8017894-9093

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

ORLICA 60

(Orlistat Capsules)

COMPOSITION

Each hard gelatin capsule contains :

Orlistat 60 mg

(as pellets 50 % w/w)

Approved colours used in empty hard gelatin capsule shells

DESCRIPTION

Orlistat is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats.

Orlistat is (S)-{(S)-1-{(2S,3S)-3-hexyl-4-oxo oxetan-2-yl}tridecan-2-yl}2-formamido-4-methyl pentanoate. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight is 495.7. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529 nm.

CLINICAL PHARMACOLOGY

Mechanism of Action

Orlistat is a reversible inhibitor of lipases. It exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are thus unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric deficit may have a positive effect on weight control. Systemic absorption of the drug is therefore not needed for activity. At the recommended therapeutic dose of 120 mg three times a day, orlistat inhibits dietary fat absorption by approximately 30%.

Pharmacokinetics

Absorption

Systemic exposure to orlistat is minimal. Following oral dosing with 360 mg ^{14}C - orlistat, plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact orlistat were near the limits of detection (< 5 ng/ml). In therapeutic studies involving monitoring of plasma samples, detection of intact orlistat in plasma was sporadic and concentrations were low (<10 ng/ml or 0.02 μM), without evidence of accumulation, and consistent with minimal absorption.

Distribution

In vitro orlistat was > 99% bound to plasma proteins (lipoproteins and albumin were major binding proteins). Orlistat minimally partitioned into erythrocytes.

Metabolism

Two major metabolites of orlistat have been identified in relatively high concentrations compared with those of the parent drug in the plasma of obese patients. Orlistat undergoes hydrolysis at the Beta-lactone ring to form M1, with subsequent ester hydrolysis of the N-formyl leucine side-chain on M1 to form M3. M1 and M3 plasma concentrations were 20 to 25 and 30 to 40 times higher, respectively, than unchanged plasma orlistat concentrations.

Three other metabolites, M9, M13 and M13-glucuronic acid conjugate, were found in the urine up to 24 hours after a single radiolabelled dose of orlistat in obese volunteers. M1 has a short elimination half-life of approximately 2 hours, while M3 disappears from plasma more slowly.

Elimination

Following a single oral dose of 360 mg ^{14}C-orlistat in both normal weight and obese subjects, fecal excretion of the unabsorbed drug was found to be the major route of elimination. Orlistat and its M1 and M3 metabolites were also subject to biliary excretion. Approximately 97% of the administered radioactivity was excreted in feces; 83% of that was found to be unchanged orlistat. The cumulative renal excretion of total radioactivity was < 2% of the given dose of 360 mg ^{14}C - orlistat. The time to reach complete excretion (fecal plus urinary) was 3-5 days. The disposition of orlistat appeared to be similar between normal weight and obese subjects. Based on limited data, the half-life of the absorbed orlistat is in the range of 1-2 hours.

INDICATIONS AND USAGE

Orlistat is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. Orlistat is also indicated to reduce the risk for weight regain after prior weight loss. Orlistat is indicated for obese patients with an initial body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

CONTRAINDICATIONS

Orlistat is contraindicated in patients with chronic malabsorption syndrome or cholestasis, and in patients with known hypersensitivity to orlistat or to any component of this product.

WARNINGS

Organic causes of obesity (e.g., hypothyroidism) should be excluded before prescribing orlistat. Preliminary data from an orlistat and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when orlistat was coadministered with cyclosporine. Therefore, orlistat and cyclosporine should not be coadministered. To reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 2 hours before or after orlistat in patients taking both drugs. In addition, in those patients whose cyclosporine levels are being measured, more frequent monitoring should be considered.

PRECAUTIONS

Patients should be advised to adhere to dietary guidelines. Gastrointestinal events may increase

when orlistat is taken with a diet high in fat (>30% total daily calories from fat). The daily intake of fat should be distributed over 3 main meals. If orlistat is taken with any 1 meal very high in fat, the possibility of gastrointestinal effects increases. Patients should be counseled to take a multivitamin supplement that contains fat-soluble vitamins to ensure adequate nutrition because orlistat has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene. In addition, the levels of vitamin D and beta-carotene may be low in obese patients compared with non-obese subjects.

The supplement should be taken once a day at least 2 hours before or after the administration of orlistat, such as at bedtime.

Pregnancy

(Teratogenic Effects, Pregnancy Category B)

Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryotoxicity or teratogenicity. This dose is 23 and 47 times the daily human dose calculated on a body surface area (mg/m^2) basis for rats and rabbits, respectively.

There are no adequate and well-controlled studies of orlistat in pregnant women. Because animal reproductive studies are not always predictive of human response, orlistat is not recommended for use during pregnancy.

Nursing Mothers

It is not known if orlistat is secreted in human milk. Therefore, orlistat should not be taken by nursing women.

Special Populations

Pediatrics

Orlistat has not been studied in pediatric patients below the age of 12 years. The safety and efficacy of orlistat have been evaluated in obese adolescent patients aged 12-16 years. Use of orlistat in this age group is supported by evidence from adequate and well-controlled studies of orlistat in adults with additional data from a 54-week efficacy and safety study and a 21-day mineral balance study in obese adolescent patients aged 12-16 years.

Geriatric Use

Clinical studies of orlistat did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

Drug-Drug Interactions

Drug-drug interaction studies indicate that orlistat had no effect on pharmacokinetics and/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release tablets), oral contraceptives, phenytoin, pravastatin, or warfarin. Alcohol did not affect the pharmacodynamics of orlistat.

Adverse effects

Most Frequent: Oily spotting, Flatulence with Discharge, Fecal Urgency, Oily Evacuation, Increased Defecation, Fecal Incontinence, Oily Rectal Leakage, Upper Respiratory Infection, Steatorrhea.

Less Frequent: Gingival Disorders, Nausea, Rectal Irritation, Tooth Disorder

OVERDOSAGE

Single doses of 800 mg orlistat 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. Should a significant overdose of orlistat occur, it is recommended that the patient be observed for 24 hours. Based on human and animal studies, systemic effects attributable to the lipase-inhibiting properties of orlistat should be rapidly reversible.

DOSAGE AND ADMINISTRATION

Administration

Orlistat is administered orally 3 times daily, during (or up to 1 hour after) each main meal containing fat. However, administering the drug up to 2 hours after midmeal does not appear to affect efficacy.

Dosage

The dosage of orlistat for the management of obesity and weight regain in adults is 120 mg 3 times daily with each main meal containing fat. Daily intake of fat (30% of calories), carbohydrate, and protein should be distributed evenly over 3 main meals. If a meal occasionally is missed or contains no fat, the dose of orlistat may be omitted. Dosages exceeding 120 mg 3 times daily have not been shown to provide additional benefit. The recommended dose of orlistat is 120 mg 3 times a day with each main meal containing fat (during or up to 1 hour after the meal).

The patient should be on a nutritionally balanced, reduced-calorie diet that contains approximately 30 % of calories from fat. The daily intake of fat, carbohydrate, and protein should be distributed over 3 main meals. If a meal is occasionally missed or contains no fat, the dose of orlistat can be omitted.

Because Orlistat has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counseled to take a multivitamin containing fat-soluble vitamins to ensure adequate nutrition. The supplement should be taken at least 2 hours before or 2 hours after the administration of orlistat, such as at bedtime.

EXPIRY DATE

Do not use later than the date of expiry

STORAGE

Store below 25^{O}C. Protect from light and moisture. Keep out of reach of children.

PRESENTATION

ORLICA 60 capsule is available in blister strips of 10 capsules.

TORRENT PHARMA

Marketed by :
TORRENT PHARMACEUTICALS LTD.
Indrad-382 721, Dist. Mehsana, INDIA.

Manufactured by :
Biocon Limited.
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