MODULE -1
ADMINISTRATIVE AND PRODUCT INFORMATION OF REESHAPE CAPSULES

1.3 PRODUCT INFORMATION:

1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. Name of the Medicinal Product

1.1 Product Name **:** Reeshape Capsules

1.2 Strength **:** Each hard gelatin capsule contains:

Orlistat USP 120 mg

Excipients q.s.

Approved colours used in capsule shells.

1.3 Pharmaceutical Dosage Form **:** Capsules

2. Quality and Quantitative Composition

2.1 Qualitative Declaration

Active Ingredients:

Orlistat USP

2.2 Quantitative Declaration

Components (INN)	Mg per capsule
Orlistat USP	120 mg
Microcrystalline Cellulose BP (PH 101)	83.8 mg
Sodium Starch Glycolate BP	10 mg
Sodium Lauryl Sulphate BP	7 mg
Polyvinylpyrrolidone BP (PVP K-30)	12 mg
Methylene Chloride	q.s
Purified Talc BP	0.5 mg
Microcrystalline Cellulose BP (PH 101)	39.5 mg

MODULE -1
ADMINISTRATIVE AND PRODUCT INFORMATION OF REESHAPE CAPSULES

3. Pharmaceutical Form

Dark Green/ Red coloured hard gelatin size “1” capsule with monogram “REESHAPE” on cap & “120” on body printed in white ink. (Circular printing)

4. Clinical Particulars

4.1 Therapeutic indications

Orlistat is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet in patients with an initial BMI > 30 kg/m2 or > 27 kg/m2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia). Orlistat is also indicated to reduce the risk for weight regain after prior weight loss. Adding orlistat as a pharmacological treatment to conventional diabetic treatment is a better option for overweight and obese patients with type 2 diabetes. Orlistat is a useful adjunct in the treatment of PCOS (polycystic ovarian syndrome).

4.2 Posology and method of administration

The recommended dose of Reeshape is one 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 orlistat can be omitted.

Because orlistat has been shown to reduce the absorption of some fat-soluble vitamins and beta-carotene, patients should be counseled to take multivitamin containing fat-soluble vitamins to ensure adequate nutrition. The supplement should be taken at least 2 hours before or after the administration of orlistat, 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.

Orlistat should not be used after the given expiration date.

MODULE -1
ADMINISTRATIVE AND PRODUCT INFORMATION OF REESHAPE CAPSULES

Method of administration:

Oral

4.3 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.

4.4 Special warning and precautions for use

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

Patients should be advised to adhere to dietary guidelines. Gastrointestinal events may increase when orlistat is taken with a diet high in 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.

4.5 Interaction with other medicinal products and other forms of interactions

Alcohol: In a multiple-dose study in 30 normal weight subjects, co-administration of orlistat and 40 grams of alcohol (e.g., 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 a orlistat and cyclosporine drug interaction study indicate a reduction in cyclosporine plasma levels when orlistat was coadministered with cyclosporine

Digoxin: In 12 normal-weight subjects receiving orlistat120 mg three times a day for 6 days, orlistat did not alter the pharmacokinetics of a single dose of digoxin.

Fat-soluble Vitamin Supplements and Analogues: 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 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): In 17 normal-weight subjects receiving orlistat 120 mg three times a day for 6 days, orlistat did not alter the bioavailability of nifedipine (extended-release tablets).

Oral Contraceptives: In 20 normal-weight female subjects, the 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: In 12 normal-weight subjects receiving orlistat 120 mg three times a day for 7 days, orlistat did not alter the pharmacokinetics of a single 300-mg dose of phenytoin.

Pravastatin: In a 2-way crossover study of 24 normal-weights, mildly hypercholesterolemic patients receiving orlistat 120 mg three times a day for 6 days, orlistat did not affect the pharmacokinetics of pravastatin.

Warfarin: In 12 normal-weight subjects, administration of 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.

Simvastatin: There was no effect of orlistat on the pharmacokinetics of fluoxetine, and simvastatin (highly lipophilic drugs) when these drugs were taken concomitantly with orlistat.

Minerals: Administration of orlistat had no significant effect on the balance of six minerals: calcium, phosphorus and magnesium, iron, zinc and copper in adolescent obese patients.

Antidepressant, antihypertensive & Antidiabetics: There was no effect of orlistat on the pharmacokinetics of amitriptyline, atorvastatin, losartan, metformin, and phentermine, when these drugs were taken concomitantly with orlistat.

4.6 Pregnancy and lactation

Teratogenic Effects: Pregnancy Category B. Teratogenicity studies were conducted in rats and rabbits at doses up to 800 mg/kg/day. Neither study showed embryotoxicity or teratogenicity. This dose is 23 and 47 times the daily human dose calculated on a body surface area (mg/m2) basis for rats and rabbits, respectively.

The incidence of dilated cerebral ventricles was increased in the mid- and high-dose groups of the rat teratology study. These doses were 6 and 23 times the daily human dose calculated on a body surface area (mg/m2) basis for the mid- and high-dose levels, respectively. This finding was not reproduced in two additional rat teratology studies at similar doses.

There are no adequate and well-controlled studies of orlistat in pregnant women. Because animal reproductive studies are not always predictive of human response, 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.

4.7 Effects on ability to drive and use machine

None

4.8 Undesirable effects

None

4.9 Overdose

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.

5. Pharmacological Properties

5.1 Pharmacodynamics Properties

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%.

5.2 Pharmacokinetic Properties

Absorption:

Systemic exposure to orlistat is minimal. 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). 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. The average absolute bioavailability of intact orlistat was assessed in studies with male rats at oral doses of 150 and 1000 mg/kg/day and in male dogs at oral doses of 100 and 1000 mg/kg/day and found to be 0.12%, 0.59% in rats and 0.7%, 1.9% in dogs, respectively.

Distribution:

In vitro orlistat was >99% bound to plasma proteins (lipoproteins and albumin were major binding proteins). Orlistat minimally partitioned into erythrocytes.

Metabolism:

Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. 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. 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 the low plasma levels at the therapeutic dose (average of 26 ng/mL and 108 ng/mL for M1 and M3, respectively, 2 to 4 hours after a dose), these metabolites are considered pharmacologically inconsequential. 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, steadystate plasma levels of M1, but not M3, increased in proportion to orlistat doses.

Elimination:

Following a single oral dose of 360 mg 14C-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 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 disposition of orlistat appeared to be similar between normal weight and obese subjects. Based on limited 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. 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.

5.3 Preclinical safety Data

NA

MODULE -1
ADMINISTRATIVE AND PRODUCT INFORMATION OF REESHAPE CAPSULES

6. Pharmaceutical Particulars

6.1 List of excipients

Microcrystalline Cellulose BP (PH 101)

Sodium Starch Glycolate BP

Sodium Lauryl Sulphate BP

Polyvinylpyrrolidone BP (PVP K-30)

Methylene Chloride

Purified Talc BP

BP: British Pharmacopoeia

MS: Meyer Specification

6.2 Incompatibilities

Not Known

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store below 30°C, in a dry place. Protect from light.

Capsules are for oral administration. Keep medicines out of reach of children.

6.5 Nature and contents of container

Each carton contains 3 strips of 10 capsules each.

7. Marketing Authorization Holder

MEYER ORGANICS PVT. LTD

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Bangalore 560058.India