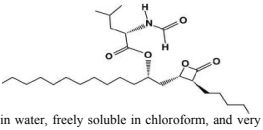
ORLIRISE™ Capsule
(O r l i s t a t)

اورلیرائز کیپسول

QUALITATIVE & QUANTITATIVE COMPOSITION
Each capsule contains:
Orlistat.....120 mg

DESCRIPTION
ORLIRISE (Orlistat) is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats. Orlistat is (S)-2-formylamino-4-methyl-pentanoic acid (S)-1-[[(2S, 3S)-3-hexyl-4-oxo-2 9 oxetanyl] methyl]-dodecyl ester. 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.



Orlistat is practically insoluble in water, freely soluble in chloroform, and very soluble in methanol and ethanol. Orlistat has no pKa within the physiological pH range.

CLINICAL INFORMATION
Indications
ORLIRISE (Orlistat) 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/m², or overweight patients (BMI ≥ 28 kg/m²) with associated risk factors such as type II diabetes, hyperlipidemia and hypertension.
In non-diabetic patients, treatment with ORLIRISE (Orlistat) should be started only if diet alone has previously produced a weight loss of at least 2.5kg over a period of 4 consecutive weeks. Treatment with ORLIRISE (Orlistat) should be discontinued after 12 weeks if patients have been unable to lose at least 5 % of the body weight as measured at the start of therapy.

Dosage and Administration
The recommended dose of ORLIRISE (Orlistat) is one 120 mg capsule Doses of ORLIRISE (Orlistat) above 120 mg three times daily have not been shown to provide additional benefit. The effect of ORLIRISE (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.

Dosage and Adjustment
Pediatric, Elderly, Renal and Hepatic Impairment
Data regarding the effect of ORLIRISE (Orlistat) in patients with hepatic and/or renal impairment, children and elderly patients is not available. There is no relevant indication for use of ORLIRISE (Orlistat) in children.

Administration Requirements
ORLIRISE (Orlistat) should be 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 ORLIRISE (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.

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

Contraindications
- Hypersensitivity to the active substance or to any of the excipients.
- Chronic malabsorption syndrome.
- Cholestasis.
- Breast-feeding.

Warnings and Precautions
- The decrease in bodyweight with Orlistat treatment is less in type II diabetic patients than in non-diabetic patients. Anti-diabetic medicinal product treatment may have to be closely monitored when taking Orlistat.
- Co-administration of Orlistat with ciclosporin is not recommended.
- Patients should be advised to adhere to the dietary recommendations they are given.
- The possibility of experiencing gastrointestinal adverse reactions 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 reactions may increase.
- Rectal bleeding may be observed with Orlistat. 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 diarrhea.
- Coagulation parameters should be monitored in patients treated with concomitant oral anticoagulants.
- The use of Orlistat 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.
- 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.
- Antiepileptic patients: Orlistat may unbalance anticonvulsant treatment by decreasing the absorption of antiepileptic drugs, leading to convulsions.
- Orlistat may potentially reduce the absorption of antiretroviral medicines for HIV and could negatively affect the efficacy of antiretroviral medications for HIV.

Interactions
Ciclosporin
A decrease in ciclosporin plasma levels may be observed when Orlistat is 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 ciclosporin blood levels should be performed both after addition of Orlistat and upon discontinuation of Orlistat in ciclosporin treated patients. Ciclosporin blood levels should be monitored until stabilized.
Acarbose
Since much pharmacokinetic data is not available, the concomitant administration of Orlistat with acarbose should be avoided.
Oral anticoagulants
When warfarin or other anticoagulants are given in combination with Orlistat, international normalized 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 slight decrease in plasma levels of amiodarone, when given as a single dose, may be observed in some patients receiving Orlistat concomitantly. In patients receiving amiodarone treatment, the clinical relevance of this effect remains unknown but may become clinically relevant in some cases. In patients receiving concomitant amiodarone treatment, reinforcement of clinical and ECG monitoring is warranted.
Antiepileptic medicinal products
Convulsions may be observed 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.
Levothyroxine
Rare occurrence of hypothyroidism and/or reduced control of hypothyroidism may occur when Orlistat and levothyroxine are taken at the same time. The mechanism, although not proven, may involve a decreased absorption of iodine salts and/or levothyroxine.
Antiretrovirals for HIV, antidepressants, antipsychotics and benzodiazepines
Efficacy of antiretroviral HIV medicines, antidepressants, antipsychotics (including lithium) and benzodiazepines may be reduced 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.

Pregnancy and Breastfeeding
Pregnancy Category B
For Orlistat no clinical data on exposed pregnancies are available.
As it is not known whether Orlistat is secreted into human milk, Orlistat is contra-indicated during breast-feeding.

Adverse Reactions
Gastrointestinal (GI) symptoms are the most common adverse reactions associated with the use of Orlistat and are primarily a manifestation of the mechanism of action.
These and other common adverse reactions are generally mild and transient, and they decrease during the second year of treatment. In general, the first occurrence of these events may be within 3 months of starting therapy. Overall, approximately 50% of all episodes of GI adverse events associated with Orlistat treatment may last for less than 1 week, and a majority may last for no more than 4 weeks. However, GI adverse events may occur in some individuals over a period of 6 months or longer.

Overdose
Single doses of 800 mg Orlistat and multiple doses of up to 400 mg three times daily for 15 days in normal weight and obese subjects may not lead to any significant adverse findings. The majority of Orlistat overdose cases may have either no adverse events or adverse events that are similar to those reported with recommended dose.

PHARMACOLOGICAL PROPERITIES
Pharmacotherapeutic group: Peripherally acting antiobesity agent, ATC code A08AB01.
Mechanism of Action
Orlistat is a potent, specific and reversible long acting inhibitor of gastrointestinal lipases. It exerts its therapeutic activity in the lumen of the stomach and the small intestine by forming a covalent bond with the serine residue of the active site of 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. As undigested triglycerides are not absorbed, the resulting caloric deficit has a positive effect on the weight control.
Pharmacokinetic properties
Absorption
The extent of absorption of Orlistat is minimal. Plasma concentrations of intact Orlistat arre non-measurable (< 5 ng/ml) eight hours following oral administration of Orlistat.
In general, at therapeutic doses, detection of intact Orlistat in plasma is sporadic and concentrations are 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. Orlistat is > 99% bound to plasma proteins (lipoproteins and albumin were the major binding proteins). Orlistat minimally partitions into erythrocytes.
Metabolism
It is likely that the metabolism of Orlistat occurs mainly within the gastrointestinal wall. Of the minimal fraction of the dose that is absorbed systemically, two major metabolites, M1 (4-member lactone ring hydrolysed) and M3 (M1 with N-formyl leucine moiety cleaved), account 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
Faecal excretion of the unabsorbed drug is 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 is < 2% of the given dose. The time to reach complete excretion (faecal plus urinary) is 3 to 5 days. The disposition of Orlistat appears to be similar between normal weight and obese patients. Orlistat, M1 and M3 are all subject to biliary excretion.

PHARMACEUTICAL INFORMATION
Shelf life
2 Years

Special Precautions for Storage
As prescribed by the physician.
Do not store above 25ºC, excursion permitted between 15 to 30ºC.
Protect from light and moisture. Keep out of the reach of children.

Nature and contents of container
ORLIRISE (Orlistat) 120 mg capsules are available in a blister pack of 10's (2x5's).

ہدایات:
ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۲۵ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں۔
درجہ حرارت کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔
دوا کو روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

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