XENICAL®
Orlistat

1. PHARMACEUTICAL FORM
XENICAL 120 mg hard capsules. The capsule has a turquoise cap and turquoise body bearing the imprint of "XENICAL 120".

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each hard capsule contains 120 mg orlistat. For excipients, see 5.1.

3. CLINICAL PARTICULARS
3.1 Therapeutic indications
Xenical is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) greater or equal to 30 kg/m^2, or overweight patients (BMI ≥ 28 kg/m^2) with associated risk factors.

Treatment with Xenical should be discontinued after 12 weeks if patients have been unable to lose at least 5% of their body weight as measured at the start of drug therapy.

In type 2 diabetic patients who are overweight (BMI ≥ 28kg/m^2) or obese (BMI ≥ 30kg/m^2), clinical studies conducted over one year showed Xenical, in conjunction with a mildly hypocaloric diet, provides additional glycemic control when used in combination with anti-diabetic agents such as metformin, sulfonylurea and/or insulin. No studies have been done in patients receiving concomitant treatment with thiazolidinedione. The efficacy of Xenical as a monotherapy treatment for type 2 diabetes has not been established.

3.2 Posology and method of administration
The recommended dose of orlistat is one 120 mg capsule taken with water immediately before, during or up to one hour after each main meal. If a meal is missed or contains no fat, the dose of orlistat should 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 of orlistat above 120 mg three times daily have not been shown to provide additional benefit.

The effect of orlistat results in an increase in faecal fat as early 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. The safety and effectiveness of Xenical beyond 4 years have not been determined at this time; therefore, the duration of treatment with Xenical should not be longer than 4 years.

Special populations
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.

3.3 Contraindications
- Chronic malabsorption syndrome
- Cholestasis
- Breastfeeding
- Hypersensitivity to the active substance or to any of the excipients. Xenical is not recommended for use during pregnancy.

3.4 Warnings and precautions for use
In clinical trials, the decrease in bodyweight with orlistat treatment was less in type II diabetic patients than in non-diabetic patients. Antidiabetic drug treatment may have to be closely monitored when taking orlistat.

Co-administration of orlistat with cyclosporine is not recommended (see section 3.5).

Patients should be advised to adhere to the dietary recommendations they are given (see section 3.2 Posology and method of administration). The possibility of experiencing gastrointestinal events (see section 3.8 Undesirable effects) may increase when orlistat 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 orlistat is taken with a meal very high in fat, the possibility of gastrointestinal adverse events 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 3.5).

Coagulation parameters, such as international normalized ratio (INR) values, should be monitored in patients treated with concomitant oral anticoagulants (see section 3.5 and 3.8).

The use of orlistat may be associated with hyperoxaluria and oxalate nephropathy in patients with underlying chronic kidney disease and/or volume depletion (see section 3.8).

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 3.5).

Antiepileptics patient: Orlistat may unbalance anticonvulsivant treatment by decreasing the absorption of antiepileptic drugs, leading to convulsions (see section 3.5).

3.5 Interaction with other medicinal products and other forms of interaction
Cyclosporine
A decrease in cyclosporine plasma levels has been observed in a drug-drug-interaction study and also reported in several cases, when orlistat was administered concomitantly. This can lead to a decrease of immunosuppressive efficacy. Therefore the combination is not recommended. However, if such concomitant use is unavoidable, more frequent monitoring of cyclosporine blood levels should be performed both after addition of orlistat and upon discontinuation of orlistat in cyclosporine treated patients. Cyclosporine blood levels should be monitored until stabilised.

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

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

Fat soluble vitamins
Treatment with orlistat may potentially 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 orlistat in clinical studies had vitamin A, D, E and K and beta-carotene levels that stayed within normal range. In order to ensure adequate nutrition, patients on a weight control diet should be advised to have a diet rich in fruit and vegetables and use of a multivitamin supplement could be considered. If a multivitamin supplement is recommended, it should be taken at least two hours after the administration of orlistat or at bedtime.

Amiodarone
A small decrease in plasma levels of amiodarone, when given as a single dose, has been observed in a limited number of healthy volunteers who received orlistat concomitantly; in patients receiving amiodarone treatment, the clinical relevance of this effect remains unknown but may be of minor relevance. However, 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 drugs, e.g. valproate, lamotrigine, for which a causal relationship to an interaction cannot be excluded. Therefore, these 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.

Lack of interactions
No interactions with amitriptyline, atorvastatin, biguanides, digoxin, fibrates, fluoxetine, losartan, phenytoin, oral contraceptives, phentermine, pravastatin, nifedipine Gastrointestinal Therapeutic System (GITS), nifedipine slow release, sibutramine or alcohol have been observed. The absence of these interactions has been demonstrated in specific drug-drug-interaction studies.

The absence of an interaction between oral contraceptives and orlistat has been demonstrated in specific drug-drug interaction studies. However, orlistat may indirectly reduce the availability of oral contraceptives and lead to unexpected pregnancies in some individual cases. An additional contraceptive method is recommended in case of severe diarrhoea.

3.6 Pregnancy and lactation
For orlistat no clinical data on exposed pregnancies are available.

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see 4.3, Preclinical safety data). However, Xenical is not recommended for use during pregnancy in the absence of clinical data.

As it is not known whether orlistat is secreted into human milk, orlistat is contraindicated during breastfeeding.

3.7 Effects on ability to drive and use machines
Xenical has no influence on the ability to drive and use machines.

3.8 Undesirable effects
Adverse reactions to orlistat are largely gastrointestinal in nature. The incidence of adverse events decreased with prolonged use of orlistat.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000) including isolated reports.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 reaction/event
Nervous system disorders		
	Very common:	Headache
Respiratory, thoracic and mediastinal disorders		
	Very common:	Upper respiratory infection
	Common:	Lower respiratory infection
Gastrointestinal disorders		
	Very common:	Abdominal pain/discomfort
		Oily spotting from the rectum
		Flatus with discharge
		Faecal urgency
		Fatty/oily stool
		Flatulence
		Liquid stools
		Oily evacuation
		Increased defecation
		Rectal pain/discomfort
	Common:	Soft stools
		Faecal incontinence
		Abdominal distension*
		Tooth disorder
		Gingival disorder
Renal and urinary disorders		
	Common:	Urinary tract infection
Metabolism and nutrition disorders		
	Very common:	Hypoglycemia*
Infections and infestations		
	Very common:	Influenza
General disorders and administration site conditions		
	Common:	Fatigue
Reproductive system and breast disorders		
	Common:	Menstrual irregularity
Psychiatric disorders		
	Common:	Anxiety

* 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.

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 four year period.

The following table of undesirable effects is based on post-marketing spontaneous reports, and therefore the frequency remains unknown:

System organ class	Adverse reaction
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 orlistat (see section 3.5).
Gastrointestinal disorders	Rectal bleeding Diverticulitis Pancreatitis
Skin and subcutaneous tissue disorders	Bullous eruptions
Immune system disorders	Hypersensitivity (e.g. pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis)
Hepatobiliary disorders	Cholelithiasis Very rare cases of bullous eruption, increase in liver transaminases and in alkaline phosphatase, and exceptional cases of severe liver injury, some resulting in liver transplant or death, have been reported.
Renal and urinary disorders	Oxalate nephropathy Hyperoxaluria

3.9 Overdose

Single doses of 800 mg orlistat 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 tid have been administered to obese patients for 6 months. The majority of 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 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.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamic properties

Orlistat is a potent, 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 active serine site of the gastric and pancreatic lipases. The inactivated enzyme is thus unavailable to hydrolyse dietary fat, in the form of triglycerides, into absorbable free fatty acids and monoglycerides.

In the 2-year studies and the 4-year study, a hypocaloric diet was used in association with treatment in both the orlistat and the placebo treated groups.

Pooled data from five 2 year studies with orlistat and a hypocaloric diet showed that 37 % of orlistat patients and 19 % of placebo patients demonstrated a loss of at least 5 % of their baseline body weight after 12 weeks of treatment. Of these, 49 % of orlistat treated patients and 40 % of placebo treated patients went on to lose ≥ 10 % of their baseline body weight at one year. Conversely, of patients failing to demonstrate a loss of 5 % of their baseline body weight after 12 weeks of treatment, only 5 % of orlistat treated patients and 2 % of placebo treated patients went on to lose ≥ 10 % of their baseline body weight at one year. Overall, after one year of treatment, the percentage of patients taking 120 mg orlistat who lost 10 % or more of their body weight was 20 % with orlistat 120 mg compared to 8 % of patients taking placebo. The mean difference in weight loss with the drug compared to placebo was 3.2 kg.

Data from the 4-year XENDOS clinical trial showed that 60 % of orlistat patients and 35 % of placebo patients demonstrated a loss of at least 5 % of their baseline body weight after 12 weeks of treatment. Of these, 62 % of orlistat treated patients and 52 % of placebo treated patients went on to lose ≥ 10 % of their baseline body weight at one year. Conversely, of patients failing to demonstrate a loss of 5 % of their baseline body weight after 12 weeks of treatment, only 5 % of orlistat treated patients and 4 % of placebo treated patients went on to lose ≥ 10 % of their baseline body weight at one year. After 1 year of treatment, 41 % of the orlistat treated patients versus 21 % of placebo treated patients lost ≥ 10 % of body weight with a mean difference of 4.4 kg between the two groups. After 4 years of treatment 21 % of the orlistat treated patients compared to 10 % of the placebo treated patients had lost ≥ 10 % of body weight, with a mean difference of 2.7 kg.

More patients on orlistat or placebo lost baseline body weight of at least 5 % at 12 weeks or 10 % at one year in the XENDOS study than in the five 2-year studies. The reason for this difference is that the five 2-year studies included a 4-week diet and placebo lead-in period during which patients lost on average 2.6 kg prior to commencing treatment.

Data from the 4-year clinical trial also suggested that weight loss achieved with orlistat delayed the development of type 2 diabetes during the study (cumulative diabetes cases incidences: 3.4 % in the orlistat group compared to 5.4 % in the placebo-treated group). The great majority of diabetes cases came from the subgroup of patients with impaired glucose tolerance at baseline, which represented 21 % of the randomised patients. It is not known whether these findings translate into long-term clinical benefits.

In the 1-year adolescent study, a hypocaloric diet was used in association with treatment in both the orlistat and the placebo treated groups. In the 1-year multi-centre (US, Canada), parallel-group, double-blind, placebo-controlled study, 539 obese adolescents patients were randomized to receive either 120mg orlistat (n=357) or placebo (n=182) three times daily as an adjunct to a hypocaloric diet and exercise. The average weight of patients on placebo and orlistat, respectively, was 95.11 kg and 97.71 kg with a BMI of 35.43 kg/m^2 and 35.72 kg/m^2. Body mass index (BMI) was the primary efficacy parameter because it takes into account changes in height and body weight, which occur in growing children.

Data from the study showed 13.3 % of the orlistat treated patients versus 4.5 % of placebo treated patients showed a reduction of ≥ 10 % in BMI. BMI decreased by an average of 0.55 kg/m^2 in the orlistat treated patients and increased by an average of 0.31 kg/m^2 in the placebo-treated patients. 9.5 % of the orlistat treated patients versus 3.3 % of placebo treated patients lost ≥ 10 % of body weight after 1 year with a mean difference of 2.6 kg between the two groups. Changes in body composition measured by Dual Energy X-ray Absorptiometry (DEXA) were similar in the orlistat and placebo treatment groups with the exception of fat mass, which was significantly reduced in patients treated with orlistat compared to patients treated with placebo. The side effects were generally similar to those observed in adults. However, there was an unexplained increase in the incidence of bone fractures (6 % versus 2.8 % in the orlistat and placebo groups, respectively). The safety and efficacy of orlistat in adolescents was not assessed beyond 1 year.

In obese type 2 diabetic patients insufficiently controlled by antidiabetic agents, data from four one-year clinical trials showed that the percentage of responders (≥ 10 % of body weight loss) was 11.3 % with orlistat as compared to 4.5 % with placebo. In orlistat-treated patients, the mean difference from placebo in weight loss was 1.83 kg to 3.06 kg and the mean difference from placebo in HbA_{1c} reduction was 0.18 % to 0.55 %. It has not been demonstrated that the effect on HbA_{1c} is independent from weight reduction.

The pooled data from the four one year studies and three six month studies of Xenical as an adjunct to antidiabetic medications are summarised in the following table:

Parameter	Sulfonylurea		Metformin		Insulin	
	Xenical (n=741)	Placebo (n=749)	Xenical (n=550)	Placebo (n=538)	Xenical (n=262)	Placebo (n=268)
Body Weight (kg)						
Baseline mean	94.99	94.45	96.10	96.39	101.93	101.65
LSM change from Baseline	-3.41*	-1.30	-3.80*	-1.24	-3.85*	-1.25
HbA_{1c} (%)						
Baseline mean	8.41	8.39	8.65	8.72	8.97	9.01
LSM change from Baseline	-0.62*	-0.20	-0.82*	-0.48	-0.62*	-0.27
% patients with reduction in HbA_{1c}						
≥0.5% decrease	55**	38	61**	49	51**	40
≥1.0% decrease	39**	25	46**	33	32**	22
Fasting plasma glucose (mmol/L)						
Baseline mean	10.18	9.88	10.78	10.49	10.91	11.15
LSM change from Baseline	-1.06*	0.12	-1.73*	-0.64	-1.73*	-1.00
Post-prandial plasma glucose (mmol/L)						
Baseline mean	14.56	14.01	14.54	13.92	ND	ND
LSM change from Baseline	-1.64*	-0.20	-1.28*	0.15	ND	ND
Changes in anti-diabetic medication						
% Patients with decreases	23$^+$	15	16$^+$	13	42$^+$	31
% Patients with increases	9$^+$	17	11$^+$	19	14$^+$	32

LSM = Least squares mean; ND = Not done

*p < 0.05 based on LSM differences Xenical v. placebo; **p < 0.05 based on Cochran-Mantel-Haentzel test.

$^+$ P value < 0.05 for overall change in anti-diabetic medication

4.2 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 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 µmol), with no evidence of accumulation, which is consistent with minimal absorption.

Distribution:

The volume of distribution cannot be determined because the drug 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 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 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 beta-lactone ring and extremely weak lipase inhibitory activity (1000 and 2500 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 drug 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.

Pharmacokinetics in Special Populations

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

4.3 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. To date, active substances responsible for malformations in man have been found teratogenic in animals when well-conducted studies were performed in two species.

5. PHARMACEUTICAL PARTICULARS

5.1 List of excipients

Capsule filling: Microcrystalline cellulose (E460), sodium starch glycollate, povidone (E1201), sodium lauryl sulphate and talc.

Capsule shell:
Gelatine, indigo carmine (E132), titanium dioxide (E171).

5.2 Stability

This medicine should not be used after the expiry date (EXP) shown on the pack. See also outer pack for storage remark.
Do not store above 25°C. Store in original package and keep the blister in the outer carton, in order to protect from light and moisture.

6. Packs

Capsules 120mg 21, 42, 84

Medicine: keep out of reach of children

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CHEPLAPHARM Arzneimittel GmbH, Greifswald, Germany