AUSTRALIAN PRODUCT INFORMATION – ORLISTAT VIATRIS (ORLISTAT) CAPSULES

1 NAME OF THE MEDICINE

Orlistat

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ORLISTAT VIATRIS is available as hard gelatin capsules containing 120 mg of orlistat.

Excipients with known effect: sugars as lactose

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

ORLISTAT VIATRIS capsules 120 mg are hard gelatin capsules with turquoise cap and body bearing the imprint of "LO1" in black ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

At the recommended therapeutic dose, the inhibition of the absorption of approximately one-third of dietary fat produces meaningful weight loss and reduces risk factors. At the same time, this effect allows absorption of adequate amounts of dietary fat and other nutrients that are essential for the maintenance of good health.

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

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

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

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

Special Patient Groups

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

Children: The use of ORLISTAT VIATRIS in patients under 18 years of age is not recommended (see Section 4.4 Special warnings and precautions for use – Paediatric use).

Body Mass Index (BMI) Calculation

BMI (kg / m^2) = weight (kilograms) / height^2 (metres)

Body Mass Index Table																
	Overweight					Obese										
BMI	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Height (cm)	**Body Weight (kg)**															
147	54	56	59	61	63	65	67	69	72	74	76	78	80	82	84	87
150	56	58	60	63	65	67	69	72	74	76	79	81	83	85	88	90
152	58	60	63	65	67	69	72	74	76	79	81	84	86	88	90	93
155	60	62	65	67	69	72	74	77	79	82	84	86	89	91	94	96
157	62	64	67	69	72	74	77	79	82	84	87	89	92	94	97	99
160	64	66	69	72	74	77	79	82	84	87	89	92	94	97	100	102
163	66	69	71	74	77	79	82	84	87	89	93	95	98	100	103	105
165	68	71	74	76	79	82	84	87	90	93	95	98	101	104	106	109
168	70	73	76	79	81	84	87	90	93	95	98	101	104	107	109	112
170	72	75	78	81	84	87	90	93	96	99	101	104	107	110	113	116
173	74	78	80	84	86	89	92	95	98	101	104	107	110	113	116	119
175	77	80	83	86	89	92	95	98	101	104	107	110	114	117	119	123
178	79	82	85	89	92	95	98	101	104	107	110	114	117	120	123	126
180	81	84	88	91	94	98	101	104	107	110	114	117	120	123	127	130
183	84	87	90	94	97	100	104	107	110	114	117	120	123	127	130	133
185	86	89	93	96	99	103	107	110	114	117	120	123	127	131	134	137
188	88	92	95	99	102	106	109	113	116	120	123	127	130	134	138	141
191	91	94	98	102	105	109	113	116	120	123	127	130	134	138	141	145
193	93	97	100	104	108	112	115	119	123	127	130	134	138	142	145	149

4.3 CONTRAINDICATIONS

ORLISTAT VIATRIS is contraindicated in patients with:

- hypersensitivity to orlistat or to any of the excipients in the capsule
- pancreatic enzyme deficiency or chronic pancreatitis and major gastrointestinal surgery
- chronic malabsorption syndrome
- cholestasis
- during pregnancy or breastfeeding.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

No serious adverse reactions or safety hazards related to the use of ORLISTAT VIATRIS have been reported to date during large, long-term clinical trials (see Section 4.8 Adverse effects (Undesirable effects)).

In addition to clinical trial data, post-marketing information is now available (see Section 4.8 Adverse effects (Undesirable effects), Post-Marketing Experience).

Information for Patients

Patients should be advised to adhere to dietary guidelines (see Section 4.2 Dose and method of administration). The possibility of experiencing gastrointestinal events (see Section 4.2 Dose and method of administration) may increase when ORLISTAT VIATRIS is taken with a diet high in fat (in a 8.4 kilojoule/day diet (2000 calorie/day), a diet high in fat would contain > 30% calories from fat, which equates to > 67 g fat). The daily intake of fat should be distributed over three main meals. If ORLISTAT VIATRIS is taken with any one meal very high in fat, the possibility of gastrointestinal effects may increase.

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

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

A reduction in ciclosporin plasma levels has been observed when ORLISTAT VIATRIS is co-administered. Therefore, it is recommended to monitor more frequently than usual the ciclosporin plasma levels when ORLISTAT VIATRIS is co-administered (see Section 4.5 Interactions with other medicines and other forms of interactions).

Weight loss induced by ORLISTAT VIATRIS is accompanied by improved metabolic control in type 2 diabetics which might allow or require reduction in the dose of hypoglycaemic medication (e.g. sulfonylureas) (see Section 4.5 Interactions with other medicines and other forms of interactions).

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

The use of an additional contraceptive method is recommended to prevent possible failure of oral contraception that could occur in case of severe diarrhoea (see Section 4.5 Interactions with other medicines and other forms of interactions).

Coagulation parameters should be monitored in patients treated with concomitant oral

anticoagulants (see Section 4.5 Interactions with other medicines and other forms of interactions, and Section 4.8 Adverse effects (Undesirable effects)).

Rare occurrence of 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 (see Section 4.5 Interactions with other medicines and other forms of interactions).

Antiepileptics patient: Orlistat may unbalance anticonvulsant treatment by decreasing the absorption of antiepileptic drugs, leading to convulsions (see Section 4.5 Interactions with other medicines and other forms of interactions).

Antiretrovirals for HIV: Orlistat may potentially reduce the absorption of antiretroviral medicines for HIV and could negatively affect the efficacy of antiretroviral medications for HIV (see Section 4.5 Interactions with other medicines and other forms of interactions).

Use in Patients with Other Disorders

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

Use in Patients with Vitamin Deficiency

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

Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E and K). ORLISTAT VIATRIS should be administered with due caution in those patients who have a deficiency of fat-soluble vitamins (A, D, E and K). Patients taking ORLISTAT VIATRIS showed a greater reduction in vitamins D, E and beta carotene levels compared to placebo during two or more consecutive visits in studies of 1 – 2 years duration. These patients did not receive prior vitamin supplementation. In order to ensure adequate nutrition, the use of a multivitamin supplement should be considered.

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

Use in hepatic impairment

Clinical investigations in patients with hepatic impairment have not been undertaken.

Use in renal impairment

The use of orlistat may be associated with hyperoxaluria and oxalate nephropathy leading sometimes to renal failure. This risk is increased in patients with underlying chronic kidney disease and/or volume depletion (see Section 4.8 Adverse effects (Undesirable effects)).

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

Use in the elderly

Clinical investigations in geriatric patients have not been undertaken.

Paediatric use

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

Effects on laboratory tests

Coagulation parameters, such as international normalised ratio (INR) values, should be monitored in patients treated with concomitant oral anticoagulants.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Oral Contraceptives (various ethinyloestradiol and gestagen combinations commercially available): In 20 normal weight female subjects, the treatment of orlistat (XENICAL) 120 mg three times daily for 23 days resulted in no changes in the ovulation-suppressing action of oral contraceptives. However, it should be borne in mind that orlistat-induced bowel irregularities may impair the efficacy of oral contraceptives. An additional contraceptive method should therefore be used, particularly in the event of diarrhoea.

Nifedipine (Extended-release tablets): No interactions based on specific drug-drug-interaction studies with nifedipine Gastrointestinal Therapeutic System (GITS) and nifedipine slow release have been observed. In 17 normal weight subjects receiving orlistat (XENICAL) 120 mg tid for 6 days, orlistat (XENICAL) did not alter the bioavailability of nifedipine extended-release tablets.

Ciclosporin: A reduction in ciclosporin plasma levels has been observed when orlistat (XENICAL) is co-administered (see Section 4.4 Special warnings and precautions for use). Therefore, it is recommended to monitor more frequently than usual the ciclosporin plasma levels when ORLISTAT VIATRIS is co-administered (see Section 4.4 Special warnings and precautions for use).

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

Amiodarone: In a pharmacokinetic study, oral administration of amiodarone during orlistat

(XENICAL) treatment demonstrated a 25 - 30% reduction in the systemic exposure to amiodarone and desethylamiodarone. The pharmacokinetics of amiodarone are complex. The effect of commencing orlistat (XENICAL) treatment in patients on stable amiodarone therapy has not been studied, but reduced systemic exposure to amiodarone and desethylamiodarone is possible, especially after chronic dosage with orlistat (XENICAL). A reduced therapeutic effect of amiodarone is possible. In patients receiving concomitant amiodarone treatment, reinforcement of clinical and ECG monitoring is warranted.

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

No interactions based on specific drug-drug-interaction studies with amitriptyline, atorvastatin, biguanides, fibrates, fluoxetine, losartan, phentermine, pravastatin, or sibutramine have been observed.

Rare occurrence of 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.

There are some case reports of reduced efficacy of antiretroviral HIV medicines, antidepressants, antipsychotics (including lithium) and benzodiazepines coincidental to the initiation of orlistat treatment in previously well-controlled patients. Therefore, orlistat treatment should only be initiated after careful consideration of the possible impact in these patients.

Metabolic Agents

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

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

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

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

Narrow Therapeutic Index Medicines

Drug interaction studies were performed with orlistat (XENICAL) and a number of medicines with a narrow therapeutic index. orlistat (XENICAL) had no inhibitory effects on pharmacokinetic or

pharmacodynamic parameters of the following medicines:

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

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

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

Fat-soluble Vitamin Supplements and Analogues

Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E and K). During clinical studies of orlistat (XENICAL) there were decreases in levels of some fat- soluble vitamins and analogues.

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

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

Other Concomitant Medications

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy – Pregnancy Category B1

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

Administration of orlistat to rats from late gestation to weaning at oral doses up to 400 mg/kg/day, associated with systemic exposures (plasma C_{max} for parent drug) of 50 times that in humans at the recommended dose, did not affect pup survival or development.

However, the safety of ORLISTAT VIATRIS has not been established in pregnant women, and because animal reproduction studies are not always predictive of human response, ORLISTAT VIATRIS is contraindicated during pregnancy.

Use in lactation

The secretion of orlistat in human breast milk has not been investigated. ORLISTAT VIATRIS is contraindicated during breastfeeding.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

The majority of GI symptoms were mild and transient. Commonly or very commonly observed adverse events that were considered by the investigator to be possibly or probably related to study medication were oily spotting, flatus with discharge, faecal urgency, fatty/oily stool, flatulence, abdominal pain, oily evacuation, liquid stools, increased defecation and faecal incontinence. The incidence of these increases the higher the fat content of the diet. Patients should be counselled as to the possibility of gastrointestinal effects occurring and how best to handle them such as reinforcing the diet, particularly the percentage of fat it contains. Consumption of a diet low in fat will decrease the likelihood of experiencing adverse gastrointestinal events and this may help patients to monitor and regulate their fat intake.

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

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

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

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

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

Common = ≥ 1/100 and < 1/10 patients (1 to < 10%)

Uncommon = ≥ 1/1000 and < 1/100 patients (0.1 to < 1%)

Rare = ≥ 1/10000 and < 1/1000 patients (0.01 to < 0.1%)

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

Skin and Subcutaneous Tissue Disorders: Uncommon: xeroderma, rash, pruritus ani, nail disorder, abnormal hair texture, pruritus, eczema, acne, increased sweating.

Nervous System Disorders: Common: headache; Uncommon: dizziness, vertigo, paraesthesia.

General Disorders and Administration Site Conditions: Common: asthenia; Uncommon: oedema, insomnia, influenza syndrome.

Musculoskeletal and Connective Tissue Disorders: Uncommon: leg cramps, back pain, myalgia, pain in ribs.

Metabolism and Nutrition Disorders: Uncommon: hypoglycaemia, increased appetite, thirst.

Hepatobiliary Disorders: Uncommon: cholelithiasis, biliary colic, cholecystitis.

Infections and Infestations: Uncommon: upper respiratory tract infection, lower respiratory tract infection, influenza, urinary tract infection.

Psychiatric Disorders: Uncommon: depression, anxiety.

Cardiac Disorders: Uncommon: chest pain.

Two cases of each of the following adverse events have been reported during clinical trials of orlistat (XENICAL) considered by the investigator to be possibly or probably related to study medication: gastrointestinal disorder, solid stools, lower abdominal pain, epigastric pain not food-related, hard

stools, diverticulum caecum, papular rash, brittle nails, loss of appetite, fever, fatigue, malaise, muscle cramps, decreased appetite, hypokalaemia, avitaminosis, sinusitis, pharyngitis, unpleasant smelling urine, polyuria, dysmenorrhoea, amenorrhoea, menstrual irregularity, palpitation, blurred vision, dermal bleeding, bitter taste, tumour.

Post-Marketing Experience

Gastrointestinal Disorders: Very rare: pancreatitis.

Immune System Disorders: Rare: hypersensitivity reactions including urticaria, pruritus, rash, angioedema, bronchospasm and anaphylaxis.

Skin and Subcutaneous Tissue Disorders: Very rare: cases of bullous eruptions have been reported during post-marketing experience.

Investigations: reports of decreased prothrombin, increased INR and unbalanced anti- coagulant treatment resulting in change to haemostatic parameters have been reported in patients treated concomitantly with orlistat (XENICAL) and anti-coagulants during post-marketing experience (see Section 4.5 Interactions with other medicines and other forms of interactions). Very rare: increases in transaminases and in alkaline phosphatase.

Hepatobiliary Disorders: Very rare: hepatitis that may be serious, exceptional cases of severe liver injury, some fatal cases or cases requiring liver transplantation have been reported. No causal relationship or physiopathological mechanism between liver injury and orlistat (XENICAL) therapy has been established.

Nervous System Disorders: Convulsions have been reported in patients treated concomitantly with orlistat (XENICAL) and anti-epileptic medicines (see Section 4.5 Interactions with other medicines and other forms of interactions).

Renal and Urinary Disorders: Cases of hyperoxaluria and oxalate nephropathy that may lead to renal failure have been reported.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.
Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Overdose of orlistat (XENICAL) has not been reported. Single doses of 800 mg orlistat (XENICAL) and multiple doses of up to 400 mg three times daily for 15 days have been studied in normal weight and obese subjects without significant adverse findings. In addition, doses of 240 mg three times daily have been administered to obese patients for 6 months without significant increase of adverse

findings. Doses above the recommended dose of 120 mg three times daily have not been found to appreciably improve efficacy and may increase gastrointestinal events.

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

Should a significant overdose of ORLISTAT VIATRIS 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Therapeutic / Pharmacological class of drug: Peripherally acting anti-obesity agent, ATC code A08AB01.

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

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

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

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

Clinical trials

Observational epidemiologic studies have established a relationship between obesity, visceral fat and the risks for cardiovascular disease, type II diabetes, certain forms of cancer, gallstones, certain respiratory disorders and an increase in overall mortality. These studies suggest that weight loss, if

maintained, may produce health benefits for obese patients who have or are at risk of developing weight-related comorbidities. Since fat provides twice the number of calories per gram as carbohydrates and protein, a selective reduction of calories from the dietary fat intake is a more efficient way of producing weight loss. The long-term effects of ORLISTAT VIATRIS on morbidity and mortality have not been established.

The effects of orlistat (XENICAL) on weight loss, weight maintenance, weight regain and on a number of comorbidities were assessed in the 4-year XENDOS study and in seven multicentre phase III double-blind, placebo-controlled, parallel group studies of 1- to 2-years duration. During the first year of therapy, the studies of 2-year duration assessed weight loss and weight maintenance. During the second year of therapy, some studies assessed continued weight loss and weight maintenance and others assessed the prevention of weight regain.

These studies included over 2800 patients treated with orlistat (XENICAL) and 1400 patients treated with placebo. The majority of studies had inclusion criteria of a body mass index (BMI) of 28 - 43 and age greater than 18 years. orlistat (XENICAL) also demonstrated beneficial effects in those patients who were diet-resistant. In the XENDOS study, which included 3304 patients, the time to onset of non-insulin dependent diabetes mellitus was assessed in addition to long- term weight management.

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

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

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

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

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

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

During the weight loss and weight maintenance period, a well-balanced mildly hypocaloric diet that provided 30% calories from fat was recommended. The diet was calculated using initial body weight

to provide a caloric deficit of 2.1 to 3.3 kilojoules (500 to 800 calories) per day, which represents an average caloric decrease of 20%. In addition, all patients were offered nutritional counselling.

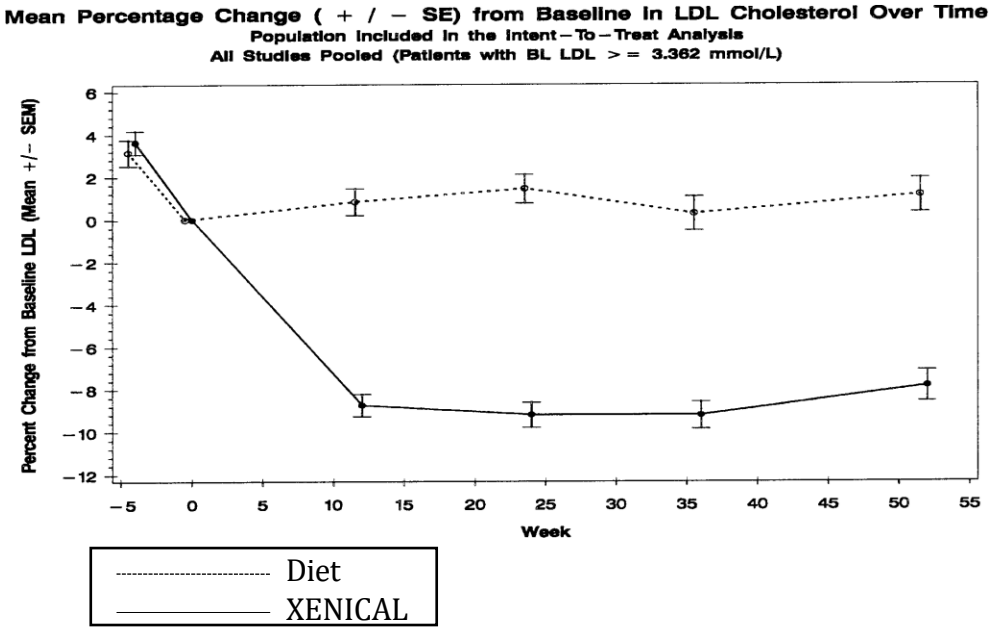
The percentages of patients achieving a > 5% and > 10% weight loss after 1 year in the largest multicentre study (Protocol BM 14119C) for the intent-to-treat population are shown in Table 1.

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

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

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

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



The reduction in total cholesterol and LDL cholesterol and the rapid improvement in LDL/HDL ratio produced by orlistat (XENICAL) is independent of weight loss as was demonstrated in an 8-week

study in normal weight hyperlipidaemic patients (see *Short-term Studies*).

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

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

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

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

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

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

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

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

Prevention of Weight Regain

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

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

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

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

In the XENDOS study (a 4-year multicentre, randomised, double-blind, parallel group, placebo-controlled trial), the effects of orlistat (XENICAL) treatment on long-term weight management and progression to non-insulin dependent diabetes mellitus (type 2 diabetes) in obese patients (BMI ≥ 30 kg/m^2 in males and females) were compared to placebo in 3304 obese patients who had either normal or impaired glucose tolerance at baseline.

Thirty-four percent of the 1655 patients who were randomised to the placebo group and 52% of the 1649 patients who were randomised to the orlistat (XENICAL) group completed the 4-year study. Patients were aged between 30 – 60 years at the time of enrolment.

Orlistat (XENICAL) was shown to be more effective than placebo in long-term weight control. Results showed that 73% of the orlistat (XENICAL) treated patients 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 orlistat (XENICAL) treated patients 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 orlistat (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 orlistat (XENICAL) treated patients 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 orlistat (XENICAL) treatment group compared to -3.03 kg for the placebo treatment group ($p < 0.001$).

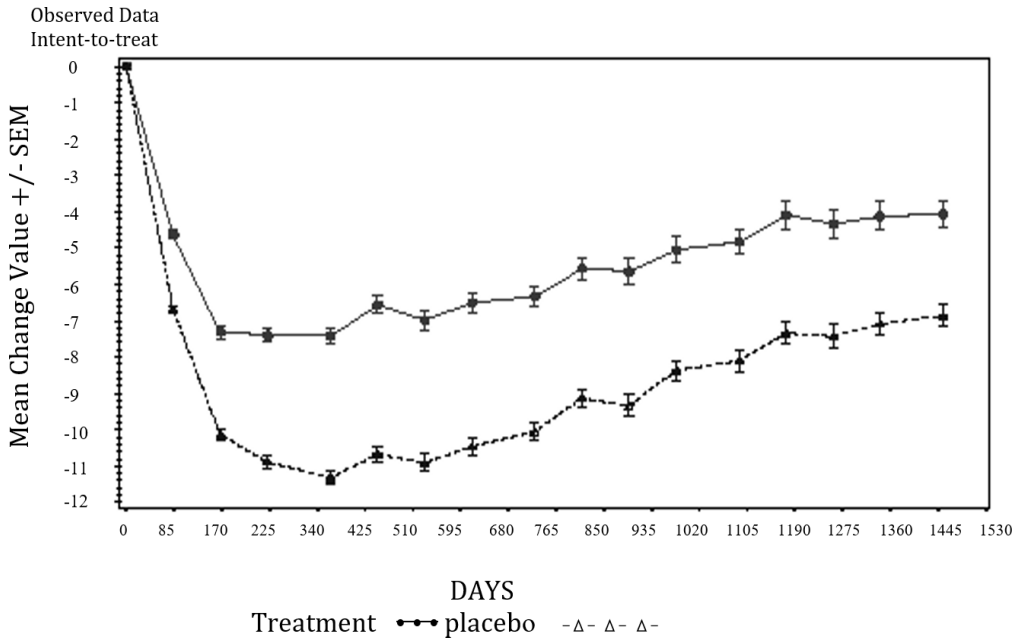
Throughout the entire four-year treatment period, orlistat (XENICAL) treated compared to placebo-treated patients had statistically significant ($p < 0.001$) reductions in several metabolic risk factors in addition to BMI. These included total cholesterol, LDL cholesterol, LDL:HDL ratio, fasting insulin,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

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

Risk Factor	**XENICAL 120 mg**	**Placebo**	***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) , µmol/L	-3.17	-0.57	<0.001
Cardiovascular:			
Systolic Blood Pressure, mm Hg	-4.12	-2.60	<0.001
Diastolic Blood Pressure, mm Hg	-1.93	-0.87	<0.001
Anthropometric:			
Waist Circumference, cm	-5.78	-3.99	<0.001

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

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



Study of Patients with Non-insulin Dependent Diabetes Mellitus

A 1-year double-blind, randomised, placebo-controlled study (Protocol NM 14336) in non-insulin dependent diabetics stabilised on sulfonylureas, was conducted. The results indicate that 49% of patients treated with orlistat (XENICAL) (*n* = 163) achieved a > 5% reduction in body weight compared to only 23% of the diet-alone patients (*n* = 159). orlistat (XENICAL) also improved glycaemic control in these patients as evidenced by statistically significant reductions in the doses of sulfonylureas, fasting blood glucose levels and haemoglobin A1c levels (0.5% improvement versus placebo). In this study, 43% of patients treated with orlistat (XENICAL) were able to reduce or discontinue their oral hypoglycaemic medications compared to 29% of the patients receiving placebo. There were also statistically significant improvements in total cholesterol, LDL-cholesterol, LDL/HDL ratio and triglycerides in the group treated with orlistat (XENICAL) compared to diet alone.

Glucose Tolerance in Obese Patients

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

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

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

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

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

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

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

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

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

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

Short-term Studies

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

In several studies of 6-weeks duration, the effects of therapeutic doses of orlistat (XENICAL) on gastrointestinal and systemic physiological processes were assessed in normal weight subjects. There were no clinically significant changes observed in gall bladder motility, bile composition and

lithogenicity or colonic cell proliferation rate, and no clinically significant reduction of gastric emptying time and gastric acidity. In addition, no effect on plasma triglyceride metabolism, systemic lipases, plasma and urinary minerals or electrolytes has been observed with the administration of orlistat (XENICAL) in these studies.

Obese Adolescents

Only limited data on the safety and efficacy of orlistat (XENICAL) in adolescents is available. One clinical trial showed that obese adolescents (12-16 years at screening) treated with orlistat (XENICAL) for one year had a decreased BMI, while those in the placebo group had an increased BMI. The magnitude of the effect seen with orlistat (XENICAL) on adolescents in this study was substantially less than that seen in adults in other studies. The adverse events profile was generally similar to that observed in adults (see Section 4.8 Adverse effects (Undesirable effects)). However, there was an unexplained increase in the incidence of bone fractures (6% versus 2.8% in the orlistat (XENICAL) and placebo groups, respectively).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

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

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

Distribution

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

Metabolism

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

Excretion

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

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

Long Term Administration

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

Special Populations

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

5.3 PRECLINICAL SAFETY DATA

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

In animal reproductive studies, no teratogenic effect was observed. In the absence of a teratogenic effect in animals, no malformative effect is expected in man.

Genotoxicity

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

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each capsule also contains the inactive ingredients: microcrystalline cellulose, lactose monohydrate, sodium lauryl sulfate, povidone, and purified talc. Each capsule shell contains gelatin, indigo carmine, and titanium dioxide. The printing ink contains shellac, ethanol absolute, isopropyl alcohol, butan-1-ol, propylene glycol, strong ammonia solution, iron oxide black, and potassium hydroxide.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine. Refer to section 4.5 Interactions with other medicines and other forms of interactions.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25 °C.

Keep the blister packs inside the original carton in order to protect from light and moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

Orlistat capsules are packed in PVC/PE/PVDC-Alu blister packs of 42 and 84 capsules.

Australian Register of Therapeutic Goods (ARTG)

AUST R 453806 – ORLISTAT VIATRIS orlistat 120 mg capsule blister pack.

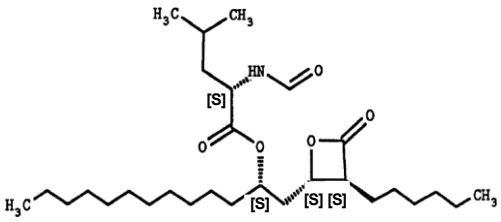
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

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

Chemical structure



The chemical name for orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl]-dodecyl ester. The molecular formula is $C_{29}H_{53}NO_5$. Orlistat has a molecular weight of 495.7.

CAS number

96829-58-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Pharmacist Only Medicine: Schedule 3

8 SPONSOR

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9 DATE OF FIRST APPROVAL

27th of June 2024

10 DATE OF REVISION

29th of May 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Change in tradename from ORLIZEN to ORLISTAT VIATRIS

2	Editorial change to update excipients section.
6.5	Include AUST R number