PROFESSIONAL INFORMATION

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

XENICAL® Capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Capsules

Each hard capsule contains 120 mg orlistat as the active substance.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Gelatine hard capsules with a turquoise cap and turquoise body containing white to off white pellets.

Black imprint XENICAL 120.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

XENICAL is indicated in conjunction with a reduced daily energy content in the diet, for the treatment of obese patients with a Body Mass Index (BMI) ≥ 30 kg/m^2 and overweight patients with a BMI ≥ 27 kg/m^2 in the presence of other risk factors.

Treatment with XENICAL should be discontinued after 12 weeks if a patient has been unable to lose at least 5 % of his/her body weight as measured at the start of therapy.

4.2 Posology and method of administration

Posology

Adults:

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

The patient should be on a nutritionally balanced, reduced energy 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.

The incidence of gastrointestinal side-effects 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.

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

The effect of XENICAL on faecal fat measurements is seen within 24 to 48 hours. Upon discontinuation of therapy, faecal fat content usually returns to pre-treatment levels, within 48 to 72 hours.

Safety and efficacy have been studied in clinical trials of up to 4 years.

The effect of XENICAL in patients with hepatic and/or renal impairment, children and elderly patients has not been studied. XENICAL is not intended to be used in children under the age of 12 years.

4.3 Contraindications

XENICAL is contraindicated in:

- patients with known hypersensitivity to orlistat or to any of the other excipients contained in XENICAL (See section 6.1);
- patients with chronic malabsorption syndrome;
- cholestasis;
- breastfeeding;
- patients with eating disorders (e.g. bulimia) other than obesity;
- patients younger than 12 years.
- XENICAL should not be co-administered with ciclosporin, acarbose and amiodarone.

4.4 Special warnings and precautions for use

Blood glucose levels of patients with type 2 diabetes mellitus and oral hypoglycaemic agents should be closely monitored when taking XENICAL. Weight loss induced by XENICAL in type 2 diabetics might need adjustment in the dose of hypoglycaemic medication as hypoglycaemia may occur.

In clinical trials, the decrease in bodyweight with XENICAL treatment was less in type II diabetes patients than in non-diabetic patients. Anti-diabetic treatment must be closely monitored when taking XENICAL.

Patients should be advised to adhere to the dietary recommendations they are given (see section 4.2).

Co-administration of orlistat with ciclosporin is not recommended (see section 4.5).

The possibility of experiencing gastrointestinal events may increase when XENICAL is taken with a diet high in fat (e.g. in a 2 000 kcal/day diet, > 30 % of calories from fat equating to > 67 g of fat). The daily intake of fat should be distributed over three main meals. If XENICAL is taken with a meal very high in fat, the possibility of gastrointestinal adverse effects may increase.

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).

Coagulation parameters should be monitored in patients treated with concomitant oral anticoagulants (see section 4.5 and 4.8).

The use of XENICAL 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).

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: XENICAL may unbalance anticonvulsant treatment by decreasing the absorption of antiepileptic drugs, leading to convulsions (see section 4.5).

Antiretrovirals for HIV: XENICAL 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).

This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants: When warfarin or other anticoagulants are given in combination with XENICAL the INR values should be monitored more frequently.

Ciclosporin: A decrease in ciclosporin plasma levels has been observed in an interaction study and also reported in several cases when XENICAL was administered concomitantly. This can lead to a decrease of immunosuppressive efficacy. Therefore, the combination is not recommended. More frequent monitoring should be performed both after addition of XENICAL and upon discontinuation of XENICAL in ciclosporin treated patients. Ciclosporin plasma levels should be monitored until stabilised.

Amiodarone: A decrease in plasma levels of amiodarone, when given as a single dose, has been observed in healthy volunteers who received XENICAL concomitantly; in patients receiving amiodarone treatment, the clinical relevance of this effect remains unknown.

Fat soluble vitamins: Treatment with XENICAL may impair the absorption of fat-soluble vitamins (A, D, E and K). The vast majority of patients receiving up to four full years of treatment with XENICAL in clinical studies had vitamin A, D, E and K and beta-carotene levels within the normal range. However, in order to ensure adequate nutrition, patients on XENICAL should be advised to have a diet rich in fruit and vegetables and the use of multivitamin products containing fat soluble vitamins should be considered. If a multivitamin supplement is recommended, it should be taken at least two hours after the administration of XENICAL or at bedtime.

Convulsions have been reported in patients treated concomitantly with XENICAL 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.

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 4.4).

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

Concomitant use of XENICAL and atorvastatin or phentermine increases the gastrointestinal side-effects of XENICAL.

Lack of interactions: No interactions with commonly prescribed medications such as amitriptyline, biguanides, digoxin, fibrates, fluoxetine, losartan, phenytoin, oral contraceptives, pravastatin, nifedipine GITS, nifedipine retard, sibutramine, captopril, atenolol or alcohol have been observed. The absence of these interactions has been demonstrated in specific interaction studies.

The absence of an interaction between oral contraceptives and XENICAL has been demonstrated in specific drug-drug interaction studies. However, XENICAL 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 diarrhoea (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

The safety of XENICAL in pregnant women has not been established.

Lactation

The safety of XENICAL in breastfeeding women has not been established.

XENICAL is contraindicated during breastfeeding (see section 4.3)

4.7 Effects on ability to drive and use machines

No effects on the patient's ability to drive and use machines have been reported.

4.8 Undesirable effects

a. Summary of the safety profile: No text

b. Tabulated list of adverse reactions:

Adverse reactions to XENICAL are largely gastrointestinal in nature. The incidence of adverse events decreased with prolonged use of XENICAL.

The following table of undesirable effects (first year of treatment) is based on adverse events that occurred at a frequency of > 2 % and with an incidence ≥ 1 % above placebo in clinical trials of 1- and 2-years duration:

System Organ Class	Adverse Event	XENICAL	Placebo
Infections and infestations	*Very common (≥ 10 %):*		
	Influenza	39,7 %	36,2 %
Metabolism and nutrition disorders	*Very common (≥ 10 %):*		
	*Hypoglycaemia**	13,0 %	10,0 %
Psychiatric disorders	*Common (1 - < 10 %):*		
	Anxiety	4,7 %	2,9 %
Nervous system disorders	*Very common (≥ 10 %):*		
	Headache	30,6 %	27,6 %
Respiratory, thoracic and mediastinal disorders	*Very common (≥ 10 %):*		
	Upper respiratory infection	38,1 %	32,8 %
	Common (1 - < 10 %):		
	Lower respiratory infection	7,8 %	6,6 %
Gastrointestinal disorders	*Very common (≥ 10 %):*		
	Oily spotting from the rectum Abdominal	26,6 %	1,3 %
	pain/discomfort	25,5 %	21,4 %
	Flatus with discharge	23,9 %	1,4 %
	Faecal urgency	22,1 %	6,7 %
	Fatty/oily stool	20,0 %	2,9 %
	Flatulence	16,0 %	13,1 %
	Liquid stools	15,8 %	11,4 %
	Oily evacuation	11,9 %	0,8 %
	Increased defecation	10,8 %	4,1 %
	Common (1 - < 10 %):		
	Soft stools	8,8 %	6,8 %
	Faecal incontinence	7,7 %	0,9 %
	Abdominal distension*	6,0 %	4,0 %
	Rectal pain/discomfort	5,2 %	4,0 %

	Tooth disorder Gingival disorder	4,3 % 4,1 %	3,1 % 2,9 %
Renal and urinary disorders	*Common (1 - < 10 %):* Urinary tract infection	 7,5 %	 7,3 %
Reproductive system and breast disorders	*Common (1 - < 10 %):* Menstrual irregularity	 9,8 %	 7,4 %
General disorders and administrative site conditions	*Common (1 - < 10 %):* Fatigue	 7,2 %	 6,4 %

* only unique treatment adverse events that occurred at a frequency of > 2 % and with an incidence ≥ 1 % above placebo in obese type 2 diabetic patients.

Post-marketing reports

The following undesirable effects are based on post-marketing spontaneous reports:

Immune system disorders: Hypersensitivity (e.g. pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis).

Gastrointestinal disorders: Diverticulitis, pancreatitis, rectal bleeding.

Hepatobiliary disorders: Cholelithiasis. Hepatitis that may be serious. Some fatal cases or cases requiring liver transplantation have been reported.

Skin and subcutaneous tissue disorders: Bullous eruptions.

Renal and urinary disorders: Hyperoxaluria. Oxalate nephropathy that may lead to renal failure.

Investigations: Increase in liver transaminases and in alkaline phosphatase. Decreased prothrombin, increased INR and unbalanced anticoagulant treatment resulting in variations of haemostatic parameters have been reported in patients treated with anticoagulants in association with XENICAL.

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

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. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptomatic and supportive.

Single doses of 800 mg XENICAL and multiple doses of up to 400 mg three times per 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 per day have been administered to obese patients for 6 months. Doses above the recommended dose of 120 mg three times per day have not been found to appreciably improve efficacy and may increase gastrointestinal events.

XENICAL 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 XENICAL should be rapidly reversible.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Peripherally acting anti-obesity agent, ATC code: A08AB01

Mechanism of action

Orlistat is a specific and 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 the 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. Undigested triglycerides are not absorbed. Systemic absorption of the medicine is therefore not needed for activity.

The effect of orlistat on faecal fat measurements is seen within 24 to 48 hours. Upon discontinuation of therapy, faecal fat content usually returns to pre-treatment levels, within 48 to 72 hours.

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 nearly non-measurable (< 5 ng/mL) eight hours following a single oral administration of orlistat. In general, 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 medicine is minimally absorbed and has no defined systemic pharmacokinetics. 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 pre-clinical data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on a study in obese patients, of the minimal 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. M1 and M3 have an open ß-lactone ring and extremely weak lipase inhibitory activity (1 000 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 considered to be pharmacologically inconsequential.

Elimination

Studies in normal weight and obese subjects have shown that faecal excretion of the unabsorbed medicine 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.

Special populations

Adolescents: Plasma concentrations of orlistat and metabolites were slightly lower in adolescents than those found in adults at the same dose levels. Daily faecal fat excretions were 27 % and 7 % of dietary intake in orlistat and placebo treatment groups, respectively.

5.3 Preclinical safety data

Non-clinical 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: microcrystalline cellulose, sodium starch glycollate, povidone, sodium lauryl sulphate, talc, gelatine, indigo carmine and titanium dioxide

6.2 Incompatibilities

Not available

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C. Store in original package and keep blister in outer carton in order to protect from light and from moisture.

Keep out of reach of children.

6.5 Nature and contents of container

PVC/Al blister packs. Packs containing 42 or 84 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Disposal of unused/expired medicines: The release of pharmaceuticals in the environment should be minimised. Medicines should not be disposed of via wastewater and disposal through household waste should be avoided. Use established “collection systems”, if available in your location.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaco Distribution (Pty) Ltd.

3 Sandown Valley Crescent,

South Tower, 1st Floor

Sandton, 2196

South Africa

Ethical assistance Line: +27 (0)11 784 0077

8. REGISTRATION NUMBER(S)

32/11.3.1/0475

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21 June 1999

10. DATE OF REVISION OF THE TEXT

07 July 2026