PRESCRIBING INFORMATION : For the use of a registered medical practitioner or a hospital or a laboratory.

VYFAT

(Orlistat capsules 120 mg)

COMPOSITION

Each hard gelatin capsule contains
Orlistat ..... 120 mg

DESCRIPTION

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. It is a single diastereomeric molecule that contains four chiral centers, with a negative optical rotation in ethanol at 529 nm.
Orlistat is a white to off-white crystalline powder. Orlistat is practically insoluble in water, freely soluble in chloroform, and very soluble in methanol and ethanol.

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:
Orlistat was >99% bound to plasma proteins (lipoproteins and albumin were major binding proteins). Orlistat minimally partitioned into erythrocytes.
Metabolism:
It is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Two metabolites, M_1 (4-member lactone ring hydrolyzed) and M_3 (M_1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of total radioactivity in plasma. M_1 and M_3 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 the therapeutic dose, these metabolites are considered pharmacologically inconsequential. The primary metabolite M_1 had a short half-life (approximately 3 hours) whereas the secondary metabolite M_3 disappeared at a slower rate (half-life approximately 13.5 hours). In obese patients, steady-state plasma levels of M_1, but not M_3, increased in proportion to orlistat doses.
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 M_1 and M_3 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 to 5 days. The disposition of orlistat appeared to be similar between normal weight and obese subjects. Based on data, 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, pediatric, different races, patients with renal and hepatic insufficiency) were not conducted.

DRUG INTERACTIONS

Administration of alcohol with orlistat did not alter the pharmacokinetics of alcohol as well as pharmacodynamics of orlistat (fecal fat excretion) or systemic absorption to orlistat. Also with nifedipine, patients receiving orlistat 120 mg thrice a day for 6 days does not affect the bioavailability of nifedipine.
In patients receiving orlistat 120 mg three times a day for 6, 7 & 23 days for digoxin, phenytoin & oral contraceptives respectively do not result into any alteration in pharmacokinetics of single dose of these drugs.
No drug interaction studies have been conducted with orlistat and cyclosporine. Since changes in cyclosporine absorption have been reported with variations in dietary intake, caution is advised in the concomitant use of orlistat plus diet in patients receiving cyclosporine therapy.
A pharmacokinetic interaction study showed a 30% reduction in beta-carotene supplement absorption when concomitantly administered with orlistat. 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.
In patients receiving orlistat 80 mg three times a day for 5 days, orlistat did not alter the pharmacokinetics or pharmacodynamics (blood glucose-lowering) of glyburide.
Hypercholesterolemic subjects receiving orlistat 120 mg three times a day for 10 days, the effect of orlistat was additive to the lipid-lowering effect of pravastatin. Modest increases (approximately 30%) in pravastatin plasma concentrations were observed during co administration with orlistat.
Administration of 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.

INDICATIONS

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. Also it is indicated for obese patients with the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia).

DOSAGE AND ADMINISTRATION

Orlistat 120 mg three times a day given along with meal as an adjuvant to diet and exercise.
Patients should be advised 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.

SIDE EFFECTS

Commonly observed side effects are oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation, fecal incontinence.
Less frequently observed side effects are infectious diarrhea, rectal pain/discomfort, tooth disorder, gingival disorder, vomiting, lower respiratory infection, pain in lower extremities, arthritis, myalgia, joint disorder, tendonitis.
Headache, dizziness, fatigue, sleep disorder, rash, menstrual irregularity, vaginitis, urinary tract infection, psychiatric anxiety, depression, otitis, edema.

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.
Orlistat had no detectable mutagenic or genotoxic activity.
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.

Pregnancy:

Teratogenic effect & Pregnancy category B

Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryo toxicity or teratogenicity. This dose is 23 and 47 times the daily human dose respectively.

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 in pediatric patients have not been established.

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.

WARNINGS

Organic causes of obesity (e.g., hypothyroidism) should be excluded before prescribing orlistat.

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). If orlistat is taken with meal very high in fat, the possibility of gastrointestinal effects increases.
Patients should be advised 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.
Some patients may develop increased levels of urinary oxalate following treatment with orlistat. Caution should be exercised when prescribing orlistat to patients with a history of hyperoxaluria or calcium oxalate nephrolithiasis.
Weight-loss induction by orlistat may be accompanied by improved metabolic control in diabetics, which might require a reduction in dose of oral hypoglycemic medication (e.g., sulfonylureas, metformin) or insulin.

Misuse Potential

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

Information for Patients

Patients should read the patient information before starting treatment with orlistat and each time their prescription is renewed.

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.
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.

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.

STORAGE CONDITIONS:

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F). Keep bottle tightly closed.
Orlistat should not be used after the given expiration date.

PRESENTATION:

Vyfat capsule is available in strip of 10 Capsules.

Manufactured by :
(INTAS)
INTAS PHARMACEUTICALS
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