Slimaim
(ORLISTAT)

Each Capsule contains
Orlistat 120mg

Slimaim is a lipase inhibitor for obesity management that acts by inhibiting the absorption of dietary fats. **Slimaim** works in intestines, where it blocks some of the fat from being absorbed. This undigested fat is then eliminated in bowel movements. **Slimaim** should be used together with a reduced-calorie diet recommended by doctor.
Excess weight has been proven to contribute to an increased risk of developing many medical problems, including high blood pressure, high cholesterol, heart disease, and diabetes. The consumption of excess fatty food and calories plays a significant role in the development of excess weight. While fat is an important component of a balanced diet, the consumption of excess fat contributes to excess body weight, since fat provides twice the number of calories per gram of weight as carbohydrates and protein. Reduction of dietary fat intake is one potential way of losing weight.

Clinical Particulars

Therapeutic Indications

Slimaim is indicated for treatment of obese patients or severely over weight patients in conjunction with a mildly hypocaloric diet.

Dosage and Method of Administration

Standard Dosage

The recommended dose of **Slimaim** is one 120mg capsule with each main meal (during or up to one hour after the meal). If a meal is missed or contains no fat, the dose of **Slimaim** may be omitted. The patient should be on a nutritionally balanced, mildly hypocaloric diet that contains approximately 30% of calories form fat. The daily intake of fat, carbohydrate and protein should be distributed over three main meals. Doses above 120mg three times daily have not been shown to provide additional benefit. Based on fecal fat measurements, the effect of **Slimaim** is seen as soon as 24-48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to pretreatment levels, within 48--72 hours.

Special Dosage Instructions

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

Contraindications

Slimaim is contraindicated in patients with chronic mal-absorption syndrome, cholestasis and in patients with known hypersensitivity to **Slimaim** or any of the components contained in the medicinal product.

Special Warnings and Special Precautions of Use

The majority of patients in up to two full years of treatment had vitamin A, D, E and K and beta-carotene levels stayed within normal range. In order to ensure adequate nutrition, the use of a multivitamin supplement could be considered.
Patients should be advised to adhere to dietary guidelines (See Dosage and Method of Administration). The possibility of experiencing gastrointestinal events (see Undesirable Effects) may increase when **Slimaim** is taken with a diet high in fat (e.g. in a 2000 calories/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 **Slimaim** is taken with any one meal very high in fat, the possibility of gastrointestinal effects may increase. Weight loss induced by **Slimaim** is accompained by improved metabolic control in type 2 diabetics which might allow or require reduction in the dose of oral hypoglycemic medication (e.g. sulfonylureas). A reduction in cyclosporin plasma levels has been observed when **Slimaim** is co-adminstered. Therefore it is recommended to monitor more frequently than usual the cyclosporin plasma levels when **Slimaim** is co-administered (see Interactions with other Meical Products and other Forms of Interaction). Coagulation parameters should be monitored in patients treated with concomitant oral anticoagulants. In a PK study, oral administration of amiodarone during **Slimaim** 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 **Slimaim** treatment in patients on stable amiodarone therapy has not been studied. A reduced therapeutic effect of amiodarone is possible.

Interactions with Medical Products and other Forms of Interaction

During pharmacokinetic studies no interactions with alcohol, digoxin, nifedipine, oral contraceptives, phenytoin, Pravastatin, warfarin or metformin have been observed. However, when warfarin or other anticoagulants are given in combination with **Slimaim**, international normalised ratio (INR) values should be monitored. Decreases in the absorption of vitamin D, E and β-carotene have been observed when co-administered with **Slimaim**. If a multivitamin supplement is recommended, it should be taken at least two hours after the administration of **Slimaim** or at bedtime.
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Pregnancy and Lactation

In animal reproductive studies, no embryotoxic or teratogenic effects were observed with **Slimaim**. In absence of a teratogenic effect in animals, no malformative effect is expected in human beings. However, **Slimaim** is not recommended for use during pregnancy in *the absence of clinical data*.
The secretion of **Slimaim** in human breast milk has not been investigated. **Slimaim** should not be taken during breast-feeding.

Undesirable Effects

Experience form Clinical Trials

Adverse reactions of **slimaim** are largely gastrointestinal in nature and related to pharmacologic effect of the drug on preventing the absorption of ingested fat. Commonly observed events are Oily spotting, flatus with discharge, fecal urgency, fatty/oily stools. 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 early in treatment (within 3 months) and most patients experienced only one episode.

Treatment-emergent GI-adverse events that occurred commonly among patients treated with **Slimaim** 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.

Post-Marketing Experience

Rare cases of hypersensitivity have been reported. Main clinical symptoms are pruritus, rash, urticaria, angioedema 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 **Slimaim** therapy has been established.

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

Overdose

Single doses of 800 mg **Slimaim** 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. In addition, doses of 240 mg three times a day 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.

If an event of significant over dosage of **Slimaim** occur, it is recommended that the patients 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.

Pharmacological Properties and effects

Pharmacodynamic Properties

Mechanism of Action

Slimaim 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 hydrolyse dietary fat, in the from 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.

Pharmacokinetic Properties

Absorption

In normal weight and obese volunteers, the systemic exposure to orlistat was minimal. Plasma concentrations of intact orlistat were nearly non-measureable (<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 (<10ng/ml or 0.02µg), without evidence of accumulation showing consistency with negligible absorption.

Distribution

The volume of distribution cannot be determined because the drug is minimally absorbed. In vitro orlistat is >99% bound to plasma proteins (lipoprotenis and albumin were the major binding proteins). Olistat minimally partitions into erythrocytes.

Metabolism

Based on animal data, it is likely that the metabolism of orlistat occurs mainly presystemically. Two major metabolites (MI and M3) accounted for approximately 42% of the total radioactivity in plasma resulting form the minute fraction of the dose that was absorbed systemically in obses 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 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 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, M1and M3 are all subject to biliary excretion.

Storage

Store below 25°C in a dry and dark place.

Presentation

Slimaim Capsules 120mg..... Available in Alu-Alu Blister Pack.

Manufactured By:
Aims Pharmaceuticals
Plot # 291, Industrial Triangle, Kahuta Road, Islamabad-Pakistan