United Pharmaceuticals

UNI-CAL®

Orlistat

Description:

UNI-CAL® (Orlistat) is a potent, specific and long-acting lipase inhibitor which exerts its therapeutic activity in the lumen of the stomach and upper small intestine by forming a covalent bond with the active serine site of gastric and pancreatic lipases. The inactivated enzyme is thus rendered unable to hydrolyze dietary fats in the form of triglycerides into absorbable free fatty acids and monoglycerides. As undigested triglycerides cannot be absorbed, a caloric deficit arises which has a positive effect on weight control. Systemic absorption of Orlistat is therefore not needed for activity.

Properties:

Orlistat and its metabolites have minimal absorption (≤ 3%); therefore, the volume of distribution cannot be determined. Plasma concentrations of intact Orlistat were non-measurable (< 5 ng/ml) after eight hours from Orlistat oral administration. Orlistat is more than 99% bound to plasma proteins and only a small amount of Orlistat is taken up into erythrocytes.

The metabolism of Orlistat occurs mainly within the gastrointestinal wall with two major metabolites M_1 and M_3 accounted for 42% of the total plasma concentration but are considered to be pharmacologically irrelevant.

Approximately 97% of the administered dose is excreted in feces and 83% of that as unchanged Orlistat. The time to complete excretion (fecal and renal) is 3 - 5 days.

Indications:

Adults:

UNI-CAL® is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) ≥ 30 kg/m^2 and overweight patients (BMI ≥ 28 kg/m^2) with associated risk factors such as type II diabetes, hyperlipidemia and hypertension.

In patients who fail to respond adequately to suitable weight reducing measures, **UNI-CAL®** can be used as an adjunct to a hypocaloric diet and physical measures in the treatment of dietary overweight.

Treatment with **UNI-CAL®** should be discontinued after 12 week in patients who have not lost at least 5% of their body weight as measured at the start of drug therapy.

Adolescents:

Obese adolescents should be treated with **UNI-CAL®** only if measures carried out in a therapeutic program over 6 month including a balanced diet appropriate to the age of the patient and a program of physical activity aimed at modifying the patient's behavior are not successful. Treatment with **UNI-CAL®** should be considered in particular if complications of obesity are present.

Dosage and administration:

The recommended dose of **UNI-CAL®** is one 120 mg capsule to be taken immediately before, during, or up to one hour after each main meal. If a meal is missed or contains no fat, the dose of **UNI-CAL®** should be omitted.

Patient notes:

- The patient should be on a nutritionally balanced, mildly hypocaloric diet in which approximately 30% of the calories are from fat. The diet should be rich in fruit and vegetables. The daily intake of fat carbohydrate, and protein should be distributed between three main meals.
- Doses of **UNI-CAL®** above 120 mg three times daily have not been shown to provide additional benefit.
- The effect of **UNI-CAL®** results in an increase in fecal fat 24 - 48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to pretreatment levels within 48 - 72 hours.
- Safety and efficacy were investigated in clinical studies lasting up to 4 years.
- In adolescents' treatment with **UNI-CAL®** should be initiated only if an adequate reduction of body weight cannot be achieved by means of diet and increased physical activity. Treatment should be given only if accompanied by determinations of vitamin levels and as part of an overall care program.

Obese adolescents should be treated with Orlistat only if their BMI is above the level indicated in the following table:

International definition of obesity as per Cole:

Age (years)	BMI male	BMI female
12	26.02	26.67
12.5	26.43	27.24
13	26.84	27.76
13.5	27.25	28.20
14	27.63	28.57
14.5	27.98	28.87

Age (years)	BMI male	BMI female
15	28.30	29.11
15.5	28.60	29.29
16	28.88	29.43
16.5	29.14	29.56
17	29.41	29.69
17.5	29.70	29.84

The duration of treatment should be limited to a year in adolescents, since no experience is available with long-term treatment.

Adolescents should take a multivitamin preparation daily during treatment with Orlistat in order to prevent vitamin deficiency during puberty and the extended growth phase. The multivitamin preparation should be taken at least two hours after the ingestion of Orlistat or at bedtime.

Special dosage instructions:

- The tolerability and efficacy of **UNI-CAL®** have not been studied in children under 12 years of age, elderly patients, or patients with hepatic and/or renal impairment.
- Orlistat is not intended for the treatment of children under 12 years of age.

Contraindications:

- Hypersensitivity to Orlistat or to any of the other ingredients of the capsules.
- Patients with chronic malabsorption syndrome.
- Patients with cholestasis.
- During breastfeeding.

Precautions:

- Patients should be informed of the possibility that gastrointestinal side effects may occur and of how these can best be managed, e. g. by paying attention to the composition, in particular the fat content, of their diet. Ingestion of low-fat food reduces the probability of gastrointestinal side effects. This can help patients to pay attention to and regulate their fat intake.

Patients should be advised to adhere to the dietary recommendations. The probability of occurrence of gastrointestinal side effects may increase when Orlistat is taken with a fatty meal (e.g. in a 2000 kcal/day diet, >30% of calories from fat is equivalent to > 67 g of fat). The daily intake of fat should be distributed between three main meals.

Use of doses above the recommended dose of 120 mg three times daily results in no detectable increase in effect, but can increase the occurrence of gastrointestinal side effects.

- In clinical trials, the decrease in body weight with Orlistat therapy was less in type 2 diabetic patients than in non-diabetic patients. Antidiabetic drug treatment should be closely monitored during Orlistat therapy. Because of the improvement in glycemic control, the close of oral antidiabetic or of insulin may need to be adjusted.
- Treatment with Orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E, and K).

In most patients who received up to 4 years of treatment with Orlistat in clinical studies, levels of vitamin A, D, E, and K and beta-carotene remained within the 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.

Use of a multivitamin supplement can be considered. If a multivitamin supplement is recommended, it should be taken at least 2 hours after the ingestion of Orlistat or at bedtime.

- Adolescents should undergo a medical review after the start of treatment, after 6 weeks, and thereafter at three-monthly intervals. Weight loss should be monitored, since massive weight loss during adolescence can negatively influence growth.
- Treatment should be stopped after three months if no reduction of BMI has occurred or if significant side effects occur. In the event of rapid weight loss the treating physician should the potential side effects on growth and puberty and If the occurrence of gallstones in order to decide whether treatment should be interrupted.
- Treatment with Orlistat is not indicated in non-obese adolescents.
- Cases of severe liver injury have been reported rarely with the use of Orlistat. At this time, a cause and effect relationship of severe liver injury with Orlistat use has not been established.
- Instruct patients to report any symptoms of hepatic dysfunction (anorexia, pruritus, jaundice "yellow eyes or skin", dark urine, light colored stools, or right upper quadrant pain) when using this medication.
- If liver injury is suspected, Orlistat should be discontinued immediately and liver function tests and ALT and AST levels obtained.
- **Effects on ability to drive and use machines:** It is not to be expected that Orlistat would impair the ability to drive or to use machines.

Use during pregnancy and lactation:

Pregnancy category **B**

Pregnancy: No clinical data are available on pregnancies exposed to Orlistat. Animal studies do not indicate direct or indirect harmful effects on pregnancy, embryo-fetal development, parturition or postnatal development.

Lactation: As it is not known whether Orlistat is excreted in breast milk, Orlistat should not be used during breastfeeding.

Drug interactions:

- Co-administration of Orlistat and Cyclosporine A led to a reduction in the Cyclosporine A plasma concentration. This can lead to a reduction in immunosuppressive effect. Therefore, this combination is not recommended. Accordingly, when Orlistst is co-administered with Cyclosporine A, Cyclosporine A plasma levels should be monitored more frequently than is usually the case; after initiation and cessation of treatment with Orlistat. Cyclosporine A plasma levels should be monitored until is stabilized. An interval of three hours between ingestion of the two medications is recommended.
- In the absence of pharmacokinetic or Pharmacodynamic interaction studies, concomitant administration of Orlistat with Acarbose, glitazones, Glinides or anorectic drugs is not recommended.
- When Warfarin or other anticoagulants are given in combination with Orlistat (high-dose or long-term therapy), international normalized ratio (INR) values (Quick test results) should be monitored.
- Orlistat can impair the absorption of fat-soluble vitamins (A, D, E, and K). Most patients who received up to four years of treatment with Orlistat in clinical studies had vitamin A, D, E, and K and beta-carotene levels within the normal range. In order to ensure adequate vitamin intake, patients following a diet should be advised to have a diet rich in fruit and vegetables and use of a multivitamin supplement could be recommended. When indicated, multivitamin supplements should be taken at least two hours after taking **UNI-CAL®** or before going to bed.
- Amiodarone administration during treatment with Orlistat shows a 25 - 30% reduction in systemic exposure to Amiodarone and desethylamiodarone. Due to the complex pharmacokinetics of Amiodarone, the clinical significance of this finding is unclear. The effect of commencing Orlistat treatment in patients on stable Amiodarone therapy has not been studied; however a reduced therapeutic effect of Amiodarone is possible.

No interactions:

No interactions have been observed with Amitriptyline, Atorvastatin, biguanides, Glibenclamide, Digoxin, Fibrates, Fluoxetine, Losartan, Furosemide, Captopril, Atenolol, Phenytoin, oral contraceptives, Phentermine, Pravastatin, Nifedipine, sibutramine or Alcohol.

Side effects:

Side effects of Orlistat are largely gastrointestinal in nature and related to the pharmacologic effect of the drug on preventing the absorption of ingested fat. Commonly observed effects are oily spotting from the rectum (27%), flatulence with defecation (24%), fecal urgency (22%), oily or fatty stool (20%), increased defecation (11%) and fecal incontinence (8%). The higher the fat content of the diet, the higher is the incidence of these side effects. Abdominal pain (20.5%) and watery stools (15.8%) can also occur.

In clinical studies these pharmacologic effects were generally mild and transient and did not lead to cessation of treatment. Gastrointestinal side effects occurred within the first 3 months of treatment and most patients experienced only one episode.

Only 3% of patients experienced more than two episodes of any one of the side effects referred below:

Immune system:

Common: Influenza.

Psychiatric disturbances:

Common: Anxiety:

Nervous system:

Common: Headache.

Respiratory organs:

Common: Upper airway infections, lower airway infections.

Gastrointestinal tract:

Very common: Abdominal pain/discomfort (21%), flatulence (24%), liquid and soft stool (16%).

Common: Involuntary defecation, rectal pain/discomfort, dental symptoms, gingival symptoms.

Liver:

Occasional: Hepatitis, elevated transaminases and alkaline phosphates.

Skin/hypersensitivity reactions:

Rare: Hypersensitivity reactions; pruritus, rash, urticana, bullous rash, angioedema, anaphylaxis.

Kidneys and urinary tract:

Common: Urinary tract infection.

Reproductive system:

Common: Irregularity of menstruation.

General:

Common: Fatigue.

Overdosage:

The cases of Orlistat overdosage reported during post-marketing experience showed either no side effects or adverse events similar to those reported with the 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.

Storage conditions:

Store up to 25ºC.

Presentation:

UNI-CAL®: Each capsule contains Orlistat 120 mg in packs of 30 capsules.

Hospital packs are also available.

This is a medicament

- Medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you.
- Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.
- Keep medicament out of the reach of children.

COUNCIL OF ARAB HEALTH MINISTERS
UNION OF ARAB PHARMACISTS

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