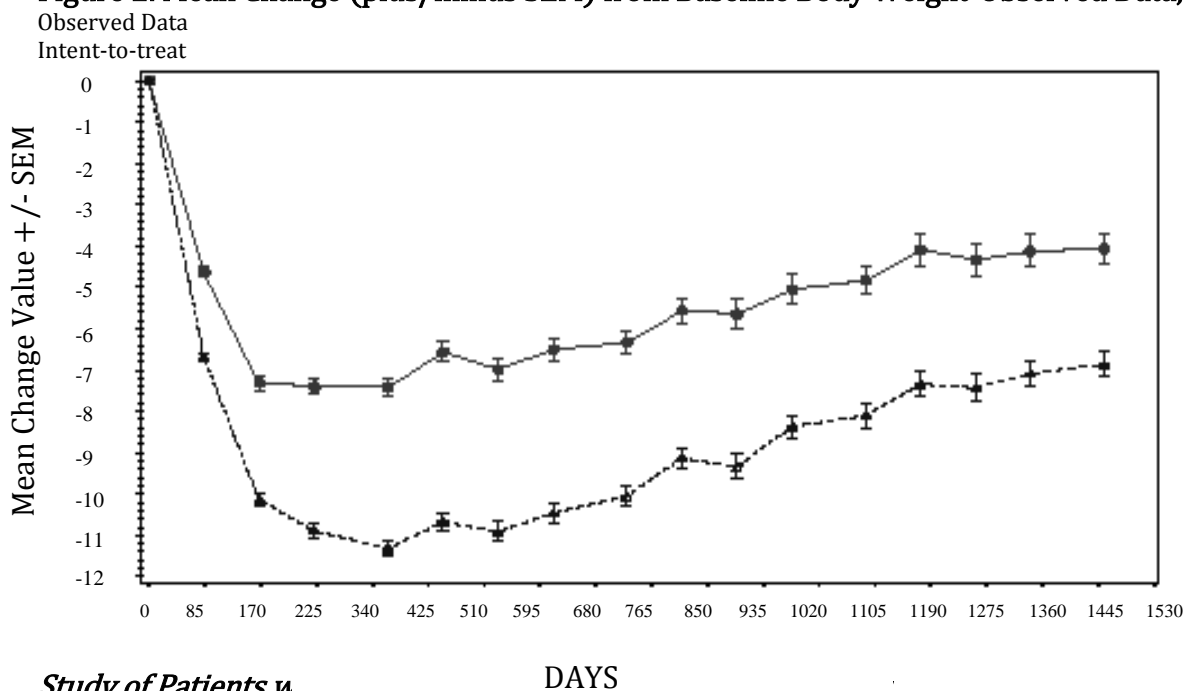
Throughout the entire four-year treatment period, XENICAL-treated compared to placebo-treated patients had statistically significant ($p < 0.001$) reductions in several metabolic risk factors in addition to BMI. These included total cholesterol, LDL cholesterol, LDL:HDL ratio, fasting insulin, fasting glucose, plasminogen activator inhibitor, and waist circumference. Statistically significant improvements over placebo in systolic and diastolic blood pressure were also observed. The relative changes in risk factors associated with obesity following 4 years of therapy are summarised in Table 3.

Table 3. Mean Change in Risk Factors From Randomisation Following 4-Years Treatment

Risk Factor	XENICAL 120 mg	Placebo	<i>p</i> -value
Metabolic:			
Total Cholesterol	-7.02%	-2.03%	<0.001
LDL-Cholesterol	-11.66%	-3.85%	<0.001
HDL-Cholesterol	+5.92%	+7.01%	0.055
LDL/HDL	-0.53	-0.33	<0.001
Triglycerides	+3.64%	+1.30	0.075
Fasting Glucose, mmol/L	+0.12	+0.23	<0.001
Fasting Insulin, pmol/L	-24.93	-15.71	<0.001
Fibrinogen, µmol/L	-0.07	+0.08	0.019
Plasminogen Activator Inhibitor (PAI-1), µmol/L	-3.17	-0.57	<0.001
Cardiovascular:			
Systolic Blood Pressure, mm Hg	-4.12	-2.60	<0.001
Diastolic Blood Pressure, mm Hg	-1.93	-0.87	<0.001
Anthropometric:			
Waist Circumference, cm	-5.78	-3.99	<0.001

During the course of the XENDOS trial weight regain was observed for both XENICAL- and placebo-treated patients (Figure 2). The difference between XENICAL vs. placebo patients narrows during the study but there remains a significant difference between XENICAL- and placebo-treated patients at four years.

Figure 2. Mean Change (plus/minus SEM) from Baseline Body Weight-Observed Data, ITT



Study of Patients w

A 1-year double-bl Treatment \rightarrow placebo \leftarrow Δ Δ Δ (Protocol NM 14336) in non-insulin dependent diabetics stabilised on sulfonylureas, was conducted. The results indicate that 49% of patients treated with XENICAL ($n = 163$) achieved a > 5% reduction in

body weight compared to only 23% of the diet-alone patients ($n = 159$). XENICAL also improved glycaemic control in these patients as evidenced by statistically significant reductions in the doses of sulfonylureas, fasting blood glucose levels and haemoglobin A1c levels (0.5% improvement versus placebo). In this study, 43% of patients treated with XENICAL were able to reduce or discontinue their oral hypoglycaemic medications compared to 29% of the patients receiving placebo. There were also statistically significant improvements in total cholesterol, LDL-cholesterol, LDL/HDL ratio and triglycerides in the group treated with XENICAL compared to diet alone.

Glucose Tolerance in Obese Patients

Two-year studies that included oral glucose tolerance tests were conducted in obese patients whose baseline oral glucose tolerance test (OGTT) status was either normal, impaired or diabetic. The baseline OGTT status improved in those patients treated with XENICAL greater than those on placebo.

The progression from normal at baseline to diabetic status in the group treated with XENICAL was 0.0%, as compared to 1.3% of placebo patients. XENICAL prevented or reversed the progression from normal to diabetes. The progression from impaired status at baseline (and thus at greatest risk for developing diabetes) to diabetic status decreased in those treated with XENICAL, whose normalisation of glucose status was markedly greater (see Table 4).

In patients found to be diabetic at baseline, the glucose status of patients treated with XENICAL improved more than placebo. For all patients, the status at baseline and the change over 2 years of treatment are given in Table 4.

Table 4. Change in Oral Glucose Tolerance Test (OGTT) Status after Two Full Years of Treatment

Baseline OGTT Status	Post-2-year OGTT Status	% XENICAL Patients at Post-treatment Status	% Placebo Patients at Post-treatment Status
Normal	Deteriorated to Impaired	2.2	7.5
	Deteriorated to Diabetic	0.0	1.3
Impaired	Deteriorated to Diabetic	4.3	25.0
	Improved to Normal	65.2	41.7
Diabetic	Improved to Normal	13.3	11.1
	Improved to Impaired	46.6	11.1

Time to Onset of Non-insulin Dependent Diabetes Mellitus in Obese Patients

In the XENDOS trial, over the 4-year treatment period there was a 37.3% relative reduction in the risk of developing non-insulin dependent diabetes mellitus in the XENICAL-treatment group compared to the placebo group. XENICAL-treatment delayed the onset of non-insulin dependent diabetes mellitus such that at the end of four years of treatment, the cumulative incidence rate of diabetes was 9.04% for the placebo group compared to 6.15% for the XENICAL group ($p < 0.01$).

For patients with impaired glucose tolerance (IGT) at baseline, the difference in the cumulative incidence rate was highly significant ($p < 0.01$). Over the 4-year treatment period, the relative risk of developing non-insulin dependent diabetes mellitus was reduced by 44.9% in the XENICAL group compared to the placebo group.

The effect of XENICAL in delaying the onset of non-insulin dependent diabetes mellitus is as a consequence of the weight loss due to XENICAL.

Treatment in the XENDOS study consisted of XENICAL or placebo plus dietary and lifestyle modifications.

Short-term Studies

In an 8-week study (Protocol S 12828), XENICAL produced a 5% greater decrease in total and LDL-cholesterol and a rapid improvement of the LDL/HDL ratio compared to placebo when administered to non-obese patients with moderate familial hypercholesterolemia (LDL-cholesterol ≥ 4.2 mmol/L). The patients were on a weight-maintaining, lipid-lowering diet for 6 weeks prior to treatment with XENICAL or placebo. A subgroup of patients with LDL-cholesterol ≥ 4.9 mmol/L had a 15% greater decrease in LDL-cholesterol compared to placebo following treatment with XENICAL. These improvements were independent of weight loss.

In several studies of 6-weeks duration, the effects of therapeutic doses of XENICAL on gastrointestinal and systemic physiological processes were assessed in normal weight subjects. There were no clinically significant changes observed in gall bladder motility, bile composition and lithogenicity or colonic cell proliferation rate, and no clinically significant reduction of gastric emptying time and gastric acidity. In addition, no effect on plasma triglyceride metabolism, systemic lipases, plasma and urinary minerals or electrolytes has been observed with the administration of XENICAL in these studies.

Obese Adolescents

Only limited data on the safety and efficacy of XENICAL in adolescents is available. One clinical trial showed that obese adolescents (12-16 years at screening) treated with XENICAL for one year had a decreased BMI, while those in the placebo group had an increased BMI. The magnitude of the effect seen with XENICAL on adolescents in this study was substantially less than that seen in adults in other studies. The adverse events profile was generally similar to that observed in adults (see ADVERSE EFFECTS). However, there was an unexplained increase in the incidence of bone fractures (6% versus 2.8% in the XENICAL and placebo groups, respectively).

INDICATIONS

XENICAL is indicated for the treatment of obese patients with a body mass index (BMI) ≥ 30 , and overweight patients with a BMI ≥ 27 in the presence of other risk factors, in conjunction with a mildly hypocaloric diet.

CONTRAINDICATIONS

XENICAL is contraindicated in patients with:

- hypersensitivity to orlistat or to any of the excipients in the capsule

- pancreatic enzyme deficiency or chronic pancreatitis and major gastrointestinal surgery
- chronic malabsorption syndrome
- cholestasis.

PRECAUTIONS

General

No serious adverse reactions or safety hazards related to the use of XENICAL have been reported to date during large, long-term clinical trials (see ADVERSE EFFECTS).

In addition to clinical trial data, post-marketing information is now available (see ADVERSE EFFECTS, Post-Marketing Experience).

Information for Patients

Patients should be advised to adhere to dietary guidelines (see DOSAGE AND ADMINISTRATION). The possibility of experiencing gastrointestinal events (see ADVERSE EFFECTS) may increase when XENICAL is taken with a diet high in fat (in a 8.4 kilojoule/day diet (2000 calorie/day), a diet high in fat would contain > 30% calories from fat, which equates to > 67 g fat). The daily intake of fat should be distributed over three main meals. If XENICAL is taken with any one meal very high in fat, the possibility of gastrointestinal effects may increase.

Consumption of a diet low in fat will decrease the likelihood of experiencing adverse gastrointestinal events and this may help patients to monitor and regulate their fat intake. Patients should be advised of the merits of reducing the saturated fats in their diet whilst preserving an adequate intake of unsaturated fats including omega fatty acids.

Patients should be on a nutritionally balanced hypocaloric diet containing no more than 30% of calories as fat (≤ 67 g of fat/day) and should also have an adequate intake of fat-soluble vitamins.

Use in Paediatric Patients

The safety and efficacy of XENICAL in children have not been established.

Use in the Elderly

No dosage adjustment is required in elderly patients.

Use in Patients with Other Disorders

XENICAL should be administered with due caution in patients with active peptic ulcer disease, chronically treated psychiatric/neurologic disorders, symptomatic cholelithiasis, postsurgical adhesions, bulimia or laxative abuse and patients with significant cardiac, renal, hepatic, GI or endocrine disorders.

XENICAL should be administered with due caution in obese patients with nephrolithiasis (renal stones) due to trends showing increased oxalate excretion in both healthy and obese subjects.

Use in Patients with Vitamin Deficiency

There are no clinical data on the use of XENICAL in patients with vitamin deficiency.

XENICAL should be administered with due caution in those patients who have a deficiency of fat-soluble vitamins (A, D, E and K). Patients taking XENICAL showed a greater reduction in vitamins D, E and beta carotene levels compared to placebo during two or more consecutive visits in studies of 1 – 2 years duration. These patients did not receive prior vitamin supplementation.

In a 4-year study, vitamin supplements were administered to patients who had low baseline vitamin values, or who experienced a decrease in their vitamin values during treatment. Over the course of the study treatment with XENICAL resulted in a decrease in the levels of fat soluble vitamins A, D, E and K. More XENICAL- than placebo-treated patients had falls in vitamins A and E. However in both XENICAL and placebo treatment groups the mean plasma levels of fat soluble vitamins remained within the normal reference ranges at all times during the study.

Effects on Ability to Drive and Use Machines

No effects on the ability to drive and to use machines have been reported by patients taking XENICAL.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenicity studies in rats and mice have not shown a carcinogenic potential for orlistat at oral doses up to 1000 mg/kg/day and 1500 mg/kg/day, respectively. Systemic exposure in these studies, in terms of the plasma C_{max} for parent drug, was at least 5 times (mouse) and 270 times (rat) that in humans at the recommended dose. There was a decreased incidence of mammary fibroadenoma in female rats in the high dose group.

Orlistat has no detectable genotoxic activity as determined by a bacterial reverse mutation assay, a mammalian forward mutation assay (V79/HGPRT), an *in vitro* clastogenesis assay in peripheral human lymphocytes, an unscheduled DNA synthesis assay (UDS) in rat hepatocytes in culture, and an *in vivo* mouse micronucleus test.

Fertility and reproductive performance were not affected in a study in rats given oral doses of up to 400 mg/kg/day which corresponds to a systemic exposure, in terms of plasma C_{max} for parent drug, at least 95 times higher than that in women at the recommended dose.

Use in Pregnancy – Category B1

Orlistat was not embryotoxic or teratogenic in rats or rabbits at oral doses of up to 800 mg/kg/day, associated with systemic exposures (in terms of plasma C_{max} for parent drug) of 100 times (rat) and 3 times (rabbit) that in humans at the recommended dose.

Administration of orlistat to rats from late gestation to weaning at oral doses up to 400 mg/kg/day, associated with systemic exposures (plasma C_{max} for parent drug) of 50 times that in humans at the recommended dose, did not affect pup survival or development. However, the safety of XENICAL has not been established in pregnant women, and because animal reproduction studies are not always predictive of human response, caution should be exercised before XENICAL is prescribed during pregnancy.

Use in Lactation

It is not known whether orlistat is excreted in human milk. XENICAL should not be taken during breast-feeding.

INTERACTIONS WITH OTHER MEDICINES

Alcohol: In a multiple-dose study in 30 normal weight subjects, coadministration of XENICAL and 40 grams of alcohol (e.g. approximately 3 glasses of wine) did not result in alteration of alcohol pharmacokinetics, XENICAL pharmacodynamics (faecal fat excretion) and systemic exposure to XENICAL.

Oral Contraceptives (various ethinyloestradiol and gestagen combinations commercially available): In 20 normal weight female subjects, the treatment of XENICAL 120 mg three times daily for 23 days resulted in no changes in the ovulation-suppressing action of oral contraceptives.

Nifedipine (Extended release tablets): In 17 normal weight subjects receiving XENICAL 120 mg tid for 6 days, XENICAL did not alter the bioavailability of nifedipine extended release tablets.

Cyclosporin: A reduction in cyclosporin plasma levels has been observed when XENICAL is co-administered. Therefore it is recommended to monitor more frequently than usual the cyclosporin plasma levels when XENICAL is co-administered.

Anti-coagulants: Coagulation parameters, including international normalised ratio (INR), should be monitored in patients treated with oral anti-coagulants given concomitantly with XENICAL.

Amiodarone: In a pharmacokinetic study, oral administration of amiodarone during XENICAL treatment demonstrated a 25 - 30% reduction in the systemic exposure to amiodarone and desethylamiodarone. The pharmacokinetics of amiodarone are complex. The effect of commencing XENICAL treatment in patients on stable amiodarone therapy has not been studied, but reduced systemic exposure to amiodarone and desethylamiodarone is possible, especially after chronic dosage with XENICAL. A reduced therapeutic effect of amiodarone is possible.

Anti-epileptic medicines: Convulsions have been reported in patients treated concomitantly with XENICAL and anti-epileptic medicines. A causal relationship has not been established; however, patients should be monitored for possible changes in the frequency and/or severity of convulsions.

Metabolic Agents

Weight loss induced by XENICAL is accompanied by improved metabolic control in Type 2 diabetes, which might allow or require reduction in the dose of hypoglycaemic medication.

Glibenclamide: In 12 normal weight subjects receiving XENICAL 80 mg three times daily for 4 1/3 days, XENICAL did not alter the pharmacokinetics or pharmacodynamics (blood-glucose-lowering) of glibenclamide.

Acarbose: No studies evaluating any possible pharmacokinetic/pharmacodynamic interactions between orlistat and the α -glucosidase inhibitor acarbose have been conducted, therefore concomitant administration with XENICAL is not recommended.

In the absence of interaction studies, the concomitant administration of XENICAL with other anti-obesity agents is not recommended.

Narrow Therapeutic Index Medicines

Drug interaction studies were performed with XENICAL and a number of medicines with a narrow therapeutic index. XENICAL had no inhibitory effects on pharmacokinetic or pharmacodynamic parameters of the following medicines:

Phenytoin: In 12 healthy normal weight subjects receiving XENICAL 120 mg three times daily for 6 days, XENICAL did not alter the pharmacokinetics of a 300 mg dose of phenytoin.

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

Digoxin: In 12 normal weight subjects receiving XENICAL 120 mg three times daily for 6 days, XENICAL did not alter the pharmacokinetics of a single dose of digoxin.

Fat-soluble Vitamin Supplements and Analogues

During clinical studies of XENICAL there were decreases in levels of some fat-soluble vitamins and analogues.

Furthermore, the absorption of supplementary doses of vitamins A, D and E and beta-carotene is significantly reduced with concomitant XENICAL administration.

If a multivitamin supplement is required, this should be taken at least 2 hours before or after the dose of XENICAL or at bedtime.

Other Concomitant Medications

During clinical studies, XENICAL was administered with a wide range of commonly prescribed medicines without evidence of clinically significant interactions.

ADVERSE EFFECTS

Gastrointestinal symptoms were the most commonly observed adverse events associated with XENICAL, and were related to its mechanism of action. There was no difference to placebo in the occurrence and intensity of adverse reactions in other body systems.

The majority of GI symptoms were mild and transient. Commonly or very commonly observed adverse events that were considered by the investigator to be possibly or probably related to study medication were oily spotting, flatus with discharge, faecal

urgency, fatty/oily stool, flatulence, abdominal pain, oily evacuation, liquid stools, increased defecation and faecal incontinence.

Very commonly observed adverse reactions were generally mild and transient. Events occurred early in treatment (within 3 months) and most patients experienced only one episode. Only 3% of patients experienced more than two episodes of any one adverse event.

During the first year of controlled clinical trials, 8.8% of patients treated with XENICAL discontinued treatment due to adverse events, compared to 4.9% of placebo treated patients. During the second year of controlled clinical trials, 3.6% of patients treated with 120 mg XENICAL for both years ($n = 613$) discontinued treatment due to adverse events, compared to 2.5% of patients treated with placebo for both years ($n = 524$). In both periods, the most common reasons for discontinuation from the XENICAL groups were gastrointestinal adverse events.

In a 4-year clinical trial, the general pattern of adverse event distribution was similar to that reported for the 1 and 2 year studies.

Other Adverse Events Observed in 1 and 2-year Placebo-controlled Clinical Trials

Events listed below are classified within body system categories possibly or probably related to study medication according to the investigator, and enumerated in order of decreasing frequency using the following definitions. All events included occur at an equal or greater frequency in the patients treated with XENICAL ($n = 2847$) compared to placebo ($n = 1741$):

<u>Common</u>	= $\geq 1/100$ and $< 1/10$ patients (1 to $< 10\%$)
<u>Uncommon</u>	= $\geq 1/1000$ and $< 1/100$ patients (0.1 to $< 1\%$)
<u>Rare</u>	= $\geq 1/10000$ and $< 1/1000$ patients (0.01 to $< 0.1\%$)

Gastrointestinal System Disorders: Common: soft stools, nausea, dyspepsia Uncommon: haemorrhoids, abdominal discomfort, discoloured faeces, vomiting, infectious diarrhoea, borborygmus, eructation, bloodstained faeces, stomach upset, anal irritation, abdominal distention, rectal haemorrhage, anal burning, abdominal fullness, dry mouth, diverticulitis, unpleasant smelling faeces, enteritis, rectal pain, gastritis, colic, painful defecation.

Skin and Appendages Disorders: Uncommon: xeroderma, rash, pruritus ani, nail disorder, abnormal hair texture, pruritus, eczema, acne.

Central & Peripheral Nervous System Disorder: Common: headache Uncommon: dizziness, vertigo, paraesthesia.

Body as a Whole/General Disorders: Common: asthenia Uncommon: oedema, insomnia.

Musculoskeletal System Disorders: Uncommon: leg cramps, back pain, myalgia, pain in ribs.

Metabolic and Nutritional Disorders: Uncommon: hypoglycaemia, increased appetite, thirst.

Liver and Biliary System Disorders: Uncommon: cholelithiasis, biliary colic, cholecystitis.

Respiratory System Disorder: Uncommon: upper respiratory tract infection, lower respiratory tract infection, influenza.

Auto-immune Disorder: Uncommon: influenza syndrome.

Autonomic Nervous System Disorder: Uncommon: increased sweating.

Psychiatric Disorders: Uncommon: depression, anxiety.

Cardiovascular Disorders: Uncommon: chest pain.

Urinary Disorders: Uncommon: urinary tract infection.

Two cases of each of the following adverse events have been reported during clinical trials of XENICAL considered by the investigator to be possibly or probably related to study medication: gastrointestinal disorder, solid stools, lower abdominal pain, epigastric pain not food-related, hard stools, diverticulum caecum, papular rash, brittle nails, loss of appetite, fever, fatigue, malaise, muscle cramps, decreased appetite, hypokalaemia, avitaminosis, sinusitis, pharyngitis, unpleasant smelling urine, polyuria, dysmenorrhoea, amenorrhoea, menstrual irregularity, palpitation, blurred vision, dermal bleeding, bitter taste, tumour.

Post-Marketing Experience

Skin and Appendages Disorders: Rare: hypersensitivity reactions including urticaria, pruritus, rash, angioedema, bronchospasm and anaphylaxis. Very rare: cases of bullous eruptions have also been reported during post-marketing experience.

Liver and Biliary System: Very rare: increases in transaminases and in alkaline phosphatase, and exceptional cases of severe liver injury, some resulting in liver transplant or death, have been reported. No causal relationship or physiopathological mechanism between liver injury and XENICAL therapy has been established.

Blood Disorders: reports of decreased prothrombin, increased INR and unbalanced anti-coagulant treatment resulting in change to haemostatic parameters have been reported in patients treated concomitantly with XENICAL and anti-coagulants during post-marketing experience (see INTERACTIONS WITH OTHER MEDICINES).

Central and Peripheral Nervous System Disorders: Convulsions have been reported in patients treated concomitantly with XENICAL and anti-epileptic medicines (see INTERACTIONS WITH OTHER MEDICINES).

Renal: Cases of hyperoxaluria and oxalate nephropathy have been reported.

DOSAGE AND ADMINISTRATION

The recommended dose of XENICAL is one 120 mg capsule with each main meal (during or up to one hour after the meal). If a meal is missed or contains no fat, the dose of XENICAL may be omitted. The therapeutic benefits of XENICAL (including weight control and improvement of risk factors) are continued with long-term administration.

At the recommended therapeutic dose, the inhibition of the absorption of approximately one-third of dietary fat produces meaningful weight loss and reduces risk factors. At the

same time, this effect allows absorption of adequate amounts of dietary fat and other nutrients that are essential for the maintenance of good health.

The patient should be on a nutritionally balanced, mildly hypocaloric diet that contains approximately 30% of calories from fat. It is recommended that the diet should be rich in fruit and vegetables. The daily intake of fat, carbohydrate and protein should be distributed over three main meals.

Because XENICAL has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counselled to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition. The supplement should be taken at least 2 hours before or after the administration of XENICAL, such as bedtime.

In the 4-year clinical trial, patients took vitamin supplements containing vitamin A 800 µg, vitamin D 5 µg, vitamin E 10 mg, vitamin K 30 µg and beta-carotene 400 µg.

Doses above 120 mg three times daily have not been shown to provide additional benefit.

Special Patient Groups

There is no dose adjustment required for the elderly, nor in hepatic and/or renal impairment.

Children: The use of XENICAL in patients under 18 years of age is not recommended (see PRECAUTIONS – Use in Paediatric Patients).

Body Mass Index (BMI) Calculation

$$\text{BMI (kg / m}^2\text{)} = \text{weight (kilograms) / height}^2 \text{ (metres)}$$

Body Mass Index Table																
	Overweight					Obese										
BMI	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Height (cm)	Body Weight (kg)															
147	54	56	59	61	63	65	67	69	72	74	76	78	80	82	84	87
150	56	58	60	63	65	67	69	72	74	76	79	81	83	85	88	90
152	58	60	63	65	67	69	72	74	76	79	81	84	86	88	90	93
155	60	62	65	67	69	72	74	77	79	82	84	86	89	91	94	96
157	62	64	67	69	72	74	77	79	82	84	87	89	92	94	97	99
160	64	66	69	72	74	77	79	82	84	87	89	92	94	97	100	102
163	66	69	71	74	77	79	82	84	87	89	93	95	98	100	103	105
165	68	71	74	76	79	82	84	87	90	93	95	98	101	104	106	109
168	70	73	76	79	81	84	87	90	93	95	98	101	104	107	109	112
170	72	75	78	81	84	87	90	93	96	99	101	104	107	110	113	116
173	74	78	80	84	86	89	92	95	98	101	104	107	110	113	116	119
175	77	80	83	86	89	92	95	98	101	104	107	110	114	117	119	123
178	79	82	85	89	92	95	98	101	104	107	110	114	117	120	123	126
180	81	84	88	91	94	98	101	104	107	110	114	117	120	123	127	130
183	84	87	90	94	97	100	104	107	110	114	117	120	123	127	130	133
185	86	89	93	96	99	103	107	110	114	117	120	123	127	131	134	137



188	88	92	95	99	102	106	109	113	116	120	123	127	130	134	138	141
191	91	94	98	102	105	109	113	116	120	123	127	130	134	138	141	145
193	93	97	100	104	108	112	115	119	123	127	130	134	138	142	145	149

OVERDOSAGE

Overdose of XENICAL has not been reported. Single doses of 800 mg XENICAL and multiple doses of up to 400 mg three times daily for 15 days have been studied in normal weight and obese subjects without significant adverse findings. In addition, doses of 240 mg three times daily have been administered to obese patients for 6 months without significant increase of adverse findings. Doses above the recommended dose of 120 mg three times daily have not been found to appreciably improve efficacy and may increase gastrointestinal events.

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

PRESENTATION AND STORAGE

120 mg hard gelatin capsules (turquoise; opaque) with the marking "XENICAL Roche 120" printed in black ink on the cap and body; blister packs of 42 and 84 capsules.

Store below 25 °C. Keep the blister packs inside the original carton in order to protect from light and moisture.

POISON SCHEDULE

Pharmacist Only Medicine: Schedule 3

NAME AND ADDRESS OF THE SPONSOR

ROCHE PRODUCTS PTY LIMITED
ABN 70 000 132 865
4-10 INMAN ROAD
DEE WHY NSW 2099
AUSTRALIA

Medical Enquiries: 1800 233 950

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

11 April 2000

DATE OF MOST RECENT AMENDMENT

18 June 2015