SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Orlos 60mg hard capsules
Orlistat 60mg hard capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 60 mg orlistat.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule

The capsule has a brightly blue body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Orlistat is indicated for weight loss in adults who are overweight (body mass index, BMI, ≥28 kg/m^2) and should be taken in conjunction with a mildly hypocaloric, lower-fat diet.

4.2 Posology and method of administration

Posology

Adults

The recommended dose of Orlistat is one 60 mg capsule to be taken three times daily. No more than three 60 mg capsules should be taken in 24 hours.

Diet and exercise are important parts of a weight loss programme. It is recommended that a diet and exercise programme is started before beginning treatment with Orlistat.

While taking orlistat, the patient should be on a nutritionally balanced, mildly hypocaloric diet that contains approximately 30% of calories from fat (e.g. in a 2,000 kcal/day diet, this equates to <67 g of fat). The daily intake of fat, carbohydrate and protein should be distributed over three main meals.

The diet and exercise programme should continue to be followed when treatment with Orlistat is stopped.
Treatment should not exceed 6 months.
If patients have been unable to lose weight after 12 weeks of treatment with Orlistat, they should consult their doctor or a pharmacist. It may be necessary to discontinue treatment.

Special populations

Elderly (>65 years old)
There are limited data on the use of orlistat in the elderly.
However, as orlistat is minimally absorbed, no dose adjustment is necessary in the elderly.

Hepatic and renal impairment
The effect of orlistat in individuals with hepatic and/or renal impairment has not been studied (see section 4.4). However, as orlistat is minimally absorbed, no dose adjustment is necessary in individuals with hepatic and/or renal impairment.

Paediatric population
The safety and efficacy of Orlistat in children below 18 years of age has not been established. No data are available.

Method of administration

The capsule should be taken with water immediately before, during or up to 1 hour after each main meal. If a meal is missed or contains no fat, the dose of orlistat should be omitted.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concurrent treatment with ciclosporin (see section 4.5).

Chronic malabsorption syndrome.

Cholestasis.

Pregnancy (see section 4.6).

Breast-feeding (see section 4.6).

Concurrent treatment with warfarin or other oral anticoagulants (see sections 4.5 and 4.8).

4.4 Special warnings and precautions for use

Gastrointestinal symptoms

Patients should be advised to adhere to the dietary recommendations they are given (see section 4.2).
The possibility of experiencing gastrointestinal symptoms (see section 4.8) may increase when orlistat is taken with an individual meal or a diet high in fat.

Fat-soluble vitamins

Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E and K) (see section 4.5). For this reason, a multivitamin supplement should be taken at bedtime.

Antidiabetic medicinal products

As weight loss may be accompanied by improved metabolic control in diabetes, patients who are taking a medicinal product for diabetes should consult a doctor before starting treatment with Orlistat, in case it is necessary to adjust the dose of the antidiabetic medicinal product.

Medicinal products for hypertension or hypercholesterolaemia

Weight loss may be accompanied by an improvement in blood pressure and cholesterol levels.
Patients who are taking a medicinal product for hypertension or hypercholesterolaemia should consult a doctor or pharmacist when taking Orlistat, in case it is necessary to adjust the dose of these medicinal products.

Amiodarone

Patients who are taking amiodarone should consult a doctor before starting treatment with Orlistat (see section 4.5).

Rectal bleeding

Cases of rectal bleeding have been reported in patients taking orlistat. If this occurs, the patient should consult a doctor.

Oral contraceptives

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).

Kidney disease

Patients with kidney disease should consult a doctor before starting treatment with Orlistat, as the use of orlistat may rarely be associated with hyperoxaluria and oxalate nephropathy ~~(see section 4.8)~~ leading sometimes to renal failure.
This risk is increased in patients with underlying chronic kidney disease and/or volume depletion.

Levothyroxine

Hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are co-administered (see section 4.5).
Patients taking levothyroxine should consult a doctor before starting treatment with Orlistat, as orlistat and levothyroxine may need to be taken at different times and the dose of levothyroxine may need to be adjusted.

Antiepileptic medicinal products

Patients taking an antiepileptic medicinal product should consult a doctor before starting treatment with Orlistat, as they should be monitored for possible changes in the frequency and severity of convulsions.
If this occurs, consideration could be given to administering orlistat and antiepileptic medicinal products at different times (see section 4.5).

Antiretrovirals for HIV

Patients should consult a physician before taking Orlistat concomitantly with antiretroviral medications. 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).

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

4.5 Interaction with other medicinal products and other forms of interaction

Ciclosporin
A decrease in ciclosporin plasma levels has been observed in a drug-drug interaction study and also reported in several cases, when orlistat was administered concomitantly. This could potentially lead to a decrease of immunosuppressive efficacy. Concurrent use of Orlistat and ciclosporin is contraindicated (see section 4.3).

Oral anticoagulants
When warfarin or other oral anticoagulants are given in combination with orlistat, international normalised ratio (INR) values could be affected (see section 4.8). Concurrent use of Orlistat and warfarin or other oral anticoagulants is contraindicated (see section 4.3).

Oral contraceptives
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 (see section 4.4).

Levothyroxine
Hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are taken at the same time (see section 4.4). This could be due to a decreased absorption of iodine salts and/or levothyroxine.

Antiepileptic medicinal products
Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic medicinal products e.g. valproate, lamotrigine, for which a causal relationship to an interaction cannot be excluded. Orlistat may decrease the absorption of antiepileptic medicinal products, leading to convulsions.

Antiretroviral medications
Based on reports from literature and post-marketing experience orlistat may potentially reduce the absorption of antiretroviral medicines for HIV and could negatively affect the efficacy of antiretroviral medications for HIV (see section 4.4).

Fat-soluble vitamins
Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E and K).
The vast majority of subjects receiving up to 4 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. However, patients should be advised to use a multivitamin supplement at bedtime to help ensure adequate vitamin intake (see section 4.4).

Acarbose
In the absence of pharmacokinetic interaction studies, Orlistat is not recommended to be used by patients receiving acarbose.

Amiodarone
A 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. The clinical relevance of this effect in patients receiving amiodarone treatment remains unknown. Patients who are taking amiodarone should consult a doctor before starting treatment with Orlistat. The dose of amiodarone may need to be adjusted during treatment with Orlistat.

Antidepressants,antipsychotics (including lithium) and benzodiazepines
There are some case reports of reduced efficacy of 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

Women of childbearing potential / Contraception in males and females

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 sections 4.4 and 4.5).

Pregnancy

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 section 5.3).

Orlistat is contraindicated in pregnancy (see section 4.3).

Breast-feeding

As it is not known whether orlistat is secreted into human milk, Orlistat is contraindicated during breast-feeding (see section 4.3).

Fertility

Animal studies do not indicate harmful effects with respect to fertility.

4.7 Effects on ability to drive and use machines

Orlistat has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

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

The gastrointestinal adverse reactions identified from clinical trials with orlistat 60 mg of 18 months to 2 years duration were generally mild and transient. They generally occurred early in treatment (within 3 months) and most patients experienced only one episode. Consumption of a diet low in fat will decrease the likelihood of experiencing adverse gastrointestinal reactions (see section 4.4).

Tabulated list of adverse reactions

Adverse reactions 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), and not known (cannot be estimated from the available data).

The frequencies of adverse reactions identified during post-marketing use of orlistat are not known as these reactions were reported voluntarily from a population of uncertain size.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class and frequency	Adverse reaction
Blood and lymphatic system disorders Not known:	Decreased prothrombin and increased INR (see sections 4.3 and 4.5).
Immune system disorders Not known:	Hypersensitivity reactions including anaphylaxis, bronchospasm, angioedema, pruritus, rash, and urticaria.
Psychiatric disorders Common:	Anxiety†
Gastrointestinal disorders Very common:	Oily spotting Flatus with discharge Faecal urgency Fatty oily stool Oily evacuation Flatulence Soft stools
Common:	Abdominal pain Faecal incontinence Liquid stools Increased defaecation
Not known:	Diverticulitis Pancreatitis Mild rectal bleeding (see section 4.4)
Hepatobiliary disorders Not known:	Hepatitis that may be serious. Some fatal cases or cases requiring liver transplantation have been reported. Cholelithiasis Increase in transaminases and in alkaline phosphatase
Skin and subcutaneous tissue disorders Not known:	Bullous eruption
Renal and urinary disorders Not known:	Oxalate nephropathy that may lead to renal failure

† it is plausible that treatment with orlistat can lead to anxiety in anticipation of or secondary to gastrointestinal adverse reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme, www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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 clinical findings. In addition, doses of 240 mg three times daily have been administered to obese patients for 6 months. The majority of orlistat overdose cases received during post-marketing reported either no adverse reactions or adverse reactions that are similar to those reported with recommended doses of orlistat.

In the event of an overdose, medical advice should be sought. 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaco-therapeutic group: antiobesity preparations, excl. diet products; peripherally acting antiobesity products, ATC code A08AB01.

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.

From clinical studies, it has been estimated that orlistat 60 mg taken three times daily blocks the absorption of approximately 25% of dietary fat. 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 returns to pre-treatment levels, usually within 48 to 72 hours.

Two double-blind, randomised, placebo-controlled studies in adults with a BMI ≥28 kg/m2 support the efficacy of orlistat 60 mg taken three times daily in conjunction with a hypocaloric, lower-fat diet.

The primary parameter, change in body weight from baseline (time of randomisation), was assessed for body weight over time (Table 1) and the percentage of subjects who lost ≥5% or ≥10% of body weight (Table 2).

Although weight loss was assessed during 12 months of treatment in both studies, most weight loss occurred within the first 6 months.

Table 1: Effect of 6 months treatment on body weight measured at baseline

	Treatment group	**N**	**Relative mean change (%)**	**Mean change (kg)**
Study 1	Placebo	204	-3.24	-3.11
	Orlistat 60 mg	216	-5.55	-5.20*
Study 2	Placebo	183	-1.17	-1.05
	Orlistat 60 mg	191	-3.66	-3.59*
Pooled data	Placebo	387	-2.20	-2.09
	Orlistat 60 mg	407	-4.60	-4.40*
* $p<0.001$ versus placebo				

Table 2: Responder analysis at 6 months

	Lost ≥5% of baseline body weight (%)		**Lost ≥10% of baseline body weight (%)**	
	Placebo	Orlistat 60mg	Placebo	Orlistat 60mg
Study 1	30.9	54.6 [a]	10.3	21.3 [b]
Study 2	21.3	37.7 [a]	2.2	10.5 [b]
Pooled data	26.4	46.7 [a]	6.5	16.2 [a]
Comparison versus placebo: [a] $p<0.001$; [b] $p<0.01$				

The weight loss induced by orlistat 60 mg conferred other important health benefits after 6 months of treatment in addition to weight loss. The mean relative change in total cholesterol was -2.4% for orlistat 60 mg (baseline 5.20 mmol/l) and +2.8% for placebo (baseline 5.26 mmol/l). The mean relative change in LDL cholesterol was -3.5% for orlistat 60 mg (baseline 3.30 mmol/l) and +3.8% for placebo (baseline 3.41 mmol/l). For waist circumference, the mean change was -4.5 cm for orlistat 60 mg (baseline 103.7 cm) and -3.6 cm for placebo (baseline 103.5 cm). All comparisons against placebo were statistically significant.

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) 8 hours following oral administration of orlistat 360 mg.

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 active substance 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.

Biotransformation

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 (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 active substance 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.

5.3 Preclinical safety data

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

The medicinal use of orlistat is unlikely to represent a risk to the aquatic or terrestrial environment. However, any possible risk should be avoided (see section 6.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling:

Microcrystalline cellulose (E460)
Sodium starch glycolate (type A)
Sillica, hydrophobic colloidal
Sodium laurilsulfhate

Capsule shell:
Gelatin
Indigo carmine (E132)
Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
24 months

6.4 Special precautions for storage
Do not store above 25°C. Store in original package in order to protect from light and moisture.

6.5 Nature and contents of container
Al/PVC/PVDC blisters with PVC\PVDC heat seal foil containing 42, 60, 84 and 90 hard capsules.

HDPE bottles with Polyethylene caps and desiccant containing 42, 60, 84, 90 and 120 capsules.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 20416/0269

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

23/01/2025