Osker™ (ORLISTATE)

60mg
120mg

اوسکر

Capsules USP

DESCRIPTION:
OSKER™ (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-oxetanyl] methyl]-dodecyl ester. Its empirical formula is $C_{29}H_{53}NO_5$, and its molecular weight is 495.7.

COMPOSITION:

OSKER™ 60mg Capsules	OSKER™ 120mg Capsules
Each capsule contains:	Each capsule contains:
Orlistat USP..... 60mg	Orlistat USP..... 120mg

CLINICAL PHARMACOLOGY:
Mechanism of Action: Orlistat is a reversible inhibitor of Lipases. It exerts its therapeutic activity in the lumen of the stomach & 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 & 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: Following oral dosing with 360 mg 14C-orlistat, plasma radioactivity peaked at approximately 8 hours; plasma concentrations of intact orlistat were near the limits of detection (5 ng/mL). **Distribution:** In vitro orlistat was 99% bound to plasma proteins (lipoproteins & albumin were major binding proteins). Orlistat minimally partitioned into erythrocytes. **Metabolism:** Based on an oral 14C-orlistat mass balance study in obese patients, two metabolites, M1 (4-member lactone ring hydrolyzed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of total radioactivity in plasma. The primary metabolite M1 had a short half-life (approximately 3 hours) whereas the secondary metabolite M3 disappeared at a slower rate (half-life approximately 13.5 hours). In obese patients, steady-state plasma levels of M1, but not M3, increased in proportion to orlistat doses. **Elimination:** 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 14C-orlistat. The time to reach complete excretion (fecal plus urinary) was 3 to 5 days. The half-life of the absorbed orlistat is in the range of 1 to 2 hours. **Special Populations:** Because the drug is minimally absorbed, studies in special populations (geriatric, different races, patients with renal and hepatic insufficiency) were not conducted. **Pediatrics:** Plasma concentrations of orlistat and its metabolites M1 and M3 were similar 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. **Drug-Drug Interactions:** Drug-drug interaction studies indicate that Orlistat had no effect on pharmacokinetics &/or pharmacodynamics of alcohol, digoxin, glyburide, nifedipine (extended-release tablets), oral contraceptives, phenytoin, pravastatin, or warfarin. Alcohol did not affect the pharmacodynamics of orlistat.

INDICATIONS AND USAGE:
OSKER™ is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. OSKER™ is also indicated to reduce the risk for weight regain after prior weight loss. OSKER™ 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 (eg, 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:
Miscellaneous: Organic causes of obesity (eg, hypothyroidism) should be excluded before prescribing Orlistat. Preliminary data from a 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:
General: 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 three main meals. If Orlistat is taken with any one meal very high in fat, the possibility of gastrointestinal effects increases. Patients should be strongly encouraged 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.

DRUG INTERACTIONS:
Alcohol: Coadministration of Orlistat and 40 grams of alcohol (eg, approximately 3 glasses of wine) did not result in alteration of alcohol pharmacokinetics, orlistat pharmacodynamics (fecal fat excretion), or systemic exposure to orlistat. **Cyclosporine:** Preliminary data from Orlistat and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when Orlistat was coadministered with cyclosporine **Digoxin:** Orlistat did not alter the pharmacokinetics of a single dose of digoxin. **Fat-soluble:** Vitamin Supplements and Analogues Orlistat inhibited absorption of a Vitamin E acetate supplement by approximately 60%. The effect of orlistat on the absorption of supplemental Vitamin D, Vitamin A, and nutritionally derived Vitamin K is not known at this time. **Glyburide:** In 12 normal-weight subjects receiving orlistat 80 mg three times a day for 5 days, orlistat did not alter the pharmacokinetics or pharmacodynamics (blood glucose lowering) of glyburide. **Nifedipine:** (extended-release tablets) Orlistat did not alter the bioavailability of nifedipine (extended-release tablets). **Oral Contraceptives:** Treatment of Orlistat 120 mg three times a day for 23 days resulted in no changes in the ovulation-suppressing action of oral contraceptives. **Phenytoin:** Orlistat did not alter the pharmacokinetics of a single 300-mg dose of phenytoin. **Pravastatin:** Orlistat did not affect the pharmacokinetics of pravastatin. **Warfarin:** Orlistat 120 mg three times a day for 16 days did not result in any change in either warfarin pharmacokinetics (both R- and S-enantiomers) or pharmacodynamics (prothrombin time and serum Factor VII). Although undercarboxylated osteocalcin, a marker of vitamin K nutritional status, was unaltered with Orlistat administration, Vitamin K levels tended to decline in subjects taking Orlistat. Therefore, as Vitamin K absorption may be decreased with Orlistat, patients on chronic stable doses of warfarin who are prescribed Orlistat should be monitored closely for changes in coagulation parameters. Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies in rats and mice did not show a carcinogenic potential for orlistat at doses up to 1000 mg/kg/day and 1500 mg/kg/day, respectively. For mice and rats, these doses are 38 and 46 times the daily human dose calculated on an area under concentration vs time curve basis of total drug-related material. Orlistat had no detectable mutagenic or genotoxic activity as determined by the Ames test, a mammalian forward mutation assay (V79/HPRT), an in vitro clastogenesis assay in peripheral human lymphocytes, an unscheduled DNA synthesis assay (UDS) in rat hepatocytes in culture, and an in vivo mouse micronucleus test. When given to rats at a dose of 400 mg/kg/day in a fertility and reproduction study, orlistat had no observable adverse effects. This dose is 12 times the daily human dose calculated on a body surface area (mg/m^2) basis.

PREGNANCY: Pregnancy Category B.: There are no adequate and well-controlled studies of Orlistat in pregnant women. 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. **Pediatric Use:** The safety and efficacy of Orlistat have been evaluated in obese adolescent patients aged 12 to 16 years. Use of Orlistat in this age group is supported by evidence from adequate and well-controlled studies. Orlistat has not been studied in pediatric patients below the age of 12 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.

ADVERSE REACTIONS:
Commonly Observed (based on first year and second year data - Orlistat 120 mg three times a day versus placebo):
Gastrointestinal (GI) symptoms were the most commonly observed treatment-emergent adverse events associated with the use of Orlistat. Overall, approximately 50% of all episodes of GI adverse events associated with orlistat treatment lasted for less than 1 week, and a majority lasted for no more than 4 weeks. However, GI adverse events may occur in some individuals over a period of 6 months or longer. **Discontinuation of Treatment:** For Orlistat, the most common adverse events resulting in discontinuation of treatment were gastrointestinal. **Pediatric Patients:** In clinical trials with Orlistat in adolescent patients ages 12 to 16 years, the profile of adverse reactions was generally similar to that observed in adults.

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:
The recommended dose of OSKER™ is one 120mg capsule three 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 three main meals. If a meal is occasionally missed or contains no fat, the dose of OSKER™ can be omitted. Because OSKER™ 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 after the administration of OSKER™, such as at bedtime. Doses above 120 mg three times a day have not been shown to provide additional benefit. Based on fecal fat measurements, the effect of Orlistat is seen as soon as 24 to 48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to pretreatment levels within 48 to 72 hours. The safety and effectiveness of Orlistat beyond 4 years have not been determined at this time.

STORAGE CONDITIONS:
Store below 30ºC. Protect from heat, light & moisture.

PRESENTATION:
OSKER™ 60mg capsules are available in Alu Alu blister pack of 3x10's.
OSKER™ 120mg capsules are available in Alu Alu blister pack of 1x10's.

ہدایات: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں، روشنی، گرمی اور نمی سے محفوظ رکھیں۔
تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

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