Only for the use of a Registered Medical Practitioner or a Hospital or a Laboratory

Orlistat Capsules

Biocon

OLISAT® - 120 ओलिसेट-६०

COMPOSITION
Orlistat capsules
Each hard gelatin capsule contains:
Orlistat 120 mg (as pellets 50% w/w)
Approved colors used in capsule shells.

PHARMACEUTICAL FORM
Capsules

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic Properties
Pharmacotherapeutic group: Peripherally acting anti-obesity products, ATC code: A08AB01.

Mechanism of Action
Orlistat is a potent, specific, and 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 active serine site of the gastric and pancreatic lipases. The inactivated enzyme is thus unavailable to hydrolyze dietary fat, in the form of triglycerides, into absorbable free fatty acids and monoglycerides.
Pharmacokinetic Properties

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) 8 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. In a study conducted in obese patients, of the minimal fraction of the dose that was absorbed systemically, 2 major metabolites, M1 (4-member lactone ring hydrolyzed) 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 low plasma levels at therapeutic doses (average of 26 ng/mL and 108 ng/mL, respectively), these metabolites are considered to be pharmacologically inconsequential.

Elimination
Studies in normal weight and obese subjects have shown that fecal excretion of the unabsorbed drug was the major route of elimination. Approximately 97% of the administered dose was excreted in feces 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 complete excretion (fecal 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.

Preclinical Safety Data
Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.
In animal reproductive studies, no teratogenic effect was observed. In the absence of a teratogenic effect in animals, no malformative effect is expected in man. To date, active substances responsible for malformations in man have been found teratogenic in animals when well conducted studies were performed in 2 species.

CLINICAL PARTICULARS
Therapeutic 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. Orlistat is indicated for obese patients with an initial body mass index (BMI) of ≥30 kg/m2 or ≥27 kg/m2 in the presence of other risk factors (eg, hypertension, diabetes, dyslipidemia).

Posology and Method of Administration
Adults
The recommended dose of OLISAT®-120 is 1 capsule taken with water immediately before, during, or up to 1 hour after each main meal. If a meal is missed or contains no fat, the dose should be avoided.
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 3 main meals.
Doses of orlistat above 120 mg 3 times daily have not shown to provide additional benefit.
The effect of orlistat results in an increase in fecal fat as early 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.
Special Populations
OLISAT®-120 should not be used in children and adolescents below 12 years of age due to insufficient data on safety and efficacy.
The safety and efficacy of orlistat has been reported in obese adolescent patients aged 12 to 16 years. In a multicenter (US, Canada), parallel group, double blind, placebo controlled study, 539 obese adolescent patients were randomized to receive either 120 mg orlistat (n=357) or placebo (n=182) 3 times daily as an adjunct to a hypocaloric diet and exercise for 52 weeks. Both populations received multivitamin supplements. The primary endpoint was the change in BMI from baseline to the end of the study. The results were significantly superior in the orlistat group (difference in BMI of 0.86 kg/m2 in favor of orlistat). Of the orlistat-treated patients, 9.5% lost 10% of body weight after 1 year versus 3.3% of the placebo-treated patients with a mean difference of 2.6 kg between the 2 groups. The difference was driven by the outcome in the group of patients with 5% weight loss after 12 weeks of treatment with orlistat representing 19% of the initial population. The side effects were generally similar to those observed in adults. However, there was an unexplained increase in the incidence of bone fractures (6% versus 2.8% in the orlistat and placebo groups, respectively).
In a 3-week study of 32 obese adolescents aged 12 to 16 years, XENICAL (120 mg 3 times a day) did not significantly affect the balance of calcium, magnesium, phosphorus, zinc, or copper. There was a decrease in the iron balance by 64.7 µ mol and 40.4 µ mol in the orlistat- and placebo treatment groups in 24 hours, respectively.
There are limited data on the use of orlistat in the elderly. However, as orlistat is minimally absorbed, no dose adjustment is necessary in the elderly.
The effect of orlistat in patients with hepatic and/or renal impairment has not been studied. However, as orlistat is minimally absorbed, no dosage adjustment is necessary in the elderly and in individuals with hepatic and/or renal impairment.

Contraindications
- Hypersensitivity to the active substance or to any of the excipients
- Concurrent treatment with cyclosporin
- Chronic malabsorption syndrome
- Cholestasis
- Breast feeding
- Concurrent treatment with warfarin or other oral anticoagulants

Special Warnings and Precautions for Use
Patients should be advised to adhere to the dietary recommendations they are given. The possibility of experiencing gastrointestinal symptoms may increase when orlistat is taken with an individual meal or a diet high in fat.
Treatment with orlistat may potentially impair the absorption of fat soluble vitamins (A, D, E, and K). For this reason, a multivitamin supplement should be taken at bedtime.
As weight loss may be accompanied by improved metabolic control in diabetes, patients who are taking a medicinal product for diabetes should consult a doctor before starting treatment with OLISAT®-120, in case it is necessary to adjust the dose of the anti-diabetic medication.
Weight loss may be accompanied by an improvement in blood pressure and cholesterol levels. Patients who are taking a medicinal product for hypertension or hypercholesterolemia should consult a doctor or pharmacist when taking OLISAT®-120, in case it is necessary to adjust the dose of these medications.
Patients who are taking amiodarone should consult a doctor before starting treatment with OLISAT®-120.
Cases of rectal bleeding have been reported in patients taking orlistat. If this occurs, the patient should consult a doctor.
The use of an additional contraceptive method is recommended to prevent possible failure of oral contraception that could occur in case of severe diarrhea.
Patients with kidney disease should consult a doctor before starting treatment with
OLISAT®-120, as the use of orlistat may rarely be associated with hyperoxaluria and oxalate nephropathy.
There have 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 pain in the right upper quadrant) while taking orlistat. When these symptoms occur, orlistat and other suspect medications should be discontinued immediately and liver function tests and ALT and AST levels obtained.
Hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are coadministered. Patients taking levothyroxine should consult a doctor before starting treatment with OLISAT®-120, as the 2 drugs may need to be taken at different times and the dose of levothyroxine may need to be adjusted.
Patients taking an antiepileptic medicinal product should consult a doctor before starting treatment with OLISAT®-120, as they should be monitored for possible changes in the frequency and severity of convulsions. If this occurs, consideration could be given to administering orlistat and antiepileptic medicinal products at different times.

Drug Interactions
Cyclosporin
A decrease in cyclosporin plasma levels has been observed in a drug drug interaction study and also reported in several cases, when orlistat was administered concomitantly. This could potentially lead to a decrease in immunosuppressive efficacy. Concurrent use of orlistat and cyclosporin is contraindicated. Oral Anticoagulants
When warfarin or other oral anticoagulants are given in combination with orlistat, international normalized ratio (INR) values could be affected. Concurrent use of orlistat and warfarin or other oral anticoagulants are contraindicated.

Oral Contraceptives
The absence of an interaction between oral contraceptives and orlistat has been demonstrated in specific drug-drug interaction studies. However, orlistat may indirectly reduce the availability of oral contraceptives and lead to unexpected pregnancies in some cases. An additional contraceptive method is recommended in case of severe diarrhea.

Only for the use of a Registered Medical Practitioner or a Hospital or a Laboratory

Orlistat Capsules

Biocon

OLISAT®- 120 ओलिसेट–६०

Levothyroxine
Hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are taken at the same time. This could be due to a decreased absorption of iodine salts and/or levothyroxine.

Antiepileptic Medicinal Products
Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic medicinal products eg, valproate, lamotrigine, for which a relationship to an interaction cannot be excluded. Orlistat may decrease the absorption of antiepileptic medicinal products, leading to convulsions.

Fat-soluble Vitamins
Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E, and K).
A vast majority of subjects receiving up to 4 full years of treatment with orlistat in clinical studies had vitamin A, D, E, and K and beta-carotene levels that stayed within normal range. However, patients should be advised to use a multivitamin supplement at bedtime to help ensure adequate vitamin intake.

Acarbose
In the absence of pharmacokinetic interaction studies, orlistat is not recommended to be used by patients receiving acarbose.

Amiodarone
A decrease in plasma levels of amiodarone, when given as a single dose, has been observed in a limited number of healthy volunteers who received orlistat concomitantly. The clinical relevance of this effect in patients receiving amiodarone treatment remains unknown. Patients who are taking amiodarone should consult a doctor before starting treatment with OLISAT®-120. The dose of amiodarone may need to be adjusted during treatment with OLISAT®-120.

Lack of Interactions
No interactions with amitriptyline, atorvastatin, biguanides, digoxin, fibrates, fluoxetine, losartan, phenytoin, phentermine, pravastatin, nifedipine gastrointestinal therapeutic system (GITS), nifedipine slow release, sibutramine, or alcohol have been observed. The absence of these interactions has been demonstrated in specific drug drug interaction studies.

Pregnancy and Lactation
No clinical data on orlistat exposed during pregnancies are available.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal or fetal development, parturition or postnatal development.

Orlistat is contraindicated in pregnancy.
As it is not known whether orlistat is secreted into human milk, orlistat is contraindicated during breast feeding.

Effects on Ability to Drive and Use Machines
OLISAT®-120 does not influence the ability to drive or use machines.

Undesirable Effects
Adverse reactions to orlistat are largely gastrointestinal in nature. The incidence of adverse events decreased with prolonged use of orlistat.
Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (1/10), common (1/100 to <1/10), uncommon (1/1,000 to <1/100), rare (1/10,000 to <1/1,000), and very rare (<1/10,000) including isolated reports.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
The following table of undesirable effects (first year of treatment) is based on adverse events that occurred in clinical trials of 1 and 2 years duration in obese type 2 diabetic patients, at a frequency of >2% and with an incidence ≥1% above placebo.:

Organ Systems Affected	*Adverse Reaction/Event*
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*

*Only unique treatment adverse events that occurred at a frequency of >2% and with an incidence ≥1% above placebo in obese type 2 diabetic patients.

In another 4-year clinical trial, the general pattern of adverse event distribution was similar to that reported for the 1 and 2 year studies with the total incidence of gastrointestinal related adverse events occurring in year 1, decreasing each year over the 4-year period.
The following table of undesirable effects is based on post marketing spontaneous reports, and therefore the frequency remains unknown:

Organ Systems Affected	Adverse Reaction
Investigations	Increase in liver transaminases and alkaline phosphatase. Decreased prothrombin, increased INR, and unbalanced anticoagulant treatment resulting in variations of hemostatic parameters have been reported in patients treated with anticoagulants in association with orlistat.
Gastrointestinal Disorders	• Rectal bleeding • Diverticulitis • Pancreatitis
Skin and Subcutaneous Tissue Disorders	Bullous eruptions
Immune System Disorders	Hypersensitivity (eg, pruritus, rash, urticaria, angioedema, bronchospasm, and anaphylaxis)
Hepatobiliary Disorders	Cholelithiasis Hepatitis that may be serious
Renal and Urinary Disorders	Oxalate nephropathy

Overdose
Single doses of 800 mg orlistat and multiple doses of up to 400 mg 3 times daily for 15 days have been studied in normal weight and obese subjects without significant adverse findings. In addition, doses of 240 mg 3 times daily 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 the recommended dose of orlistat.
In the event of an overdose, medical advice should be sought. 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.

PHARMACEUTICAL PARTICULARS
Incompatibilities
Not applicable.

Shelf Life
24 months.

Storage and Precautions
Store below 25°C. Do not freeze or refrigerate. Protect from light and moisture.
Keep out of reach of children.
Special Precautions for Disposal and Other Handling.
No special requirements.
Nature and Contents of Container
OLISAT®- 120 capsules are available in blisters of 10 capsules.

Manufactured by :
Biocon Limited
at 40/1, Mohabewala Industrial Area,
SBI Road, Dehradun - 248110.

MARKETED BY
Biocon Limited
20th K.M., Hosur Road
Electronics city
Bangalore–560 100, INDIA.
® Registered trade mark of Biocon Limited

For further details, please contact:
Medical Advisor
Biocon Limited
20th KM, Hosur Road,
Electronics City, Bangalore – 560100.

To report adverse events and/or product complaints visit our website **www.biocon.com** or call toll free number: **1800 102 9465** or e-mail us at **drugsafety@biocon.com.**

BF/LL/0161/01