ORLISLIM

Capsules

Composition
Each Capsule contains Orlistat 120 mg

Action
Mechanism of Action
Orlislim is a potent, specific and reversible long-acting 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 serine residue of the active site of gastric and pancreatic lipases. The inactivated enzyme is thus unable 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 has a positive effect on the weight control.

Pharmacokinetics
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 pre-treatment levels, within 48 to 72 hours.

Absorption
In normal weight and obese volunteers, the systemic exposure to orlistat was minimal. Plasma concentrations of intact orlistat were nearly non-measurable (< 5 ng/mL) following a single oral administration of 360 mg orlistat.

In general, after long-term treatment at therapeutic doses, detection of intact orlistat in plasma was sporadic and concentrations were extremely low (<10 ng/mL or 0.02 µM), without evidence of accumulation showing consistency with negligible absorption.

Distribution
The volume of distribution cannot be determined because orlistat is minimally absorbed. 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 presystemically. Two major metabolites (M1 and M3) accounted for approximately 42% of the total radioactivity in plasma resulting from the minute fraction of the dose that was absorbed systemically in obese patients.
These two major metabolites have very 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 pharmacologically inconsequential.

Elimination
Studies in normal weight and obese subjects have shown that fecal excretion of the unabsorbed orlistat 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 (fecal plus urinary) was 3-5 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.

Pharmacokinetics in special populations
Plasma concentrations of orlistat and its metabolites M1 and M3 were similar in paediatric patients compared 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.

Hepatic and/or renal impairment
Clinical investigations in patients with hepatic and/or renal impairment have not been undertaken.

Efficacy
Orlislim is effective in weight control (weight loss, weight maintenance and prevention of weight regain). Treatment with Orlislim results in an improvement of risk factors and co morbidities associated with obesity, including hypercholesterolemia, noninsulin dependent diabetes mellitus (NIDDM), impaired glucose tolerance, hyperinsulinemia, and hypertension and in a reduction of visceral fat.

Experience from clinical trials shows that the greatest rate of weight loss occurs within the first six months of treatment.

Doses above 120 mg three times daily have not been shown to provide additional benefit.
The efficacy and safety of Orlislim in children and adolescents below the age of 18 years have not been established.

Indications
Orlislim is for weight control, including weight loss, weight maintenance and prevention of weight regain in adults with an initial body mass index (BMI) of 30 or more.

Orlislim should be used in conjunction with a low fat, calorie controlled diet.

Contraindications
Orlistat is contraindicated in patients with chronic malabsorption syndrome, cholestasis and in patients with known hypersensitivity to orlistat or any of the components contained in the medicinal product.

Adverse Reactions
Adverse reactions to Orlistat are largely gastrointestinal in nature and related to the pharmacologic effect of orlistat on preventing the absorption of ingested fat. Commonly observed events are oily spotting, flatus with discharge, fecal urgency, fatty/oily stool, oily evacuation, increased defecation and fecal incontinence. The incidence of these increases the higher the fat content of the diet. Patients should be counseled as to the possibility of gastrointestinal effects occurring and how best to handle them such as reinforcing the diet, particularly the percentage of fat it contains. Consumption of a diet low in fat will decrease the likelihood of experiencing adverse gastrointestinal events and this may help patients to monitor and regulate their fat intake.

These adverse gastrointestinal reactions are generally mild and transient. They occurred within 3 months of commencing treatment and most patients experienced only one episode.

Treatment-emergent GI-adverse events that occurred commonly among patients treated with Orlistat were: abdominal pain/discomfort, flatulence, liquid stools, soft stools, rectal pain/discomfort, tooth disorder, gingival disorder.

Other events observed were: upper respiratory infection, lower respiratory infection; influenza; headache; menstrual irregularity; anxiety; fatigue; urinary tract infection.

Unique treatment adverse events observed in obese type 2 diabetic patients were hypoglycemia (very common) and abdominal distension (common). Weight loss induced by Orlistat is accompanied by improved metabolic control in type 2 diabetics which might allow or require reduction in the dose of hypoglycemic medication.

Post-marketing experience

Rare cases of hypersensitivity have been reported. Main clinical symptoms are pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis. Very rare cases of bullous eruption increase in transaminases and in alkaline phosphatase, and exceptional cases of hepatitis that may be serious have been reported during the post marketing. No causal relationship or physiopathological mechanism between hepatitis and orlistat therapy has been established.

Reports of decreased prothrombin, increased international normalized ratio (INR) and unbalanced anticoagulant treatment resulting in change of haemostatic parameters have been reported in patients treated concomitantly with orlistat and anticoagulants during post-marketing.

Warnings and Precautions

In order to ensure adequate nutrition, the use of a multivitamin supplement should be considered.
Patients should be advised to adhere to dietary guidelines.

The possibility of experiencing gastrointestinal events 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 any one meal very high in fat, the possibility of gastrointestinal effects may increase. If a meal is missed, the dose of Orlistat may be omitted.

Weight loss induced by Orlistat is accompanied by improved metabolic control in type 2 diabetics which might allow or require reduction in the dose of hypoglycemic medication (e.g. sulfonylureas).
A reduction in cyclosporin plasma levels has been observed when Orlistat is co-administered. Therefore it is recommended to monitor more frequently than usual the cyclosporin plasma levels when Orlistat is co-administered.

Coagulation parameters should be monitored in patients treated with concomitant oral anticoagulants.

Oral administration of amiodarone during orlistat treatment demonstrated a 25 - 30% reduction in the systemic exposure to amiodarone and desethylamiodarone. Due to the complex pharmacokinetics of amiodarone, the clinical effect of this is unclear. The effect of commencing orlistat treatment in patients on stable amiodarone therapy has not been studied. A potential reduced therapeutic effect of amiodarone is possible.

Pregnancy
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.

Nursing Mothers
The secretion of orlistat in human breast milk has not been investigated. Orlistat should not be taken during breast-feeding.

Drug Interactions

No interactions based on specific medicine-medicine-interaction studies with amitriptyline, Atorvastatin, biguanides, digoxin, fibrates, fluoxetine, losartan, phenytoin, oral contraceptives, phentermine, pravastatin, warfarin, nifedipine Gastrointestinal Therapeutic System (GITS), nifedipine slow release, sibutramine or alcohol have been observed.

However, when warfarin or other anticoagulants are given in combination with orlistat, international normalized ratio (INR) values should be monitored.

Decreases in the absorption of vitamin D, E and β-carotene have been observed when co-administered with Orlistat. If a multivitamin supplement is recommended, it should be taken at least two hours after the administration of Orlistat or at bedtime.

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Dosage and Administration

Adults

The recommended dose of Orlislim is one 120 mg capsule three times a day with each main meal (during or up to one hour after the meal).

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.
No dose adjustment is necessary for the geriatric patient.

Overdosage

Single doses of 800 mg Orlistat and multiple doses of up to 400 mg t.i.d. for 15 days have been studied in normal weight and obese subjects without significant adverse findings. In addition, doses of 240 mg t.i.d. have been administered to obese patients for 6 months without significant increase of adverse findings.

Orlistat overdose cases received during post-marketing reported either no adverse events or adverse events that are similar to those reported with recommended dose.

Should a significant overdose of Orlistat occur, 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.

Storage

Store below 25°C. Store in original package in order to protect from moisture.

Further Information

The World Health Organization (WHO) calculates Body Mass Index (BMI) using the following equation:

$$BMI = \text{weight (kg)} / [\text{height (m)}]^2$$

The body mass index (BMI) is a person's weight in kilograms (kg) divided by their height in meters (m) squared.

The WHO BMI classification for overweight adults is BMI ≥ 25, and for obese adults BMI ≥ 30.
Note, that these BMI values are age-independent and the same for both sexes. However, BMI may not correspond to the same degree of fatness across different populations due, in part, to different body proportions.

Presentation

Orlislim 120 mg capsules

Box of 30 capsules