PRODUCT MONOGRAPH

PrXENICAL®

orlistat

Capsules 120 mg

Pharmaceutical Standard: Professed

Anti-Obesity Agent/Gastrointestinal Lipase Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Oral	120 mg capsule	None
For a complete listing of non-medicinal ingredients, see Dosage Forms, Composition and Packaging section.		

INDICATIONS AND CLINICAL USE

XENICAL (orlistat), when used in conjunction with a mildly hypocaloric diet, is indicated for:

- obesity management including weight loss and weight maintenance
- reducing the risk of weight regain in obese patients after prior weight loss.

These indications for the use of XENICAL apply to obese patients with a BMI* $\geq$ 30 kg/m^2 or a BMI $\geq$ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, type 2 diabetes, dyslipidemia, excess visceral fat).

The weight loss induced by the combination of XENICAL and a mildly hypocaloric diet results in an improvement of risk factors and comorbidities including hypercholesterolemia, impaired glucose tolerance, hyperinsulinemia, hypertension, reduction of visceral fat and waist circumference.

The weight loss induced by XENICAL improves glycemic control in diabetic patients and reduces the risk of developing type 2 diabetes in obese patients (BMI* $\geq$ 30 kg/m^2) with impaired glucose tolerance. The effect of XENICAL on weight loss is adjunctive to that of diet and exercise.

XENICAL can be used in combination with anti-diabetic agents (sulphonylureas, metformin, insulin) to improve blood glucose control in overweight or obese type 2 diabetes patients who are inadequately controlled on diet, exercise, and one or more of a sulphonylurea, metformin, or insulin.

*The BMI is calculated by dividing weight in kilograms by height in metres squared.

CONTRAINDICATIONS

XENICAL (orlistat) is contraindicated in patients with chronic malabsorption syndrome, cholestasis and in patients with known hypersensitivity to XENICAL or to any component of this product (For a complete listing of components, see DOSAGE FORMS, COMPOSITION AND PACKAGING).

WARNINGS AND PRECAUTIONS

General

Patient Counselling Information: Patients should be advised to adhere to dietary guidelines (see DOSAGE AND ADMINISTRATION).

No serious adverse reactions or safety hazards related to the use of XENICAL (orlistat) have been reported to date during large, long-term clinical trials (up to 4 years) (see ADVERSE REACTIONS).

As with any weight-loss agent, the potential exists for misuse of XENICAL in inappropriate patient populations (e.g. patients with anorexia nervosa or bulimia). See the INDICATIONS AND CLINICAL USE section for appropriate prescribing guidelines.

When using XENICAL in combination with insulin or oral hypoglycemic agents in the treatment of type 2 diabetes, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to the patient, family members, caregiver or others.

For warnings and precautions involving drug interactions, see DRUG INTERACTIONS section.

Carcinogenesis and Mutagenesis

For animal data, refer to TOXICOLOGY section.

Endocrine and Metabolism

Hypothyroidism and/or reduced control of hypothyroidism may occur. The mechanism may involve a decreased absorption of iodine salts and/or levothyroxine. Patients treated concomitantly with XENICAL and levothyroxine should be monitored for changes in thyroid function (see DRUG INTERACTIONS).

Gastrointestinal

XENICAL should be used with caution in patients with pre-existing disease of the large bowel or rectum.

The possibility of experiencing gastrointestinal events (see ADVERSE REACTIONS) may

increase when XENICAL is taken with a diet high in fat (e.g. in a 2000 Calorie/day diet, a diet high in fat would contain >30% calories from fat, which equates to > 67g 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. XENICAL only inhibits the absorption of dietary fat. Patients should be advised that if the resulting caloric reduction is compensated by an increase in calories from protein or carbohydrates, the expected weight loss will not occur.

Cases of rectal bleeding have been reported with XENICAL. Prescribers should investigate further in case of severe and/or persistent symptoms.

See also WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction.

Hepatic

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

Neurologic

Anticonvulsants: Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic drugs. These patients should be monitored for possible changes in the frequency and/or severity of convulsions (see DRUG INTERACTIONS).

Renal

Renal Calculi: Some patients may develop increased levels of urinary oxalate following treatment with XENICAL. Cases of hyperoxaluria and oxalate nephropathy with renal failure have been reported in patients treated with XENICAL. Caution should be exercised when prescribing XENICAL to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.

Sexual Function/Reproduction

The use of an additional contraceptive method is recommended to prevent possible failure of oral contraception that could occur in case of severe diarrhea (see DRUG INTERACTIONS).

Special Populations

Pregnant Women: Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryotoxicity or teratogenicity. This dose is 22 and 43

times the daily human dose calculated, on a body surface area (mg/m^2) basis, for rats and rabbits, respectively.
There are no adequate and well-controlled studies of orlistat in pregnant women. Because animal reproductive studies are not always predictive of human response, XENICAL should be used during pregnancy only if the benefit clearly outweighs any potential harm, and iodine supplementation should be considered as XENICAL may impair absorption of iodine salts.

Nursing Women: It is not known if orlistat is secreted in human milk. Therefore, XENICAL should not be used by nursing women unless the benefit to the mother clearly outweighs any potential for harm to the nursing infant, and iodine supplementation should be considered as XENICAL may impair absorption of iodine salts.

Pediatrics (<12 years of age): XENICAL has not been studied in pediatric patients below the age of 12 years.

Monitoring and Laboratory Tests
Diabetic patients treated with orlistat should have tests for fasting glucose and HbA1c as required.

The patient should be on a nutritionally balanced, mildly hypocaloric diet that contains no more than 30% of calories from fat. The daily intake of fat, carbohydrate and protein should be distributed over three main meals (see DRUG INTERACTIONS, Drug-Drug Interactions, Fat Soluble Vitamin Supplements and Analogues)

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

Treatment of Obesity: *Commonly Observed:* (based on first year and second year data - 120 mg versus placebo):

Gastrointestinal symptoms are the most commonly observed treatment-emergent adverse events associated with the use of XENICAL (orlistat) in double-blind, placebo-controlled clinical trials and are primarily a manifestation of the mechanism of action. (Commonly observed is defined as an incidence of ≥ 5% and an incidence in the XENICAL 120 mg group that is at least twice that of placebo.) (see WARNINGS AND PRECAUTIONS).

Table 1:	**Percentage of Patients with *Commonly Observed* GI Adverse Events (based on first and second year data) Which Occurred with a Frequency of ≥ 5% in XENICAL 120 mg or Placebo**			
Adverse Event	**Year One**		**Year Two**	
	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

These and other commonly observed adverse reactions were generally mild and transient, and decreased during the second year of treatment. Events occurred early in treatment (within 3 months) and most patients experienced only one episode. Only 3% experienced more than two episodes of any one adverse event. The incidence of these effects is directly related to the amount of dietary fat ingested and increases or decreases with the fat content of the diet. Patients should be counselled as to the possibility of the occurrence of gastrointestinal effects and how to minimize them, such as reinforcing the diet, particularly the percentage of fat it contains. Consumption of a diet low in fat (<30%) will decrease the likelihood of experiencing the gastrointestinal effects. The occurrence of gastrointestinal effects may actually help demonstrate to patients that the medication is working and help them monitor and regulate their fat intake.

In the 4-year double-blind, placebo-controlled XENDOS study, the incidence and duration of the commonly observed adverse reactions were comparable to those observed in the 1- and 2- year studies shown above.

Discontinuation of Treatment: In controlled obesity management clinical trials of 1-, and 2-year duration, 8.8% of patients treated with XENICAL discontinued treatment due to adverse events, compared to 5.0% of placebo treated patients. Similarly, in the 4-year XENDOS clinical trial, 8.0% and 4.0% of patients treated with XENICAL and placebo, respectively, discontinued treatment due to adverse events. For XENICAL, the most common adverse events resulting in discontinuation of treatment were gastrointestinal.

Incidence in Controlled Obesity Management Clinical Trials: The following tables list other treatment-emergent adverse events from seven Phase III, multicenter, double-blind, placebo-controlled clinical trials that occurred at a frequency of ≥ 1% among patients treated with XENICAL 120 mg tid and with an incidence that was greater than placebo during year 1 and year 2, regardless of relationship to study medication.

Table 2: Other Treatment-Emergent Adverse Events From Phase III Placebo-Controlled Obesity Management Clinical Trials Year One Treatment		
Body System / Adverse Event	**XENICAL % Patients (n=1913)**	**Placebo % Patients (n=1466)**
Gastrointestinal System		
Abdominal Pain/Discomfort	25.5	21.4
Flatulence	16.0	13.1
Liquid Stools	15.8	11.4
Stools Soft	8.8	6.8
Nausea	8.1	7.3
Infectious Diarrhea	5.3	4.4
Rectal Pain/Discomfort	5.2	4.0
Tooth Disorder	4.3	3.1
Gingival Disorder	4.1	2.9
Vomiting	3.8	3.5
Oral Mucosa Disorder	1.5	0.5
Feces Discoloured	1.1	0.3
Respiratory System Disorder		
Upper Respiratory Infection	38.1	32.8
Lower Respiratory Infection	7.8	6.6
Ear, Nose and Throat Symptoms	2.0	1.6
Asthma	1.8	0.8
Resistance Mechanism		
Influenza	39.7	36.2
Musculoskeletal System		
Back Pain	13.9	12.1
Arthritis	5.4	4.8
Myalgia	4.2	3.3
Joint Disorder	2.3	2.2
Tendonitis	1.9	1.7
Injury (Nonspecific)	1.0	0.5
Central Nervous System		
Headache	30.6	27.6
Dizziness	5.2	5.0
Paresthesia	1.2	0.8
Body as a Whole		
Fatigue	7.2	6.4
Surgical Procedure	5.5	4.9
Sleep Disorder	3.9	3.3
Body Temperature Abnormal	2.1	1.5
Anxiety	1.2	0.8
Skin and Appendages		
Rash	4.3	4.0
Dry Skin	2.1	1.4
Hair Thinning	1.8	1.4
Infection	1.8	1.2
Acne	1.6	1.2
Nail Disorder	1.4	1.1
Insect Bites	1.2	1.0

Table 2: Other Treatment-Emergent Adverse Events From Phase III Placebo-Controlled Obesity Management Clinical Trials Year One Treatment		
Body System / Adverse Event	**XENICAL % Patients (n=1913)**	**Placebo % Patients (n=1466)**
Urticaria	1.1	0.9
Reproductive Disorders, Female		
Menstrual Irregularity	9.8	7.5
Vaginitis	3.8	3.6
Urinary System		
Urinary Tract Infection	7.5	7.3
Psychiatric Disorders		
Psychiatric Anxiety	4.7	2.9
Hearing and Vestibular Disorders		
Otitis	4.3	3.4
Cardiovascular Disorders		
Pedal Edema	1.2	1.1
Vascular (Extracardiac)		
Vein Disorder	1.3	1.0

Table 3: Other Treatment-Emergent Adverse Events From Phase III Placebo-Controlled Obesity Management Clinical Trials Year Two Treatment		
Body System / Adverse Event	**XENICAL % Patients (n=613)**	**Placebo % Patients (n=524)**
Gastrointestinal System		
Flatulence	4.4	3.2
Rectal Pain/Discomfort	3.3	1.9
Stools Soft	2.9	2.5
Nausea	3.6	2.7
Tooth Disorder	2.9	2.3
Gingival Disorder	2.0	1.5
Respiratory System		
Upper Respiratory Infection	26.1	25.8
Musculoskeletal System		
Pain Lower Extremities	10.8	10.3
Tendonitis	2.0	1.9
Muscle Cramps	1.1	0.8
Bone Fracture	1.0	0.8
Body as a Whole		
Fatigue	3.1	1.7
Body Temp. Abnormal	1.5	1.1

Table 3: Other Treatment-Emergent Adverse Events From Phase III Placebo-Controlled Obesity Management Clinical Trials Year Two Treatment		
Body System / Adverse Event	**XENICAL % Patients (n=613)**	**Placebo % Patients (n=524)**
Injury	1.6	1.1
Pain	1.5	1.3
Allergic Reaction	1.1	1.0
Skin and Appendages		
Pruritus	1.1	0.8
Reproductive, Female		
Vaginitis	2.6	1.9
Breast Disorder	1.6	1.0
Menopausal Syndrome	1.3	1.0
Urinary System Disorders		
Urinary Tract Infection	5.9	4.8
Psychiatric Disorder		
Psychiatric Anxiety	2.8	2.1
Depression	3.4	2.5
Hearing and Vestibular Disorders		
Otitis	2.9	2.5
Cardiovascular Disorders		
Pedal Edema	2.8	1.9

In the 4-year XENDOS study, the pattern and distribution of adverse events was similar to that reported for the 1 and 2 year studies. The total incidence of gastrointestinal related adverse events occurring in year 1 decreased progressively with each additional year of treatment, over the four year period.

Pediatric Patients

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

Trials in Patients with Type 2 Diabetes: *Commonly observed adverse events:* Mild and transient gastrointestinal effects of the same type as those seen in the obesity management trials were observed in the double-blind, placebo-controlled clinical trials for type 2 diabetes management. However, the overall difference in incidence of these adverse events between patients treated with XENICAL and patients receiving placebo was generally less than in the overall obesity trials. Marked decreases were seen in the trials in patients with type 2 diabetes in the incidence of oily spotting, fecal urgency and flatus with discharge (15.8%, 10.5%, 9.4%)*, compared to those for obesity management (25.3%, 15.4% and 22.5% respectively)*. Recurrence also decreased in the diabetes trials: 4% of the patients experienced more than one episode of each gastrointestinal event compared to 6% in the obesity trials. The 2 sets of trials were not run concurrently and thus may not be directly comparable.

Of the other treatment-emergent adverse events reported in the diabetes trials, all were similar in type and generally occurred at a lower incidence compared to those of the obesity management trials, with the exception of cough (2.8% in XENICAL vs 2.4% in placebo), abdominal distension (5.8% vs 4.1%) and hypoglycemia (13.2% vs 9.5%). The majority of hypoglycemic events were mild to moderate in intensity and most patients could control the symptoms themselves. Only two patients in the placebo treatment group and three patients in the orlistat treatment group had hypoglycemic events that would be considered severe.

Weight loss induced by XENICAL is accompanied by improved metabolic control in type 2 diabetics which might allow or require reduction in the dose of hypoglycemic medication (see WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS, Diabetes Agents).

* These values are the treatment difference between XENICAL and placebo.

Post-Market Adverse Drug Reactions

Post-Marketing Experience:
Rare cases of hypersensitivity have been reported. The main clinical symptoms were pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis.

Very rare cases of bullous eruption, increase in liver transaminases and in alkaline phosphatase, and exceptional cases of hepatitis that may be serious have been reported during the post-marketing. There have been rare reports of serious liver injury with hepatocellular necrosis or acute hepatic failure in patients treated with XENICAL observed in post-marketing surveillance with some of these cases resulting in liver transplant or death. Cases of jaundice and cholelithiasis with the use of XENICAL have been reported.

Reports of decreased prothrombin, increased international normalized ration (INR) and unbalanced anticoagulant treatment resulting in change of haemostatic parameters have been reported in patients treated concomitantly with orlistat and anticoagulants (see DRUG INTERACTIONS, Drug-Drug Interactions).

Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic drugs (see DRUG INTERACTIONS, Drug-Drug Interactions, Anticonvulsants).

Cases of rectal bleeding have been reported with XENICAL. Prescribers should investigate further in case of severe and/or persistent symptoms.

Cases of hypothyroidism and/or reduced control of hypothyroidism have been reported in patients with no history of hypothyroidism and in patients treated concomitantly with levothyroxine.

Cases of hyperoxaluria and oxalate nephropathy with renal failure have been reported in patients treated with XENICAL (see WARNINGS AND PRECAUTIONS, Renal).

Pancreatitis has been reported with the use of XENICAL.

DRUG INTERACTIONS

Drug-Drug Interactions

Cyclosporine: A reduction in cyclosporine plasma levels has been observed when XENICAL (orlistat) is co-administered. Therefore, it is recommended to monitor cyclosporine plasma levels more frequently than usual if XENICAL is co-administered.

Fat-soluble Vitamin Supplements and Analogues: A pharmacokinetic interaction study with β-carotene showed a 30% reduction in β-carotene supplement absorption when concomitantly administered with XENICAL. XENICAL inhibited absorption of a vitamin E acetate supplement by approximately 60%. The effect of orlistat on the absorption of supplemental vitamin D, vitamin A and nutritionally derived vitamin K is not known at this time. Obesity management studies indicated that some patients required vitamin D supplementation with a multivitamin to achieve desirable blood levels. The decreases in vitamin D were modest (measured by 25-OH-D) and were not associated with any changes in vitamin D metabolism, as evidenced by total or ionized calcium and parathyroid levels. Clinical studies did not reveal any interference with blood coagulation that would indicate vitamin K deficiency.

During obesity management studies, there were decreases in the levels of some fat soluble vitamins and β-carotene based on the pharmacologic action of the drug. The vast majority of patients in up to four full years of treatment had vitamin levels (vitamins A, D, E, and K, and beta-carotene) that stayed well within normal range, and there was no evidence of clinical sequelae.

The vitamin status of obese patients in general and patients on a weight control regimen, including pharmacotherapy with XENICAL, may be low. Therefore patients should be counselled to take a multivitamin which includes fat-soluble vitamins and β-carotene to ensure adequate nutrition. Pediatric patients should be instructed to take a multivitamin. The supplement should be taken at least two hours before or after the administration of XENICAL, or at bedtime.

Anticoagulants: As treatment with orlistat may potentially impair the GI absorption of vitamin K, close monitoring of the coagulation parameters, such as international normalized ratio (INR) values, is recommended when oral anticoagulants are co-administered.

Anticonvulsants: Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic drugs. XENICAL may unbalance anticonvulsive treatment by decreasing the absorption of antiepileptic drugs. A causal relationship has not been established, however patients should be monitored for possible changes in the frequency and/or severity of convulsions.

Cardiovascular Agents

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.

At 50 mg tid for 7-8 days, orlistat did not significantly alter the pharmacokinetics of atenolol, captopril, furosemide and nifedipine retard.

Amiodarone: In a pharmacokinetic (PK) study, oral administration of amiodarone during orlistat treatment demonstrated a 25 - 30% reduction in the systemic exposure to amiodarone and desethylamiodarone. Due to the complex pharmacokinetics of amiodarone, the clinical effects of this are unclear. The effect of commencing orlistat treatment in patients on stable amiodarone therapy has not been studied. A potential reduced therapeutic effect of amiodarone is possible.

No interactions based on specific drug-drug interaction studies have been observed with losartan, fibrates, or atorvastatin.

Diabetes Agents

Weight loss induced by XENICAL is accompanied by improved metabolic control in non-insulin dependent diabetics, which might allow or require reduction in dose of oral hypoglycemic medication (e.g. sulfonylureas).

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

Metformin: In 20 normal weight subjects receiving XENICAL 120 mg tid for 6 days in a two way crossover study, XENICAL did not alter the pharmacokinetics of metformin**.**

Narrow Therapeutic Index Drugs

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

Phenytoin: In 12 normal weight subjects receiving XENICAL 120 mg tid for 7 days, XENICAL did not alter the pharmacokinetics of a single 300-mg dose of phenytoin.

Warfarin: In 12 normal weight subjects, administration of XENICAL 120 mg tid 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 Vitamin K nutritional status parameters (ratios of vitamin K_1 epoxide to vitamin K_1 and undercarboxylated osteocalcin to osteocalcin) were also unaltered by orlistat, treatment with orlistat may potentially impair the GI absorption of vitamin K. Close monitoring of the coagulation parameters, including INR values, is recommended when oral anticoagulants are co-administered.

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

Other

Alcohol: In a multiple-dose study in 30 normal weight subjects, coadministration of orlistat and 40 grams of alcohol (e.g. approximately 3 glasses of wine) did not result in alteration of alcohol

pharmacokinetics, orlistat pharmacodynamics (fecal fat excretion), and systemic exposure to orlistat.

Oral Contraceptives (various ethinyl estradiol and gestagen combinations commercially available): In 20 normal weight female subjects, the treatment of XENICAL 120 mg tid for 23 days resulted in no changes in the ovulation-suppressing action of oral contraceptives. Although the absence of an interaction between oral contraceptives and orlistat has been demonstrated, orlistat may indirectly reduce the availability of oral contraceptives and lead to unexpected pregnancies in some individual cases. An additional contraceptive method is recommended in case of severe diarrhea (see WARNINGS AND PRECAUTIONS, Sexual Function/ Reproduction).

Pravastatin: In 24 normal weight, mildly hypercholesterolemic subjects receiving XENICAL 120 mg tid for 6 days in a two way cross-over study, XENICAL did not affect the pharmacokinetics or pharmacodynamics of pravastatin.

Levothyroxine: Hypothyroidism and/or reduced control of hypothyroidism may occur. The mechanism, although not proven, may involve a decreased absorption of iodine salts and/or levothyroxine. Patients treated concomitantly with XENICAL and levothyroxine should be monitored for changes in thyroid function.

No interactions based on specific drug-drug interaction studies have been observed with amitryptyline, fluoxetine, sibutramine, or phentermine.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- The patient should be on a nutritionally balanced, mildly hypocaloric diet that contains no more than 30% of calories from fat. The daily intake of fat, carbohydrate and protein should be distributed over three main meals (see DRUG INTERACTIONS, Drug-Drug Interactions, Fat Soluble Vitamin Supplements and Analogues).

- For patients with type 2 diabetes, the reduced calorie diet should be consistent with the dietary recommendations of the Canadian Diabetes Association Guidelines for the Nutritional Management of Diabetes Mellitis in the New Millennium.

Recommended Dose and Dosage Adjustment

The recommended dose of XENICAL (orlistat) is one 120 mg capsule three times daily with each main meal (during or up to 1 hour after the meal). If a meal is occasionally missed or contains no fat, the dose of XENICAL may be omitted.

Doses above 120 mg three times daily have not been shown to provide additional benefit. No dose adjustment is necessary for the geriatric patient.

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

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Single doses of 800 mg XENICAL (orlistat) and multiple doses of up to 400 mg tid for 15 days have been studied in normal weight and obese subjects without significant adverse findings. In addition, doses of 240 mg tid have been administered to obese patients for 6 months without a significant increase in adverse findings.

Orlistat overdose cases received during post-marketing reported either no adverse events or adverse events that are similar to those reported with the recommended dose.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

Pharmacokinetics

Absorption: Systemic exposure to orlistat is negligible. Following oral dosing with 360 mg ^{14}C- orlistat, plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact orlistat were nonmeasurable (<5 ng/mL). In therapeutic studies involving monitoring of plasma samples, 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.

Studies in rats and dogs indicated that the absolute bioavailability of orlistat in plasma is <2% at oral doses up to 1000 mg/kg/day.

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

Metabolism: Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on a ^{14}C -orlistat mass balance study in obese patients, of the minute fraction of the radio-labelled dose that was absorbed systemically, the presence of two metabolites, M1 (4-member lactone ring hydrolyzed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of total radioactivity in plasma. M1 and M3 have an open β-lactone ring and extremely weak systemic lipase inhibitory activity (1000 - and 2500 - fold less than orlistat, respectively). In view of this low inhibitory activity and the low plasma levels at the therapeutic dose (average of 26 ng/mL and 108 ng/mL for M1 and M3, respectively), these metabolites are considered pharmacologically inconsequential. The primary metabolite M1 had a short half-life (approximately 3 hours) whereas the secondary metabolite M3 disappeared at a slower rate (half-life approximately 13.5 hours). In obese patients, steady state plasma levels of M1, but not M3, increased in proportion to orlistat doses.

Excretion: Following a single oral dose of 360 mg ^{14}C-orlistat in both normal weight and obese subjects, fecal excretion of the unabsorbed drug was found to be the major route of elimination. Approximately 97% of the administered radioactivity was excreted in feces and 83% of that was found to be unchanged orlistat. The cumulative renal excretion of total radioactivity was <2% of the given dose of 360 mg ^{14}C-orlistat.

The time to reach complete excretion (fecal plus urinary) was 3 to 5 days. The disposition of orlistat appeared to be similar between normal weight and obese subjects. Based on limited data, the half-life of the absorbed orlistat is in the range of 1 to 2 hours. Orlistat, M1 and M3 metabolites were also subject to biliary excretion.

Special Populations and Conditions

Special Populations: Because the drug is minimally absorbed, with no defined pharmacokinetics, studies in special populations (geriatric, pediatric, different races, patients with renal and hepatic insufficiency) were not conducted.

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

Hepatic and Renal Insufficiency: Clinical investigations in patients with hepatic and/or renal impairment have not been undertaken

Effect of Orlistat on Gastrointestinal and Systemic Physiological Processes:

Adults
In several studies of up to 6-weeks duration, the effects of orlistat on gastrointestinal and systemic physiological processes were assessed in normal weight and obese subjects. Postprandial cholecystokinin plasma concentrations were lowered after multiple doses of orlistat in two studies but not significantly different from placebo in two other experiments. There were no clinically significant changes observed in gallbladder motility, bile composition or lithogenicity or colonic cell proliferation rate, and no clinically significant reduction of gastric emptying time or gastric acidity. In addition, no effect on plasma triglyceride levels, systemic lipases or balance of six minerals (calcium, magnesium, phosphorus, zinc, copper and iron) were observed with administration of orlistat in these studies.

Pediatrics
In a 3-week study of 32 obese adolescents aged 12 to 16 years, XENICAL (120 mg, three times a day) did not significantly affect the balance of calcium, magnesium, phosphorous, zinc, or copper. The iron balance was decreased by 64.7 μmol/24 hours and 40.4 μmol/24 hours in orlistat and placebo treatment groups, respectively.

STORAGE AND STABILITY

XENICAL should be stored in its original package between 15-25°C. Keep the blister package in the XENICAL outer carton, in order to protect it from light and moisture. This medicine should not be used after the expiry date shown on the pack.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Composition:
Each XENICAL 120 mg capsule contains 120 mg orlistat. Non-medicinal ingredients (alphabetical order): gelatin, indigo carmine, microcrystalline cellulose, povidone K30, sodium lauryl sulphate, sodium starch glycolate, talc, titanium dioxide.

Availability:
XENICAL 120 mg Capsules: turquoise cap and turquoise body with "XENICAL 120" printed in black ink.

XENICAL is supplied in blister packages in cartons of 84 capsules.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

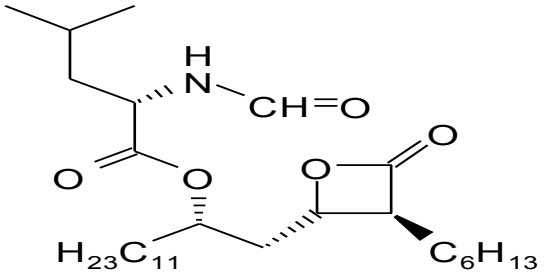
Drug Substance

Proper name: Orlistat

Chemical name: (S)-2-Formylamino-4-methyl-pentanoic acid (S)-1-[(2S,3S)-3-hexyl-4-oxo-oxetan-2-ylmethyl]-dodecyl ester

Molecular formula and molecular mass: $C_{29}H_{53}NO_5$, 495.75

Structural formula:



Physicochemical properties:

Physical Form:	Orlistat is a white to almost white fine crystalline powder or fine crystalline powder with lumps
Solubility:	Water - <0.001g/100 mL
pKa:	No value within physiological range
Partition co-efficient:	log P=4.40 (octanol/water)
Melting Point:	Approximately 44 °C

CLINICAL TRIALS

Clinical Studies*: Treatment of Obesity*: The effects of XENICAL on weight loss, weight maintenance, weight regain and on a number of comorbidities were assessed in seven multicenter, double-blind, placebo-controlled clinical trials of 1-to 2-years duration. During the first year of therapy, weight loss and weight maintenance were assessed. During the second year of therapy, some studies assessed continued weight loss and weight maintenance and others assessed the effect of orlistat on weight regain. These studies included over 2800 patients treated with XENICAL and 1400 patients treated with placebo.

An additional 4-year multicenter, double-blind, placebo-controlled study, the XENDOS study, assessed the effects of XENICAL on body weight, time to onset of type 2 diabetes, and comorbidities. The study included 3304 obese (BMI $\geq$ 30 kg/m^2) patients.

In all the above studies, treatment with XENICAL and placebo designates treatment with XENICAL plus diet and placebo plus diet, respectively.

The observations regarding the effects on comorbidities during these trials are discussed in detail below.

Efficacy Results: Weight Loss and Prevention of Weight Regain: 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. The diet was calculated using initial body weight to provide a caloric deficit of 500-800 calories per day, which represents an average caloric decrease of 20%. The percentages of patients achieving a $\geq$ 5% and $\geq$10% weight loss after 1 and 2 years treatment from two representative studies (BM14119C and BM14149) are summarized in the following tables:

Table 4: Categorical Analysis of Weight Loss Following One-Year of Treatment

Study Number	Intent to Treat Population						Completers Population					
	≥5% Weight Loss			≥10% Weight Loss			≥5% Weight Loss			≥10% Weight Loss		
	XENICAL	Placebo	P Value	XENICAL	Placebo	P Value	XENICAL	Placebo	P Value	XENICAL	Placebo	P value
BM 14119C*	68.5%	49.1%	<0.05	38.8%	17.6%	<0.05	77.2%	57.4%	<0.05	46.9%	21.3%	<0.05
BM 14149**	62.5%	43.6%	0.001	38.3%	18.8%	0.001	77.3%	57.3%	0.001	49.7%	25.7%	0.001

* Intent to treat population: placebo n=340, XENICAL n=343; completers population placebo n=249, XENICAL n=271

** Intent to treat population: placebo n=234, XENICAL n=240: completers population: placebo n=136, XENICAL n=163

Table 5: Categorical Analysis of Weight Loss Following Two Full Years Treatment												
Study Number	**Intent to Treat Population**						**Completers Population**					
	≥5% Weight Loss			**≥10% Weight Loss**			**≥5% Weight Loss**			**≥10% Weight Loss**		
	XENICAL	**Placebo**	**P Value**	**XENICAL**	**Placebo**	**P Value**	**XENICAL**	**Placebo**	**P Value**	**XENICAL**	**Placebo**	**P value**
BM 14119C*	57.1%	37.4%	0.01	33.8%	14.6%	0.006	58.4%	40.9%	0.006	38.6%	15.1%	0.006
BM 14149**	51.7%	30.3%	<0.001	24.2%	13.2%	<0.001	65.7%	37.8%	<0.001	30.8%	22.0%	<0.001

* Intent to treat population: placebo n=123, XENICAL n=133; Completers population n=93 placebo, XENICAL n=101
** Intent to treat population: placebo n=234, XENICAL n=240: placebo n=127, XENICAL n=146

At the end of 52 weeks of double-blind treatment in study BM14119C, mean weight loss for the placebo treated patients was 6.1% and 10.2% in XENICAL treated patients (intent to treat analysis). In study BM 14149, patients treated with XENICAL had lost 9.7%, compared with 6.6% for patients that received placebo (intent to treat). The findings were similar in the completers populations.

In the 4-year XENDOS trial, XENICAL was shown to be more effective than placebo in long-term weight control. Results showed that 73% of the patients treated with XENICAL lost ≥ 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 patients treated with XENICAL lost ≥ 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 patients treated with XENICAL lost ≥ 5 and ≥ 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 ($p<0.001$).

Prevention of Weight Regain Following One Year of Weight Loss: Studies NM14185 and BM14119C were designed to evaluate the effects of XENICAL compared to placebo in reducing weight regain in year-2 after previous weight loss achieved by prior treatment with XENICAL in year 1. The diet utilized during the 2nd year prevention of weight regain portion of the studies was a weight maintenance diet, rather than a weight loss diet, and patients received less nutritional counselling than patients in the first year. In study BM14119C, patients treated with placebo regained 52% of the weight they had previously lost while patients treated with XENICAL regained only 26% of the weight they had previously lost ($p<0.001$). In study, NM14185, patients treated with placebo regained 63% of the weight they had previously lost while the patients treated with XENICAL regained only 35% of the weight they had lost ($p<0.001$).

Effect on Comorbidities: At the recommended therapeutic dose of XENICAL, 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. One, 2, and 4 years treatment with XENICAL resulted in statistically significant improvements in many risk factors associated with obesity compared to placebo treatment. The statistically significant improvement of risk factors included fasting glucose and fasting insulin, total cholesterol, LDL-cholesterol, LDL/HDL ratio, waist and hip circumference. Statistically significant improvements over placebo in systolic and diastolic blood pressure were also observed after one year of treatment, and maintained for each year throughout the entire 4-year treatment period.

The relative changes in risk factors associated with obesity following 4 years of therapy are summarized in the following table:

Table 6: Mean Change in Risk Factors From Randomization Following 4-Years Treatment* (Population as Whole)

Risk Factor	XENICAL-Treatment Group†	Placebo-Treatment Group†	p-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),	-3.17	-0.57	<0.001
Cardiovascular:			
Systolic Blood Pressure, mmHg	-4.12	-2.60	<0.001
Diastolic Blood Pressure, mmHg	-1.93	-0.87	<0.001
Anthropometric:			
Waist Circumference, cm	-5.78	-3.99	<0.001

*Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
†ITT (LOCF)

Subpopulations with Abnormal Baseline Risk Factors: Patient subpopulations with the following abnormal baseline risk factors at randomization also showed statistically significant reductions in the following abnormal values relative to patients receiving placebo following one or two years treatment with XENICAL; Metabolic: LDL-cholesterol ≥ 3.362 mmol/L, LDL/HDL ratio ≥ 3.5

(year 1 only), fasting insulin ≥ 120 pmol/L. Cardiovascular: systolic BP ≥ 140 mm Hg and Diastolic BP ≥ 90mm Hg (year 1 only). Anthropometric: waist circumference >100 cm.

In the 4-year XENDOS study, the changes from randomization following 4-years of treatment in the population with abnormal lipid levels (LDL ≥ 3.362 mmol/L, HDL < 0.905 mmol/L, LDL:HDL ratio ≥ 3.5, triglycerides ≥ 2.54 mmol/L) were greater for XENICAL compared with placebo in respect to LDL (-14.86 % vs -7.34%, p<0.001), LDL/HDL (-0.87% vs -0.59%, p<0.001), and triglycerides (-15.63% vs -13.92%, p=0.562). HDL increased in the placebo group by 12.9% and in the XENICAL group by 11.6% (p=0.339). In the population with abnormal blood pressure at baseline (systolic ≥ 140 mmHg, diastolic ≥ 90 mmHg), the change in systolic blood pressure from baseline was greater for XENICAL than placebo (-11.44 mmHg vs -8.70 mmHg, p=0.002). For patients with diastolic blood pressure ≥ 90 mmHg at baseline, the decrease in diastolic blood pressure in the XENICAL patients was -8.00 mmHg vs -6.26 mmHg in the placebo treated patients (p=0.006). Fasting insulin decreased more in the XENICAL treatment group than the placebo treatment group (-47.02 pmol/L vs -37.47 pmol/L, p=0.002) from randomization to year 4 in the population with abnormal baseline values (≥ 90 mmol/L).

Predictors of Response*:* An analysis was performed with two of the European studies (BM14119C and BM14149) to determine if early response to XENICAL treatment predicts long-term weight maintenance and health benefits. It was found that patients that lost ≥ 5% of body weight at during the first 12 weeks of drug therapy achieved significantly greater weight loss after 2 years than those who lost <5% (-11.9% vs -4.7%, respectively, p=0.0001). Similarly, patients that lost ≥ 5% of their body weight during the first 12 weeks of drug treatment achieved significantly greater weight loss after 1-year of treatment, compared to patients that lost <5% (-14.5% vs -6.9%, respectively, p=0.0001). Weight loss at the end of one and two years treatment was also greater in patients that lost ≥ 5% weight at 12 weeks and ≥ 10% body weight at 6 months, compared to those patients that lost <10% at six months (year 1: -17.7% vs -11.9%; year 2: -15.0% vs -9.33%, respectively). The impact on risk factors based on whether patients achieved 5% weight loss at 12 weeks is shown in the table below for both 1 and 2 years treatment.

Table 7: Impact of <5% or ≥ 5% Weight Loss at 12 Weeks on Risk Factors following and 2 Years Treatment with XENICAL

Years on Therapy	Risk Factor[a]	12 week weight loss		P value*
		<5%	≥5%	
Year 1	Total cholesterol	-8.25 (111)**	-14.87 (102)	0.0002
	LDL cholesterol	-10.06 (111)	-18.69 (102)	0.0003
	HDL cholesterol	1.48 (111)	4.77 (102)	n.s
	Triglycerides	-1.98 (111)	-14.66 (102)	0.004
	Systolic blood pressure (mm Hg)	-7.48 (116)	-10.88 (104)	n.s
	Diastolic blood pressure (mm Hg)	-4.37 (116)	-7.65 (104)	0.013

Table 7: Impact of <5% or ≥ 5% Weight Loss at 12 Weeks on Risk Factors following and 2 Years Treatment with XENICAL				
Years on Therapy	**Risk Factor[a]**	**12 week weight loss**		**P value***
		<5%	≥5%	
Year 2	Total cholesterol	-4.87 (111)	-10.67 (98)	0.0014
	LDL cholesterol	-4.83 (111)	-11.30 (98)	0.015
	HDL cholesterol	5.06 (111)	8.38 (98)	n.s
	Triglycerides	3.27 (111)	-16.18 (98)	0.000
	Systolic blood pressure (mm Hg)	-3.66 (116)	-9.45 (104)	0.005
	Diastolic BP (mm Hg)	-2.24 (116)	-5.37 (104)	0.017

[a] Percent change unless otherwise noted.
* P value refers to the comparison of XENICAL treated patients that lost either greater than or less than 5% weight loss at 12 weeks, not to patients treated with placebo.
**Number in brackets refers to the number of patients.

Onset of Type 2 Diabetes in Obese Patients (BMI ≥ 30 kg/m^2):
In the 4-year XENDOS study, the effects of XENICAL in delaying the onset of type 2 diabetes were compared to placebo in obese patients who had either normal or impaired glucose tolerance at baseline.

Treatment with XENICAL, in combination with lifestyle changes, was shown to delay the onset of type 2 diabetes compared with treatment with placebo plus lifestyle changes ($p<0.01$). A greater proportion of placebo-treated patients developed type 2 diabetes than did patients treated with XENICAL. At the end of the 4 years, the cumulative incidence rate for the development of type 2 diabetes was 9.04% for placebo and 6.15% for XENICAL. Over the 4-year treatment period, there was a 37.3% relative reduction in the risk of developing type 2 diabetes in the patients treated with XENICAL compared to the placebo group.

Table 8: Cumulative Incidence of Diabetic Cases by Time of First Occurrence - ITT[1]				
Time Interval	**Placebo**		**XENICAL**	
	Patients diagnosed with Diabetes (%)	**Cumulative Rate of Patients Diagnosed with Diabetes (%)**	**Patients diagnosed with Diabetes (%)**	**Cumulative Rate of Patients Diagnosed with Diabetes (%)**
6 months	1.22	1.22	0.32	0.03*
1 Year	0.79	2	0.7	0.99*
2 Year	1.36	4.29	0.56	2.05*
3 Year	1.49	6.98	1.39	4.44*
4 Year	0.96	9.04	0.86	6.15*

[1]ITT: all eligible randomized patients with baseline and a follow-up efficacy assessment
*$p<0.01$, logrank test

A separate analysis was conducted in patients with impaired glucose tolerance (IGT) at baseline. In patients (ITT) with baseline IGT (placebo, N=345; XENICAL, N=352), treatment with XENICAL again was shown to delay the onset of type 2 diabetes compared with treatment with placebo. A greater proportion of placebo-treated patients developed diabetes than did patients treated with XENICAL. At the end of 4 years, the cumulative incidence rate of type 2 diabetes in patients with IGT at baseline was 28.77 % for placebo and 18.79% for XENICAL ($p<0.003$). Over the 4-year treatment period, the relative risk of developing type 2 diabetes was reduced by 44.9% in the XENICAL group compared to the placebo group. In addition, treatment with XENICAL significantly reduced the progression to type 2 diabetes when diagnosed by repeat positive testing in patients with baseline IGT. Cumulative incidence rates after 4 years were 8.3% for XENICAL and 14.2% for placebo ($p=0.0171$), corresponding to a 52% risk reduction.

Table 9: Cumulative Incidence of Diabetic Cases by Time of First Occurrence - Patients with IGT at Baseline

Time Interval	Placebo		XENICAL	
	Patients diagnosed with Diabetes (%)	Cumulative Rate of Patients Diagnosed with Diabetes (%)	Patients diagnosed with Diabetes (%)	Cumulative Rate of Patients Diagnosed with Diabetes (%)
6 months	4.94	4.94	0.89	0.89*
1 Year	3.51	8.27	2.85	3.71*
2 Year	4.61	15.70	1.87	6.80*
3 Year	4.83	23.52	6.28	16.32*
4 Year	1.82	28.77	0.63	18.79*

*p <0.01, logrank test

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 at randomization was either normal, impaired or diabetic. The progression from a normal OGTT at randomization to a diabetic or impaired OGTT following two years treatment with XENICAL (n=251) or placebo (n=207) were compared. Following treatment with XENICAL, 0.0% and 7.2 % of the patients progressed from normal to diabetic and impaired OGTT respectively, compared to 1.9 % and 12.6% of the placebo group respectively (p=0.01).

In patients found to have an impaired OGTT at baseline, the percent of patients improving to normal or deteriorating to diabetic status following one or two years of treatment with XENICAL compared to placebo are presented below and the difference between treatment groups was significant:

Table 10: The Percentage of Patients Improving to Normal or Deteriorating to Diabetic Status Following One or Two Years With XENICAL Versus Placebo		
Baseline OGTT Status Intent to Treat Population	**Patients Normal*** Post- Treatment**	**Patients Diabetic*** Post-Treatment**
Impaired***	One year of treatment	One year of treatment
Placebo n=48	45.8%	10.4%
Orlistat[*,1] n=115	72.2%	2.6%
Impaired ***	2 years of treatment	2 years of treatment
Placebo n=40	50.0 %	7.5%
Orlistat[**,1] n=60	71.7%	1.7%

* $p<0.01$ and ** $p=0.059$, Fisher's Exact Test

*** OGTT status in mmol/L at 120 min: normal <7.77; impaired ≥7.77 and <11.1; diabetic ≥11.1.

[1] Treatment refers to orlistat plus diet or placebo plus diet.

Type 2 Diabetes: Seven randomized, double-blind, placebo-controlled trials of one-year (4 trials) and six-months (3 trials) duration were conducted to evaluate the use of XENICAL in combination with sulfonylureas, metformin or insulin in overweight and obese patients with type 2 diabetes. During these studies, patients were maintained on a well-balanced, reduced-calorie diet consistent with the dietary recommendations of the Canadian Diabetes Association. An additional six-month trial was conducted to evaluate the metabolic effects of XENICAL combined with lifestyle intervention compared with lifestyle intervention alone in obese patients with type 2 diabetes.

One year Results: Maximum improvements in fasting glucose were observed as early as two weeks of initiation of therapy. Improvements in weight loss were observed as early as four weeks of initiation of therapy. Improvements in HbA1c were seen at the time of the first assessment point at twelve weeks.

A total of 1729 overweight and obese patients with type 2 diabetes participated in four double-blind, placebo-controlled one-year studies conducted to assess the efficacy of XENICAL in combination with antidiabetic agents such as insulin, metformin and sulfonylureas. In these studies XENICAL and diet, used in combination with antidiabetic agents, showed significant reductions in hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), postprandial glucose (PPG) and body weight compared to placebo and diet used in combination with antidiabetic agents.

Table 11: Mean Changes in Glycemic Control Parameters and Body Weight in Patients with Type 2 Diabetes, 1-Year Studies*

Study Numbers:	M37047 XENICAL/Insulin Study		M37048 XENICAL/Metformin Study		M37002 XENICAL/Sulfonylurea Study		M14336 XENICAL/Sulfonylurea Study	
Parameters:	XENICAL N=266	Placebo N=269	XENICAL N=250	Placebo N=254	XENICAL N=189	Placebo N=180	XENICAL N=162	Placebo N=159
HbA1c (%)								
Baseline (mean)	9.0	9.0	8.9	8.8	8.3	8.2	7.5	7.5
Mean Change from Baseline	-0.62‡	-0.27	-0.75§	-0.41	-0.62‡	-0.06	-0.14‡	+0.32
% Patients with Reduction in HbA1c								
≥0.5% decrease in HbA1c	52‡	40	61‡	43	54‡	33	44‡	20
≥1.0% decrease in HbA1c	32†	22	46‡	29	33†	22	22‡	11
FPG (mmol/L)								
Baseline (mean)	10.9	11.2	11.6	11.1	10.2	9.8	7.9	7.9
Mean Change from Baseline	-1.63†	-1.08	-2.02‡	-0.69	-0.95‡	+0.34	+0.04‡	+0.73
PPG (mmol/L)								
Baseline (mean)	-	-	-	-	12.6	12.3	-	-
Mean Change from Baseline	N/D	N/D	N/D	N/D	-1.13‡	+0.36	N/D	N/D
Decrease in antidiabetic med								
% Patients, Orlistat vs placebo	41	31	17	8.2	10	9	42	30
Increase in antidiabetic med.	15	32	12	22	14	18	7	18
% Patients, Orlistat vs placebo								
Weight (kg)								
Baseline (mean)	102.0	101.8	102.2	101.2	97.6	96.5	97.5	97.5
Mean Change from Baseline	-3.89‡	-1.27	-4.66‡	-1.82	-3.49‡	-1.46	-3.83‡	-1.35

*The diet utilized during the studies was a reduced-calorie diet consistent with the dietary recommendations of the Canadian Diabetes Association.

H $p<0.05$ based on statistical analysis XENICAL compared to placebo (least squares mean)

I $p<0.01$ based on statistical analysis XENICAL compared to placebo (least squares mean)

$p<0.01$, Cochran-Mantel-Haenszel

§ Results were not statistically significant likely due to the study design in which the dose and antidiabetic medication could be changed during the conduct of the study depending on the glycemic control response. Reanalysis of this study excluding the assessments done after any change in antidiabetic therapy resulted in a mean decrease from baseline in HbA1c of -0.73% in the XENICAL group and -0.36% in the placebo group ($p<0.01$).

N/D = Not done

Orlistat has an additional glucose-lowering effect in obese and overweight type 2 diabetic patients receiving antidiabetic medication separate from its effect on body weight.

An analysis of pooled data from patients who completed one year of treatment was conducted for HbA1c in patients losing ≤ 1% of their baseline body weight. The mean change in body weight from baseline in these patients was +1.35 kg in the patients treated with XENICAL and + 1.53 kg in the placebo treatment group; however, patients receiving orlistat had a significantly greater mean decrease in HbA1c compared to the placebo treatment group (-0.29% vs +0.14%, $p<0.0008$), respectively. XENICAL in combination with antidiabetic agents had favourable effects on lipids, blood pressure and waist circumference, risk factors associated with type 2 diabetes and excess body weight.

In a six-month single centre, randomized, double-blind, placebo-controlled study in patients with type 2 diabetes, patients were randomized to receive XENICAL plus lifestyle intervention, or placebo plus lifestyle intervention. A significant improvement ($p<0.05$) in insulin sensitivity was observed in the XENICAL group (+2.2 ±0.4 mg.min-1.kg-1) compared with the placebo group (+1.2 ±0.4 mg.min-1.kg-1), which was attributed to the significant decrease ($p<0.01$) in fasting plasma free fatty acids observed in the XENICAL group (-154 ±22 µmol/L) compared to the placebo group (-51 ±33 µmol/L), after adjusted for effects of weight loss.

The changes from randomization following treatment in the type 2 diabetic population with abnormal baseline lipid levels, blood pressure and waist circumference (pooled data for 7 clinical trials) are summarized in the table below. One year of therapy with XENICAL in combination with other antidiabetic medications resulted in statistically significant improvements in many of these risk factors.

Table 12: Mean Change in Risk Factors From Randomisation - Population with Abnormal Risk Factors[1]

Risk Factor - Value at Randomization	XENICAL 120 mg + Diet[2] + Antidiabetic Medications			Placebo +Diet[2] + Antidiabetic Medications			
Lipids:	**N**	**Baseline Mean**	**Mean Change From Baseline**	**N**	**Baseline Mean**	**Mean Change From Baseline**	**P Value**
LDL-Cholesterol ≥3.362 mmol/L	496	4.12	-11.56%	462	4.09	-2.13%	0
HDL-Cholesterol < 0.905 mmol/L	298	0.77	+14.18%	301	0.78	+19.19%	0.0287
LDL/HDL ≥3.5	368	4.43	-0.81	343	4.45	-0.61	0.0210
Triglycerides ≥2.54 mmol/L	335	4.11	-6.42%	328	4.17	-3.94%	0.5913
Blood Pressure:							
Systolic Blood Pressure ≥130 mm Hg	813	143.36	-6.08	781	143.30	-4.41	0.0251
Diastolic Blood Pressure ≥ 80 mm Hg	814	86.42	-4.53	776	86.47	-3.77	0.0772
Anthropometric:							
Waist Circumference, cm ‡	1008	111.39	-4.82	968	111.53	-2.41	0.0000

[1]Intent-to-treat population: observed data based on pooled data from 7 studies
[2]The diet utilized during the studies was a reduced-calorie diet consistent with the dietary recommendations of the American Diabetes Association; ‡≥102 cm for males and ≥88 cm for females at baseline.

Six-Month Results: A total of 779 overweight and obese patients with type 2 diabetes participated in three double-blind, placebo controlled 24-week studies also conducted to assess the efficacy of XENICAL in combination with antidiabetic agents. In these studies, improvements similar to those for the one-year results were observed in glycemic control, weight loss and effects on risk factors were also observed.

Pediatric Clinical Studies

The effects of XENICAL on body mass index (BMI) and weight loss were assessed in a 54-week multicenter, double-blind, placebo-controlled study in 539 obese adolescents (357 receiving XENICAL 120 mg three times a day, 182 receiving placebo), aged 12 to 16 years.

BMI was the primary efficacy parameter as it takes into account changes in height and body weight, which occur in growing children.

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

Approximately 65% of patients in each treatment group completed the study.
Following one year of treatment, BMI decreased by an average of 0.55 kg/m^2 in the XENICAL-treated patients and increased by an average of 0.31 kg/m^2 in the placebo-treated patients (p=0.001). The percentages of patients achieving 5% and 10% reduction in BMI and body weight after 52 weeks of treatment for the intent-to-treat population are presented below.

Table 13: Percentages of Patients with ≥5% and ≥10% Decrease in Body Mass Index and Body Weight After 1-Year Treatment*

Intent-to-Treat Population†						
Parameter	**≥5% Decrease**			**≥10% Decrease**		
	XENICAL Treatment Group	**Placebo Treatment Group**	**p-value**	**XENICAL Treatment Group**	**Placebo Treatment Group**	**p-value**
BMI**	26.5%	15.7%	0.005	13.3%	4.5%	0.002
Body Weight**	19.0%	11.7%	0.032	9.5%	3.3%	0.011

*Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet
†Last observation carried forward
** BMI: placebo n=178, XENICAL n=347; Body Weight: placebo n=180, XENICAL n=348

In a subgroup of 152 XENICAL-treated and 77 placebo-treated patients from the 54-week study, changes in body composition measured by DEXA were similar in both treatment groups with the exception of fat mass, which was significantly reduced in patients treated with XENICAL compared to patients treated with placebo (-2.5 kg vs -0.6 kg, p=0.033).

Table 14: Least Squares Mean Change from Baseline in DEXA[1] Total Body Assessments

Parameter	**XENICAL Treatment Group***	**Placebo Treatment Group ***	**p-value**
Fat Mass (kg)	-2.5	-0.6	0.033
Fat Free Mass Soft Tissue (kg)	+2.0	+2.1	0.929
Bone Mineral Content (g)	+182	+177	0.857
Bone Mineral Density (g/cm2)	+0.04	+0.04	0.666

[1]DEXA: Dual-Energy X-ray Absorptiometry
*Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet

DETAILED PHARMACOLOGY

Animal Pharmacology

No effect on arterial blood pressure, heart rate and gross spontaneous behaviour was observed in conscious dogs after either oral or intravenous administration of orlistat at doses of 1 g/kg and 1, 3 and 10 mg/kg, respectively. In preclinical models, orlistat demonstrated potent anti-obesity and some hypolipemic properties. These therapeutic effects are attributable to the inhibitory action of orlistat on digestive lipases in the gastrointestinal lumen which results in the reduction of fat and cholesterol absorption. Orlistat increased the fecal concentration of unesterified fatty acids and diglycerides in animal studies, but decreased levels of bile acids. This effect differs from that observed following an increase in dietary fat alone, in which case bile acids also increased. Increased exposure of the colonic mucosa to fatty acids and diglycerides did not lead to histopathological observations indicative of pre-neoplastic alterations (see Toxicology section).

Human Pharmacology

Dose-response Relationship: A simple maximum effect (E_{max}) model was used to define the dose-response curve of the relationship between XENICAL (orlistat) daily dose and fecal fat excretion as representative of gastrointestinal lipase inhibition. E_{max}, the maximum attainable intensity of effect produced by XENICAL and presented as percentage of ingested fat excreted, was 37% ±2 (SE). The dose-response curve demonstrated a steep portion for doses up to 400 mg daily, followed by a plateau for higher doses. In a dose which was above that recommended for therapy (360 mg -120 mg tid), the percentage increase was minimal.

TOXICOLOGY

Table 15: Acute Toxicity

Species	Strain (#/sex/grp.)	Route of Admin.	Doses (mg/kg)	Obs. Period (days)	Principal Findings*
Mouse	Fü-albino (10)	p.o. (gavage)	5000	14	MNLD = > 5000 mg/kg; no observed clinical adverse effects
	Fü-albino (10)	i.v. (25 ml/kg)	0, 100	14	MNLD = > 100 mg/kg; short-lived (1-4 min.) CNS depression following both vehicle and test article
	Fü-albino (5)	i.v. (3 ml/kg)	0, 150	14	MNLD = > 150mg/kg; no observed clinical adverse effects
Rat	Fü-albino (5)	p.o. (gavage)	5000	14	MNLD = > 5000 mg/kg; no observed clinical adverse effects
	Fü-albino (5)	p.o. (gavage)	3000	14	MNLD = > 3000 mg/kg; no observed clinical adverse effects; plasma levels of unchanged drug were BLQ
	Fü-albino	i.v.	0, 100	14	MNLD = > 100 mg/kg; short-lived (1-4 min.) CNS depression following both vehicle and

Table 15: Acute Toxicity

Species	Strain (#/sex/grp.)	Route of Admin.	Doses (mg/kg)	Obs. Period (days)	Principal Findings*
	(5)	(10 ml/kg)			test article
	Fü-albino (5)	i.v. (3 ml/kg)	0, 150	14	MNLD = > 150 mg/kg; no observed clinical adverse effects
Rat (2-week old)	Crl:CD®BR (5)	p.o. (gavage)	0, 2000	14	MNLD = > 2000 mg/kg; no observed clinical adverse effects
Dog	Beagle (1)	p.o. (capsule)	50, 100, 200, 400, 600, 800, & 1000†	1 day following last dose	MNLD = > 1000 mg/kg; no observed clinical adverse effects

*MNLD = Maximum Non-lethal Dose
†This was a pyramiding dose toxicity study; doses were escalated daily. The female dog received approximately 972 mg as final dose.

Multiple Dose Toxicity and Reproduction and Teratology Studies
-See Tabular Summaries which follow

The following abbreviations are used throughout these tables (and the Special Toxicity Tabulations); ↑(increased), ↓ (decreased), ALP (alkaline phosphatase), ALT (alanine aminotransferase), AUC (area under the curve), BW (body weight), clin.obs (clinical observations-in life), clin.path (clinical pathology), diet.admix (dietary admixture), DR (drug related), emul (emulsion), F (female), food cons. (food consumption), Histopath. (histopathology), M (male), met.act. (metabolic activation), min. (minutes), MNLD (maximum non-lethal dose), mos. (months), NOAE [no-observed-adverse-effect(s)], org.wt (organ weight), pp-hyptri (post-prandial hypertriglyceridemia).

Table 16: Long-term Toxicology Studies

Species	Strain (#/sex/grp.)	Route of Admin.	Doses (mg/kg/d)	Duration (weeks)	Principal Findings
Mouse	Ibm: MORO (SPF) (high dose & control: 15 all others: 10)	p.o. (diet admix)	0, 10, 65, 400, 2500	13	Mortality: NOAE Clin. Obs.: DR incr. food cons. in M @ 400 & 2500 and in F @ all doses Hematology: not done Clin. Path.: DR decr. in plasma cholesterol @ 65 & higher; DR incr. in plasma triglycerides @ 65 & higher (400 @ ≅ 2500); DR decr. in hepatic vitamins A & E conc. Necropsy: NOAE Organ Wt.: NOAE Histopath.: NOAE
Rat	Fü-albino (10 + 4 for toxicokin.)	p.o. (diet admix)	0, 50, 150, 450	13	Mortality: NOAE Clin. Obs.: incr. food intake @ all doses Ophthalmoscopy: NOAE Hematology: 20-25%. decr. in WBC @ 450 after 13 wks; lipemic plasma @ 150 & 450 Clin.Path.: after 13 wks - bilirubin & cholesterol 2-3 X incr. @ 450; DR incr. triglycerides (27 X @ 450); decr. hepatic Vit A (~ 60%) & Vit E (~60-75%) @ 450 Urinalysis: NOAE Necropsy: NOAE Organ Wt.: incr. (~10%). liver in F @ 450; incr. (~10-20%) adrenal in M+F @ 450 Histopath.: NOAE

Table 17: Long-term Toxicology Studies

Species	Strain (#/sex/grp.)	Route of Admin.	Doses (mg/kg/d)	Duration (weeks)	Principal Findings
Rat	Fü-albino (20)	p.o. (diet admix)	0, 250, 500, 1000, 2500	13	Mortality: NOAE Clin. Obs.: ~ 13-14% decr. B.W. gain @ 2500; incr. food intake @ all doses Ophthalmoscopy: NOAE Hematology: NOAE Clin. Path.: DR incr. pp-hyptri. @ ≥ 500 (7-25 X @ 2500); DR incr. (2-9 X) bilirubin @ ≥ 500; incr. fecal total lipid (75-80% of intake) @ all doses; decr. hepatic vitamins A & E (~ 60%) @ all doses despite supplement (M >F);
					Urinalysis: NOAE Necropsy: NOAE Organ Wt.: DR incr. in F adrenal wt. incr. M adrenal wt. @ 1000 & 2500 Histopath.: fatty change, vacuolation, and/or + fat stain in bone marrow, lumen of heart vessels, hepatocytes, or adrenal glands primarily @ 1000 & 2500 Toxicokinetics: DR incr. @ wk. 5.: Male: 20, 68, 225, 1470 ng/ml Female: 32, 91, 311, 1050 ng/ml
Rat	Fü-albino (26)	p.o. (diet admix)	0, 5, 25, 125	52	Mortality: NOAE Clin. Obs.: DR incr. food cons. @ 25 & 125; dark coloured feces @ 25 & 125 Ophthalmoscopy NOAE Hematology: NOAE Clin. Path.: decr.∝ -amylase & incr. BUN @ 125; plasma levels of vit. A decr. @ 125 in M (9-20%) and a DR decr. in plasma vit. E M & F; DR decr. in hepatic vit. A & E; ± hypertriglyceridemia @ 125; DR incr. in total fecal fat
					Urinalysis: NOAE Necropsy: NOAE Organ Wt.: NOAE Histopath.: NOAE Toxicokinetics: no unchanged drug detected in plasma @ 5 or 25; up to 64 ng/ml detected at week 51 @ 125.

Table 18: Reproduction and Teratology

Study	Species Strain (#/sex/grp.)	Route of Admin.	Doses (mg/kg/d)	Duration (days)	Principal Findings
Segment I	Rat Fü-albino (32)	p.o. (gavage)	0, 25, 100, 400	M: 70 prior to & during mating F: 14 prior to, and during mating, gestation, & lactation	No parental mortality; decr. wt. gain in males @ 400; plasma triglycerides incr. in males @ 100 (51%) and 400 (111%) Parents: NOAE with respect to fertility or reproductive performance Progeny: no morphological or functional impairment observed
Segment II	Rat Fü-albino (36, F only)	p.o. (gavage)	0, 50, 200, 800	Days 7-16 of gestation (day of mating = day 1)	Dams: NOAE Progeny: slight statistically significant increase in resorptions in hysterectomy subgroup (10.9%) but not in the delivery sub-group and within the range of normal (0-23.5%; mean = 8.1%) for the laboratory Dose-related increase in the incidence of dilated cerebral ventricles statistically significant at the high dose (1, 2, 4, & 7 @ 0, 50, 200, & 800, respectively)
Segment II	Rat Fü-albino (30, F only)	p.o. (gavage)	0, 800	Days 6-15 of gestation (day of mating = day 0)	Dams: B.W. gain during gestation days 6-16 decr. ~ 16% for the treated group Progeny: NOAE
Segment II	Rat Crl:CD®BR VAF/Plus® (25, F only)	p.o. (gavage)	Ro 18-0647/002: 0, 50, 250, 800 Ro 18-0647/008: 0, 50, 250, 800	Days 6-15 of gestation (day of mating = day 0)	Ro 18-0647/002 Dams: NOAE Progeny: NOAE Ro 18-0647/008 Dams: NOAE Progeny: NOAE
Segment III	Rat Fü-albino (24, F only)	p.o. (gavage)	0, 25, 100, 400	Day 15 of gestation through day 22 of lactation	Dams: slight impairment of B.W. gain @ 400 during late gestation and lactation Progeny: slight impairment of B.W. gain @ 400 during lactation period F1-Generation: NOAE with respect to physical or functional development
Segment II	Rabbit Swiss hare (20, F only)	p.o. (gavage)	0, 100, 300, 800	Days 7-19 of gestation (Day of mating = gestation day 1)	Dams: NOAE Progeny: NOAE

Carcinogenicity Studies

Two-year oral (dietary admix) carcinogenicity studies were conducted in mice and rats at high doses of 1500 and 1000 mg/kg/day, respectively; female mice were terminated after 94 weeks of dosing because of excessive intercurrent mortality that did not distinguish treated from control animals. The incidence and nature of gross findings at necropsy and of neoplastic lesions did not distinguish treated from control mice or rats. Toxicokinetic analyses conducted at the termination of the studies showed that the systemic exposure to orlistat was 100 to 1000 times higher in mice and rats, respectively, than that observed in patients during phase III clinical trials receiving 120 mg tid, the recommended therapeutic dose of orlistat.

Mutagenicity

The mutagenic potential of orlistat was investigated in the following short-term assays; Ames Test, with and without metabolic activation (tester strains TA97, TA98, TA100, TA102, TA1535, TA1537, TA1538), mammalian cell (V79/HPRT) gene mutation assay with and without metabolic activation, unscheduled DNA synthesis in primary cultures of rat hepatocytes, clastogenesis *in vitro* in human peripheral lymphocytes with and without metabolic activation, chromosome aberration assay (mouse micronucleus test) *in vivo*. No evidence of mutagenicity or genotoxicity was associated with orlistat in any of the assays.

Special Toxicity Studies
See attached tables.

Table 19: Special Toxicity Studies

Study	Species & Strain (#/sex/grp.)	Route of Admin.	Doses (mg/kg/day)	Duration	Principal Findings
Effect(s) on fecal lipid parameters & colonic cell proliferation	Rat Wistar (6/dose; M only)	p.o. (diet admix) Note: 40% of calories from fat & 0.1% Ca^{++} (synthetic diet)	0, 8.5, 116	9 days	Low Dose: 24% inhib. of fat absorption; incr. alk. phosphatase in fecal water, increased cytolytic activity in fecal water; incr. (20 X) free fatty acids in feces; decr. conc. of bile acids in fecal water; 2.5-fold increase in colonic epithelial proliferation High Dose: ≥ 56% inhibition of fat absorption; fecal lipid parameters not adequately assessed due to marked "oily leakage" from rectum ; 10-fold increase in colonic epithelial proliferation

Table 19: Special Toxicity Studies					
Study	**Species & Strain (#/sex/grp.)**	**Route of Admin.**	**Doses (mg/kg/day)**	**Duration**	**Principal Findings**
As above	Rat Wistar (6/dose; M only)	As above	0, 8.5, 25, 127	10 days	DR[1] ↑ fecal fat excretion: +29, +58, +>75%; DR ↑ thymidine incorporation into DNA in colonic mucosa: 1.9- 2.4-, 5.0-fold; no colonic hypertrophy or hyperplasia; effects reversed after discontinuation of treatment.
As above	Wistar(8/dose; M only)	As above + group on a diet with 1% Ca^{++}	0, 8.5, 25	20 days	DR ↑ fecal fat excretion (low & high Ca^{++}). No physiologically relevant changes in colonic mucosal proliferation (low & high Ca^{++}).
Rat	Fü-albino	p.o. (diet admix) [high fat, low calcium]	70, 140, 280 & 560 ppm	4 weeks	DR ↑ in food consumption; DR ↑ in fecal fat excretion (% of intake); DR ↑ in serum urea (BUN); ↑ mean kidney wt. In M @ 280 & 560 ppm and in F @ 560 ppm (no histopathological change); DR, slight ↑ in colonic mucosal proliferation in M @ 140, 280, & 560 ppm and in F @ 280 & 560 ppm.
Rat	Wistar	p.o. (diet admix) [high fat, low calcium & high fat, normal calcium]	70, 140, & 280 ppm	39 (interim sacs @ 13 and 26 weeks)	The studies are in progress; the findings are after 26 weeks of dosing: <u>High Fat, Low Calcium</u>: DR ↑ in BW, food consumption & DR ↓ in BW gain (reversed in recovery rats); NOAE with respect to colonic mucosal proliferation (PCNA), aberrant crypt foci (ACF), or histopathology (H&E staining) of the colon. <u>High Fat, Normal Calcium</u>: As above

[1]DR = Dose Related

Table 20: Special Toxicity Studies					
Study	**Species & Strain (#/sex/grp.)**	**Route of Admin.**	**Doses (mg/kg/day)**	**Duration**	**Principal Findings**
Dog (expl. RF; high fat, low Ca^{++} diet)	Beagle (3; M only)	p.o. (diet admix)	0, 0.3, 1.0, 3.0, 9.0	2 (17-18 days)	Mortality: NOAE Clin.Obs.: NOAE Hematology: NOAE Clin. Path.: DR ↓ serum cholesterol (18.2-47.4%); DR ↓ serum ∝ -tocopherol (9.2-59.9%) Urinalysis: NOAE Necropsy: NOAE Organ Wt.: NOAE Histopath.: NOAE

[1]DR = Dose Related

Table 21: Special Toxicity Studies

Study	Species & Strain (#/sex/grp.)	Route of Admin.	Doses (mg/kg/day)	Duration	Principal Findings
Dog (study conducted with a "high fat" diet)	Beagle (4 except 6 in the high-dose group)	p.o. (diet admix)	0, 10, 100, 1000	52	Mortality: None Clin. Obs.: ↑ food consumption Ophthalmoscopy: NOAE Hematology: NOAE Clin. Path.: DR ↑ plasma urea (33-63% for M & 34-39% for F), ↓ plasma cholest. (49-69% for M & 56-73% for F), ↓ plasma cholecalciferol (58-66% for M & 42-61% for F), ↓ plasma tocopherol (77-81% for M & 81-83% for F), ↓ hepatic retinol (50-88% for M & 49-57% for F), ↓ hepatic tocopherol (73-80% for M & 71-86% for F), pp-hypertri. @ mid- & high-dose. Urinalysis: NOAE EKG: NOAE Necropsy: NOAE Organ Wt.:NOAE Histopath.: NOAE Toxicokinetics: Continuous systemic exposure throughout the study; @ high dose: C_{max} was 500-4000 ng/ml & AUC was 4-5 to 50 µg.h/ml. Metabolite (Ro 42-3988) was 10-30% the level of Ro 18-0647.

[1]DR = Dose Related

REFERENCES

1. Chanoine JP et al. Effect of orlistat on weight and body composition in obese adolescents: A randomized controlled trial. JAMA 2005:293:2873-83.

2. Davidson MH et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. JAMA 1999; 281:235-42.

3. Drent ML, Van der Veen EA. Lipase Inhibition: A novel concept in the treatment of Obesity. Int J Obes Relat Metab Disord 1993; 17:241-4.

4. Drent ML, Van der Veen EA. Tetrahydrolipstatin treatment in obese patients. Int J Obesity 1991; 15:24 abstract #033.

5. Guzelhan C, et al. Influence of dietary composition on the inhibition of fat absorption by orlistat. J International Med Res 1994; 22:255-65.

6. Hadvary P, Lengsfeld H, Wolfer H. Inhibition of pancreatic lipase In Vitro by the covalent inhibitor tetrahydrolipstatin. Biochem J 1988; 256:357-61.

7. Harp JB. An assessment of the efficacy and safety of orlistat for the long-term management of obesity. J Nutr Biochem 1998; 9:516-21.

8. Hollander PA et al. Role of orlistat in the treatment of obese patients with type 2 diabetes. A 1-year randomized double-blind study. Diab Care 1998;21:1288-94.

9. James WP et al. A one-year trial to assess the value of orlistat in the management of obesity. Int J Obes Relat Metab Disord 1997;21 Suppl 3:S24-30.

10. Kelley et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes. Diabetes Care 2002; 25 (6); 1033-1041.

11. Kelley et al. Effects of moderate weight loss and orlistat on insulin resistance, regional adiposity, and fatty acids in type 2 diabetes. Diabetes Care 2004; 27 (1); 33-39.

12. Melia AT, Koss-Twardy SG, Zhi J. The effect of orlistat, an inhibitor of dietary fat absorption on the absorption of vitamins A and E in healthy volunteers. J Clin Pharmacol 1996; 36(7):647-53.

13. Miles et al. Effect of orlistat in overweight and obese patients with type 2 diabetes treated with metformin. Diabetes Care 2002; 25(7): 1123-1128.

14. Reitsma JB, et al. Relationship between improved postprandial lipemia and low-density lipoprotein metabolism during treatment with tetrahydrolipstatin, a pancreatic lipase inhibitor. Metabolism 1994; 43(3):293-8.

15. Sjörström L et al. Randomized placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. Lancet 1998; 352:167-72.

16. Torgerson JS et al. XENICAL in the Prevention of Diabetes in Obese Subjects (XENDOS) Study. Diabetes Care 2004; 27: 155-61.

17. Van Gaal F et al. Efficacy and tolerability of orlistat in the treatment of obesity: a 6-month dose-ranging study. Orlistat Dose-Ranging Study Group. Eur J Clin Pharmacol 1998; 54:125-32.

18. Zavoral JH. Treatment with orlistat reduces cardiovascular risk in obese patients. J Hypertens 1998; 16:2013-7.

19. Zhi J et al. Long-term systemic exposure of orlistat, a lipase inhibitor, and its metabolites in obese patients. J Clin Pharmacol 1999; 39:41-6.

20. Zhi J et al. Review of limited systemic absorption of orlistat, a lipase inhibitor, in healthy human volunteers. J Clin Pharmacol 1995; 35:1103-8.

21. 1998 Clinical Practice Guideline for the management of diabetes in Canada. CMAJ supplement 1998; 159 (8 Suppl).

PART III: CONSUMER INFORMATION

PrXENICAL®
orlistat

This leaflet is part III of a three-part "Product Monograph" published when XENICAL (pronounced Zen-e-cal) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about XENICAL. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

XENICAL is used along with a mildly reduced calorie diet to assist in weight loss and to maintain the weight loss in obese patients and overweight patients who have health risk factors such as type 2 diabetes, high blood pressure, and blood lipid problems. The weight loss will contribute to lowering the blood pressure and cholesterol and blood sugar levels.

Even a modest weight loss of 5-10% can lower your risk of developing health problems.

The weight loss achieved with XENICAL, along with a mildly reduced calorie diet, may also help reduce the risk of developing type 2 diabetes if you have impaired glucose tolerance.

XENICAL is recommended for:

- patients with a Body Mass Index (BMI*) greater than or equal to 30 kg/m^2, or
- patients with a BMI* greater than or equal to 27 kg/m^2 who have health problems, such as type 2 diabetes, high blood pressure, high cholesterol or a large waist measurement.

* *BMI is a simple measurement to estimate how overweight a person is. See your doctor to have your BMI measured.*

What it does:

- XENICAL is a prescription medicine when, combined with a mildly reduced calorie diet (average 20% decrease in daily calories, and no more than 30% of calories from fat), can help you lose weight and keep it off.
- XENICAL is a fat blocker. Fats from foods need to be broken down before they can be absorbed into the body. To break down fat, your body uses enzymes, called lipases. XENICAL, when taken with meals, prevents these enzymes from working. This blocks the absorption of about one third (30%) of the fat in food. The fat that is not absorbed passes out of the body in bowel movements, called stools. When you absorb less fat, you take in fewer calories, which leads to weight loss.
- XENICAL taken in combination with diabetes medications such as insulin, metformin and/or a sulfonylurea (like glyburide) may help you manage your type 2 diabetes by lowering your blood sugar.
- XENICAL does not suppress or change your appetite. It does not affect the brain like other medicines used for weight loss. Less than 1% of XENICAL is absorbed and the rest leaves the body in the stool.

When it should not be used:

XENICAL should not be used in patients with chronic malabsorption syndrome, cholestasis and in patients with known hypersensitivity with orlistat or to any component of XENICAL. (See "What the important non-medicinal ingredients are")

Chronic malabsorption syndrome is when the body has trouble absorbing nutrients from the intestine into the bloodstream. Cholestasis is caused by an obstruction in the liver where bile, a fluid made in the liver, is not able to be eliminated from the body through the intestine normally.

XENICAL is not intended to be used in children under 12 years of age, as this medicine has not been studied in this age group.

What the medicinal ingredient is:
Each capsule contains 120 mg of the active ingredient, orlistat.

What the important non-medicinal ingredients are:
The capsules contain non-medicinal or inactive ingredients. These are:

- microcrystalline cellulose, povidone, sodium starch glycolate, sodium lauryl sulphate, talc.

The capsule shell contains:

- gelatin, indigo carmine, titanium dioxide, edible printing ink.

What dosage forms it comes in:
XENICAL is a turquoise capsule with "XENICAL 120" printed in black ink.

WARNINGS AND PRECAUTIONS

BEFORE you use XENICAL talk to your doctor or pharmacist and make sure they know if:

- you have ever had a bad reaction to orlistat (XENICAL) or any of the inactive ingredients of XENICAL
- you are allergic to other medicines, foods and dyes
- you are taking cyclosporine
- you are taking diabetes medicines such as insulin, metformin and/or a sulfonylurea
- you are taking any other medicines including those not prescribed by your doctor
- you always have problems absorbing your food (chronic malabsorption syndrome)
- you have bowel or rectal problems
- you have gallbladder problems
- you have kidney problems. Kidney injury has been reported in patients treated with XENICAL.
- you are pregnant, plan on becoming pregnant, or are breastfeeding.
- you are taking birth control pills to prevent pregnancy. If you experience severe diarrhea, your birth control pills might not work as well and you might need to use an additional birth control method
- you are taking medicines to control seizures
- you are taking levothyroxine

Severe liver injury in patients taking XENICAL have been rarely reported. Promptly discontinue XENICAL and talk to your doctor if you have 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 that may be accompanied by nausea and vomiting.

This information will help your doctor and you decide whether you should use XENICAL, and what extra care may need to be taken while you are on the medicine.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with XENICAL include cyclosporine , amiodarone, and levothyroxine.

If you experience severe diarrhea, your birth control pills might not work as well and you might need to use an additional birth control method.

PROPER USE OF THIS MEDICATION

Usual dose:

Your doctor has prescribed XENICAL after carefully studying your case. Other people may not benefit from taking this medicine, even though their problems may seem similar to yours. Do not give your XENICAL to anyone else.

Weight Management:

- Take one capsule (120 mg) during or just following each main meal (breakfast, lunch and dinner). Swallow the capsule whole along with some water. Take the capsule no later than 1 hour after the meal is eaten.
- For example, if you just finished eating lunch at 12:30 p.m., you should take your lunchtime dose before 1:30 p.m.
- XENICAL should be taken with a mildly reduced calorie diet that contains no more than 30% of calories from fat as recommended by your doctor, dietitian or other healthcare professional.
- XENICAL can reduce the absorption of fat-soluble vitamins and beta-carotene. In clinical studies, most people's vitamin and beta-carotene levels were within the normal range. However, your doctor may tell you to take a daily multivitamin supplement while taking XENICAL. If you are between the ages of 12 to 16, you should take a multivitamin while taking XENICAL. A multivitamin should be taken two hours before or after your XENICAL capsule, or at bedtime.
- If you occasionally miss a main meal or if your meal contains no fat, do not take your XENICAL capsule.
- Take this medicine only as directed by your doctor. Do not take more of it, do not take it more often, and do not take it for a longer time than your doctor ordered.
- You will not lose more weight or lose it more quickly if you take more XENICAL capsules than your doctor has instructed.

If You Have Type 2 Diabetes:

- Your reduced calorie diet should be consistent with the dietary recommendations of the Canadian Diabetes Association Guidelines for the Nutritional Management of Diabetes Mellitus in the New Millennium.
- You should talk with your doctor about diabetes medications you may be taking, as this dosage might need to be lowered.

Taking XENICAL can help you reach a healthier weight. This medicine works best when you take it as directed, eat less fat and become more physically active.

What else should you remember while you are taking XENICAL?

- As XENICAL works by partially blocking dietary fat absorption, the expected weight loss will not occur if you replace the fat calories with carbohydrates or protein.
- Eat foods from all food groups (for example, see "Canada's Food Guide to Healthy Eating").
- Divide your day's calories and fat over 3 meals.
- Choose foods that have a lower fat content.
- Add less fat (butter, margarine or oils) to the foods you prepare.
- Develop healthy eating habits, like eating more fruits and vegetables.
- Gradually increase your physical activity as recommended by your doctor.
- If you have to go to the hospital or if you are given a new prescription medicine, you should tell the doctor(s) that you are taking XENICAL.
- Losing weight can affect the dose of other medicines you need, such as those for diabetes, high blood pressure or high cholesterol. Your doctor may need to adjust the doses of your other medicines. He or she may ask you to have regular blood tests to check your blood sugar and/or cholesterol level.
- If you have type 2 diabetes, you should follow the dietary recommendations of the Canadian Diabetes Association and test blood sugar and HbA1c levels regularly.

Missed Dose:

- If you forget to take a dose, it can be taken up to one hour after a meal and still be effective. Do not take double the amount if you miss one dose. XENICAL cannot work properly if many doses are missed.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Unwanted effects are possible with all medicines. Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking XENICAL.

Weight Management:

The most common possible side effects from XENICAL are directly related to the way XENICAL works. By blocking the absorption of some dietary fat, it is likely that you will experience some change in bowel habits. These effects are generally mild and transient (occur for a short period of time). They can increase if you eat high fat foods. In clinical studies, only 3% of people experienced one of these effects more than twice:

- oily spotting
- gas with discharge
- urgent need to have a bowel movement
- fatty/oily stools
- oily discharge
- increased number of bowel movements
- inability to control bowel movements.

Due to the presence of undigested fat, the oil in your bowel movement may be clear, orange or brown in colour. These bowel changes are a natural effect of blocking the fat from being absorbed and indicate that XENICAL is working.

How can you deal with these unwanted effects?

- Unwanted side effects are more likely to occur if you eat meals that contain large amounts of fat. Sticking to a diet that contains no more than 30% of calories from fat in each meal will reduce side effects.
- Try to avoid eating fatty foods.

Some unwanted side effects may go away during treatment as your body adjusts to the medicine.

Pancreatitis (inflammation of the pancreas) has been reported with the use of XENICAL.

Kidney problems, including kidney failure, have been reported with the use of XENICAL. Your doctor may do certain tests to check your kidney function while you are taking XENICAL.

If You Have Type 2 Diabetes:

Also, symptoms of hypoglycemia (low blood sugar) may occur, such as:

- sweating
- dizziness
- shakiness
- hunger
- confusion

Talk to your doctor for advice about how you can help avoid these symptoms and whether the dosage of the diabetes medications you may be taking might need to be lowered or discontinued.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect**	**Talk with your doctor or pharmacist**		**Stop taking drug and seek immediate medical help**
	Only if severe	**In all cases**	
Allergic reaction – Signs and symptoms include the following: wheezing, unexplained rash, difficulty swallowing or breathing, unexplained swelling, hives.			✓
Formation of gallstones – Signs and symptoms include the pain in the upper right portion of the abdomen that may be accompanied by nausea and vomiting.		✓	
Bleeding from the back passage (rectum)			✓
Kidney stones – Signs and symptoms include the following: back pain, blood in the urine.		✓	
Liver injury (including severe liver injury) – Signs and symptoms include the following: loss of appetite, itching, yellowing of the skin, dark urine, light colored stools, or right upper quadrant pain that may be accompanied by nausea and vomiting.			✓
Pancreatitis (inflammation of the pancreas) – Signs and symptoms include the following: upper abdominal pain, abdominal pain that radiates to your back, abdominal pain that feels worse after eating, nausea, vomiting, tenderness when touching the abdomen.			✓
Kidney problems (including kidney failure) – Signs and symptoms include decreased or no urination, nausea, vomiting, swelling (especially of the hands or feet), painful urination, blood in the urine, severe pain the back, belly or groin			✓

If you are concerned about these or any other unexpected effects while on XENICAL, talk with your doctor or pharmacist.

This is not a complete list of side effects. For any unexpected effects while taking* XENICAL*, contact your doctor or pharmacist.

HOW TO STORE IT

How should this product be stored?

- Keep out of the reach and sight of children.
- Store XENICAL in its original labelled container at room temperature (between 15-25°C). Keep the blister package in the XENICAL outer carton, in order to protect it from light and moisture.
- Store away from heat.
  - Do not use this medicine after the expiry date on the package.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php) or by calling 1-855 788-3153.

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