NEW ZEALAND DATA SHEET

Xenical® (120 mg capsules)

Orlistat

1 PRODUCT NAME

Xenical® 120 mg capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 120 mg Orlistat

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Hard capsule.

Xenical 120 mg hard capsules have a turquoise cap and turquoise body bearing the imprint of "XENICAL 120".

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Xenical is for weight control, including weight loss, weight maintenance and prevention of weight regain in adults with an initial body mass index (BMI) of 30 or more.

Xenical should be used in conjunction with a low fat, calorie-controlled diet.

4.2 Dose and method of administration

Adults

The recommended dose of Xenical is one 120 mg capsule orally three times a day with each main meal (during or up to one hour after the meal). If a meal is missed, the dose of Xenical may be omitted.

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.

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

The World Health Organisation (WHO) calculates Body Mass Index (BMI) using the following equation:

$$\text{BMI} = \frac{\text{weight (kg)}}{[\text{height (m)}]^2}$$

The WHO BMI classification for overweight adults is BMI ≥ 25, and for obese adults BMI ≥ 30.

Note, that these BMI values are age-independent and the same for both sexes. However, BMI may not correspond to the same degree of fatness across different populations due, in part, to different body proportions.

Renal impairment

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

Hepatic impairment

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

Elderly

Clinical investigations in elderly patients have not been undertaken.

Paediatric population

The efficacy and safety of Xenical in children and adolescents below the age of 18 years have not been established.

4.3 Contraindications

Xenical is contraindicated in patients with chronic malabsorption syndrome, cholestasis, during pregnancy or breastfeeding and in patients with known hypersensitivity to orlistat or any of the components contained in the medicinal product.

4.4 Special warnings and precautions for use

A reduction in cyclosporin plasma levels has been observed when Xenical is co-administered. Therefore, it is recommended to monitor more frequently than usual the cyclosporin plasma levels when Xenical is co-administered (see Section 4.5).

Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E and K). The majority of patients in long-term studies of up to four years of treatment had vitamin A, D, E and K and beta-carotene levels within normal range. In order to ensure adequate nutrition, the use of a multivitamin supplement should be considered.

Patients should be advised to adhere to dietary guidelines (see Section 4.2). The possibility of experiencing gastrointestinal events (see Section 4.8) may increase when Xenical is taken with a diet high in fat (e.g. in a 2000 kcal/day diet, > 30% of calories from fat equates to > 67 g of 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.

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 hypoglycaemic medication (e.g. sulfonylureas).

Cases of rectal bleeding have been reported with Xenical. 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).

The use of orlistat may be associated with hyperoxaluria and oxalate nephropathy leading sometimes to renal failure. Caution should be exercised when prescribing Xenical to patients with underlying chronic kidney disease and/or volume depletion, or in those with a history of hyperoxaluria or oxalate nephrolithiasis (see Section 4.8).

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).

Antiepileptics patient: Orlistat may unbalance anticonvulsant treatment by decreasing the absorption of antiepileptic drugs, leading to convulsions (see Section 4.5).

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).

Laboratory Tests

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

4.5 Interaction with other medicines and other forms of interaction

Decreases in the absorption of vitamin D, E and β-carotene have been observed when co-administered with Xenical. If a multivitamin supplement is recommended, it should be taken at least two hours after the administration of Xenical or at bedtime.

A reduction in cyclosporin plasma levels has been observed when Xenical is co-administered. Therefore, it is recommended to monitor more frequently than usual the cyclosporin plasma levels when Xenical is co-administered (see Section 4.4).

In a pharmacokinetic 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 effect of this is unclear. The effect of commencing orlistat treatment in patients on stable amiodarone therapy has not been studied. A reduced therapeutic effect of amiodarone is possible. In patients receiving concomitant amiodarone treatment, reinforcement of clinical and ECG monitoring is warranted.

Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic 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 medicine-medicine-interaction studies with amitriptyline, atorvastatin, biguanides, digoxin, fibrates, fluoxetine, losartan, phenytoin, phentermine, pravastatin,

warfarin, nifedipine Gastrointestinal Therapeutic System (GITS), nifedipine slow release, sibutramine or alcohol have been observed.

However, when warfarin or other anticoagulants are given in combination with orlistat, international normalised ratio (INR) values should be monitored.

In the absence of pharmacokinetic interaction studies, the concomitant administration of orlistat with acarbose should be avoided.

In specific interaction studies no interaction was observed between orlistat and 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

In animal reproductive studies, no embryotoxic or teratogenic effects were observed with orlistat. In absence of a teratogenic effect in animals, no malformative effect is expected in human beings. However, Xenical is not recommended for use during pregnancy in the absence of clinical data.

Breastfeeding

The secretion of orlistat in human breast milk has not been investigated. Xenical should not be taken during breast-feeding.

Fertility

No information available.

4.7 Effects on ability to drive and use machines

No information available.

4.8 Undesirable effects

Summary of the safety profile

Adverse reactions to Xenical are largely gastrointestinal in nature and related to the pharmacologic effect of orlistat on preventing the absorption of ingested fat.

Tabulated list of adverse reactions

The adverse reactions listed in the tables below have been reported in clinical trials and during the post-marketing period. Adverse reactions are presented by MedDRA System Organ Class and frequency (very common (1/10); common (1/100 to < 1/10); rare (1/10,000 to < 1/1,000); very rare (< 10,000); not known (cannot be estimated from the available data)).

Adverse reactions from clinical trials

System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Not known	Upper respiratory infection, lower respiratory infection, influenza, urinary tract infection
Psychiatric disorders	Not known	Anxiety
Nervous system disorders	Not known	Headache
Gastrointestinal disorders	Common	Oily spotting, flatus with discharge, faecal urgency, fatty/oily stool, oily evacuation, increased defaecation, faecal incontinence
	Common	Abdominal pain/discomfort, flatulence, liquid stools, soft stools, rectal pain/discomfort, tooth disorder, gingival disorder
Reproductive system and breast disorders	Not known	Menstrual irregularity
General disorders and administration site conditions	Not known	Fatigue

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 with the total incidence of gastrointestinal related adverse events occurring in year 1 decreasing year on year over the 4-year period.

Adverse reactions from post-marketing period

The following adverse events have been identified during post-marketing use of orlistat. Because these events are reported from a population of uncertain size, it is not always possible to reliably estimate their frequency and/or establish a causal relationship to drug exposure.

System Organ Class	Frequency	Adverse Reaction
Immune system disorders	Rare	Hypersensitivity (e.g. pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis)
Gastrointestinal disorders	Not known	Diverticulitis Pancreatitis Rectal bleeding

System Organ Class	Frequency	Adverse Reaction
Hepatobiliary disorders	Not known	Cholelithiasis Hepatitis that may be serious. Some fatal cases or cases requiring liver transplantation have been reported
Skin and subcutaneous tissue disorders	Very rare	Bullous eruption
Renal and urinary disorders	Not known	Hyperoxaluria Oxalate nephropathy that may lead to renal failure
Investigations	Very rare	Increase in liver transaminases and in alkaline phosphatase

Exceptional cases of severe liver injury, some resulting in liver transplant or death, have been reported. No causal relationship or physiopathological mechanism between liver injury and orlistat therapy has been established.

Reports of decreased prothrombin, increased international normalised ratio (INR) and unbalanced anticoagulant treatment resulting in change of haemostatic parameters have been reported in patients treated concomitantly with orlistat and anticoagulants during post-marketing (see Section 4.5).

Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic medicines (see Section 4.5).

Some patients taking Xenical may develop an increased risk for the development of kidney stones. Promptly report any symptoms of back pain or blood in the urine.

Description of selected adverse reactions

The incidence of gastrointestinal reactions increases with increasing 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.

These adverse gastrointestinal reactions are generally mild and transient. They occurred early in the treatment period (within 3 months) and most patients experienced only one episode.

Unique treatment adverse events observed in obese type 2 diabetic patients were hypoglycaemia (very common) and abdominal distension (common). 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 hypoglycaemic medication (see Section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

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 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.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Peripherally acting anti-obesity agent

ATC code: A08AB01

Mechanism of action

Xenical is a potent, specific and reversible long-acting inhibitor of gastrointestinal lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the serine residue of the active site of gastric and pancreatic lipases. 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 the weight control.

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

Efficacy/Clinical studies

Obese adults

Clinical trials have demonstrated that orlistat promotes weight loss, exceeding that achieved with diet alone. Weight loss was apparent within 2 weeks of initiation of treatment and continued for a duration of 6 to 12 months, even in individuals who failed to respond to dieting alone. Over 2 years,

statistically significant improvements in metabolic risk factors associated with obesity were observed. Orlistat was also effective in prevention of weight regain, with approximately half of the patients regaining no more than 25% of lost weight and about half of these regaining no weight or even continuing to lose weight.

Obese patients with Type 2 diabetes

Clinical trials conducted over a period of 6 months to one year showed that overweight or obese patients with type 2 diabetes had greater weight loss compared to dieting alone. It was also demonstrated that the weight loss was primarily due to decreased body fat. Additionally, despite receiving anti-diabetic medication, the average patient had poor glycaemic control, prior to study entry, but showed statistically significant (and clinically meaningful) improvements in glycaemic control following treatment with orlistat. Furthermore, anti-diabetic medication usage decreased, insulin levels were lower and decreased insulin resistance was apparent.

Delay in onset of Type 2 diabetes in obese patients

A clinical trial conducted over a 4-year period, showed that orlistat significantly reduced the risk of onset of type 2 diabetes, with the risk decreased by approximately 37%, compared to the placebo group. The decrease in risk for patients with impaired glucose tolerance at baseline was even more marked, at approximately 45%. Additionally, weight loss was significantly greater in the orlistat group than in the placebo group, and was maintained throughout the 4-year study period. Furthermore, orlistat-treated patients showed significant reductions in metabolic risk factors compared to placebo.

Obese adolescents

A clinical trial conducted over 1 year showed that obese adolescents treated with orlistat had a decreased BMI, compared to those in the placebo group, who had an increased BMI. Furthermore, those in the orlistat group had significantly decreased fat mass and waist and hip circumference compared to those in the placebo group. Diastolic blood pressure was also significantly reduced in the orlistat group compared to placebo.

5.2 Pharmacokinetic properties

Absorption

In normal weight and obese volunteers, the systemic exposure to orlistat was minimal. Plasma concentrations of intact orlistat were nearly non-measurable (< 5 ng/mL) following a single oral administration of 360 mg orlistat.

In general, after long-term treatment 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 showing consistency with negligible absorption.

Distribution

The volume of distribution cannot be determined because orlistat 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.

Biotransformation

Based on animal data, it is likely that the metabolism of orlistat occurs mainly pre-systemically. Two major metabolites (M1 and M3) accounted for approximately 42% of the total radioactivity in plasma resulting from the minute fraction of the dose that was absorbed systemically in obese patients.

These two major metabolites have very weak lipase inhibitory activity (1,000-fold and 2,500-fold less than orlistat respectively). In view of this low inhibitory activity and the low plasma levels at therapeutic doses (average of 26 ng/mL and 108 ng/mL respectively), these metabolites are pharmacologically inconsequential.

Elimination

Studies in normal weight and obese subjects have shown that faecal excretion of the unabsorbed orlistat was the major route of elimination. Approximately 97% of the administered dose was excreted in faeces and 83% of that as 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, M1 and M3 are all subject to biliary excretion.

Paediatric population

Plasma concentrations of orlistat and its metabolites M1 and M3 were slightly lower in paediatric patients compared to those found in adults at the same dose level. Daily faecal fat excretions were 27% and 7% of dietary intake in orlistat and placebo treatment groups, respectively.

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.

Teratogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Filling

microcrystalline cellulose

sodium starch glycolate

polyvidone K30

sodium lauryl sulphate

talc

Capsule Shell

gelatine

indigo carmine

titanium dioxide

traces of black printing ink

6.2 Incompatibilities

No known incompatibilities.

6.3 Shelf life

2 years. This medicine should not be used after the expiry date shown on the pack.

6.4 Special precautions for storage

Store below 25°C. Store in original package in order to protect from light and moisture.

6.5 Nature and contents of container

PVC/PVDC blister packs containing 84 hard capsules.

6.6 Special precautions for disposal

No special requirements.

7 MEDICINE SCHEDULE

Pharmacist Only Medicine

8 SPONSOR

Pharmaco (NZ) Ltd
PO Box 4079
Auckland 1140
NEW ZEALAND
Medical Enquiries: 0800 804 079

9 DATE OF FIRST APPROVAL

2 April 1998

10 DATE OF REVISION OF THE TEXT

25 May 2023

CCDS 5.0 September 2018

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
6.3	Reduction in shelf life from 3 years to 2 years