ORSLIM®
ORLISTAT

اورسلِم کیپسول

COMPOSITION

ORSLIM 120 mg Capsule
Each Capsule Contains:
Orlistat Pellets 50%.....240mg
equivalent to Orlistat.....120mg
(PharmEvo Specs.)

DESCRIPTION
ORSLIM (orlistat) is a gastrointestinal 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-oxetanyl] methyl]-dodecyl ester. Its molecular formula is $C_{29}H_{53}NO_5$

CLINICAL PHARMACOLOGY

Mechanism of Action
Orlistat is a reversible 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 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.

Pharmacokinetics

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. The primary metabolite M1 has a short half-life (approximately 3 hours) whereas the secondary metabolite M3 is eliminated at a slower rate (half-life approximately 13.5 hours).

Excretion
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. The primary metabolite M1 has a short half-life (approximately 3 hours) whereas the secondary metabolite M3 is eliminated at a slower rate (half-life approximately 13.5 hours).

INDICATIONS
ORSLIM (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/m2 or ≥27 kg/m2 in the presence of other risk factors (e.g. hypertension, diabetes, dyslipidemia).

Note: Treatment with 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 orlistat is one 120 mg capsule taken with water immediately before, during or up to one hour after each main 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 three main meals. It is recommended that the diet should be rich in fruit and vegetables. If a meal is occasionally missed or contains no fat, the dose of ORSLIM should be omitted.
Note: 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 vitamin supplement should be taken at least 2 hours before or after the administration of ORSLIM, such as at bedtime.

Dosage adjustment in special populations
The effect of Orlistat in patients with hepatic and/or renal impairment, children below the age of 12 and elderly patients has not been studied.
There is no relevant indication for use of Orlistat in children below 12 years of age. Limited data on safety and efficacy is available in adolescent patients 12-16 years of age. Use of Orlistat in this age group is based on prescriber's judgment and may be 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 to 16 years.

Administration requirements
ORSLIM capsules should be administered with water immediately before, during or up to one hour after each main meal containing fat.

CONTRAINDICATIONS
- Known hypersensitivity to the active substance Orlistat
- Chronic malabsorption syndrome
- Cholestasis
- Pregnancy
- Breast-feeding

WARNINGS AND PRECAUTIONS

Impairment of absorption of fat soluble vitamins
Patients should be strongly encouraged to take a multivitamin supplement that contains fat-soluble vitamins (A, D, E and K) 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.

Concomitant use with Cyclosporine
Reduction in cyclosporine plasma levels has been observed when Orlistat was co-administered with cyclosporine. This may cause a potential loss of efficacy of Cyclosporine. Therefore, Orlistat and cyclosporine should not be simultaneously used. To reduce the chance of a drug-drug interaction, cyclosporine should be taken at least 3 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.

Liver Injury
There has been rare post marketing reports of severe liver injury with hepatocellular necrosis or acute hepatic failure in patients treated with orlistat, with some of these cases resulting in liver transplant or death. Patients should be instructed to report any symptoms of hepatic dysfunction (anorexia, pruritus, jaundice, dark urine, light-colored stools, or right upper quadrant pain) while taking orlistat. When these symptoms occur, orlistat and other suspect drugs should be discontinued immediately and liver function tests and ALT and AST levels obtained.

Increases in Urinary Oxalate
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 Monitor renal function when prescribing Orlistat to patients at risk for renal impairment and use with caution in those with a history of hyperoxaluria or calcium oxalate nephrolithiasis.

Cholelithiasis
Substantial weight loss can increase the risk of cholelithiasis. Patients should be closely monitored.

Antiepileptic patient
Orlistat may unbalance anticonvulsant treatment by decreasing the absorption of antiepileptic drugs, leading to convulsions.

Antiretrovirals for HIV
Orlistat may potentially reduce the absorption of antiretroviral medicines for HIV and could negatively affect the efficacy of antiretroviral medications for HIV.

Patients with diabetes mellitus
Weight-loss with Orlistat use may positively affect glycemic control in patients with diabetes mellitus. Hypoglycemia has been reported. A reduction in dose of oral hypoglycemic medication (e.g., sulfonylureas) or insulin may be required in some patients.

Gastrointestinal adverse effects
Gastrointestinal events may increase when Orlistat is taken with a diet high in fat (>30% total daily calories from fat. Patients should be advised to adhere to dietary guidelines See section. The daily intake of fat should be distributed over three main meals. If Orlistat is taken with any one meal very high in fat, the possibility of gastrointestinal effects increases. 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.

In addition, Cases of rectal bleeding have been reported with Orlistat. Prescribers should investigate further in case of severe and/or persistent symptoms

Hypothyroidism
Organic causes of obesity (e.g., hypothyroidism) should be excluded before prescribing Orlistat. In addition, rare occurrence of hypothyroidism and/or reduced control of hypothyroidism may occur in patients prescribed Orlistat. The mechanism, although not proven, may involve a decreased absorption of iodine salts and/or levothyroxine.
For patients receiving both Orlistat and levothyroxine therapy, administer levothyroxine and Orlistat at least 4 hours apart. Patients treated concomitantly with Orlistat and levothyroxine should be monitored for changes in thyroid function.

Potential for drug abuse
As with any weight-loss agent, the potential for abuse of Orlistat exists in inappropriate patient populations (e.g., patients with anorexia nervosa or bulimia).

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

ADVERSE REACTIONS
Adverse reactions to orlistat are largely gastrointestinal in nature. The incidence of adverse events decreased with prolonged use of orlistat.

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
Common: Rectal pain/discomfort , 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

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

Investigations:
Not known: 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
Gastrointestinal disorders
Not known: Rectal bleeding, Diverticulitis, Pancreatitis
Skin and sub-cutaneous tissue disorders
Not known: Bullous eruptions
Immune system disorders
Unknown: Hypersensitivity (e.g. pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis)
Hepatobiliary disorders
Unknown: Cholelithiasis, Hepatitis that may be serious. Some fatal cases or cases requiring liver transplantation have been reported
Renal and urinary disorders
Unknown: Oxalate nephropathy that may lead to renal failure

DRUG INTERACTIONS

Ciclosporin
Data from a drug interaction study indicate a reduction in cyclosporine plasma levels when Orlistat was co-administered with cyclosporine. This can lead to a decrease or loss of immunosuppressive efficacy of Cyclosporine. Orlistat and cyclosporine should not be simultaneously used. Cyclosporine should be administered 3 hours after the administration of Orlistat. . In addition, in those patients whose cyclosporine levels are being measured, more frequent monitoring should be considered.

Oral anticoagulants (Warfarin)
Vitamin K absorption may be decreased with Orlistat. When warfarin or other anticoagulants are given in combination with orlistat, international normalised ratio (INR) values should be monitored.

Fat-soluble Vitamin Supplements and Analogues
Data from a pharmacokinetic interaction study showed that the absorption of beta-carotene supplement is reduced when concomitantly administered with Orlistat. Orlistat inhibited absorption of a vitamin E acetate supplement. The effect of Orlistat on the absorption of supplemental vitamin D, vitamin A, and nutritionally-derived vitamin K is not known at this time. Supplements containing fat-soluble vitamins should be given at least 2 hours before or after the administration of Orlistat, such as at bedtime.

Levothyroxine
Hypothyroidism has been reported in patients treated concomitantly with Orlistat and levothyroxine. Patients treated concomitantly with Orlistat and levothyroxine should be monitored for changes in thyroid function. Administer levothyroxine and Orlistat at least 4 hours apart. Exact mechanism of the interaction is unknown however; decreased absorption of Levothyroxine may be possible.

Amiodarone
A pharmacokinetic study, where amiodarone was orally administered during orlistat treatment, demonstrated a reduction in exposure to amiodarone and its metabolite, desethylamiodarone. A reduced therapeutic effect of amiodarone is possible. The effect of commencing Orlistat treatment in patients on stable amiodarone therapy has not been studied.

Antiretroviral drugs
Orlistat may potentially reduce the absorption of antiretroviral medicines for HIV and could negatively affect the efficacy of antiretroviral medications for HIV. There are some case reports of reduced efficacy of antiretroviral HIV medicines when used with Orlistat.

Psychotropic drugs
There are some case reports of reduced efficacy of mood stabilizer and anti-manic drug lithium and benzodiazepines coincidental to the initiation of Orlistat treatment in previously well-controlled patients. Therefore, Orlistat treatment should be initiated after consideration of the possible impact in these patients

Antiepileptic Drugs
Orlistat may unbalance anticonvulsant treatment by decreasing the absorption of antiepileptic drugs. Convulsions have been reported in patients treated concomitantly with Orlistat and antiepileptic drugs such as valproate, lamotrigine. Patients should be monitored for possible changes in the frequency and/or severity of convulsions.

Acarbose
The concomitant administration of Orlistat with acarbose should be avoided. Pharmacokinetic interaction studies have not been performed.

USE IN SPECIAL POPULATIONS

Pregnancy
Orlistat belongs to US FDA pregnancy category X. For Orlistat, no clinical data on exposed pregnancies is available. Orlistat is contraindicated during pregnancy, because weight loss offers no potential benefit to a pregnant woman and may result in fetal harm. A minimum weight gain, and no weight loss, is currently recommended for all pregnant women, including those who are already overweight or obese, due to the obligatory weight gain that occurs in maternal tissues during pregnancy. No embryotoxicity or teratogenicity was seen in animals that received orlistat at doses much higher than the recommended human dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard of maternal weight loss to the fetus.

Nursing mothers
It is not known if Orlistat is present in human milk. In the absence of this information, Orlistat is contraindicated in breast feeding and it is recommended that breast feeding should be discontinued while Orlistat is administered.

Pediatrics
Safety and effectiveness in pediatric patients below the age of 12 have not been established. Limited data on safety and efficacy is available in adolescent patients 12-16 years of age. Use of Orlistat in this age group is based on prescriber's judgment and may be 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 to 16 years.

Elderly
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

OVER DOSAGE
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.
If a significant overdose of orlistat occurs, 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.

PRESENTATION
Orslim 120mg : Pack of 30 capsules.

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 25 °C.

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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تمام دوائیں بچّوں کی پہنچ سے دُور رکھیں۔
صرف رجسٹرڈ ڈاکٹر کے نسخہ پر ہی فروخت کی جائے۔
روشنی، گرمی اور نمی سے محفوظ، 25 °C سے کم درجہ حرارت پر رکھیں۔

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