PACKAGE INSERT

SCHEDULING STATUS

S3

PROPRIETARY NAME AND DOSAGE FORM

XENICAL® Capsules

COMPOSITION

Each XENICAL capsule contains 120 mg orlistat.

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

PHARMACOLOGICAL CLASSIFICATION

A 11.3.1 Anorexigenics - other

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

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.

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.

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/m2 and overweight patients with a BMI ≥ 27 kg/m2 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.

CONTRAINDICATIONS

XENICAL is contraindicated in patients with chronic malabsorption syndrome, cholestasis, breastfeeding and in patients with known hypersensitivity to XENICAL or any of the other components contained in the capsule. XENICAL must not be used in patients with eating disorders (e.g. bulimia) other than obesity. Not to be used in patients younger than 12 years.

XENICAL should not be co-administered with ciclosporin, acarbose and amiodarone.

WARNINGS AND SPECIAL PRECAUTIONS

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 DOSAGE AND DIRECTIONS FOR USE. 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.

Effects on ability to drive and use machines

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

INTERACTIONS

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.

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.

PREGNANCY AND LACTATION

XENICAL is not recommended for use in pregnancy and lactation.

DOSAGE AND DIRECTIONS FOR USE

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 has 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.

SIDE-EFFECTS

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	26,6 %	1,3 %
	Abdominal 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	4,3 %	3,1 %
	Gingival disorder	4,1 %	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 administration 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.

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.
- Hepato-biliary disorders: Cholelithiasis. Hepatitis that may be serious.
- Skin and subcutaneous tissue disorders: Bullous eruptions.
- 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 INTERACTIONS.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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.

IDENTIFICATION

Gelatine capsules with a turquoise cap and turquoise body containing white to off white pellets. Black imprint XENICAL 120.

PRESENTATION

Blisters with 42 or 84 capsules.

STORAGE INSTRUCTIONS

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.

Medicine: Keep out of reach of children.

REGISTRATION NUMBER

32/11.3.1/0475

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Pharmaco Distribution (Pty) Ltd.

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