1. DESCRIPTION

1.1 Therapeutic / Pharmacological Class of Drug

Peripheral acting anti-obesity agent.

1.2 Type of Dosage Form

Capsule, hard, 120 mg.

1.3 Route of Administration

Oral

1.4 Sterile / Radioactive Statement

Not applicable.

1.5 Qualitative and Quantitative Composition

Active ingredient: Orlistat.

Excipients: Capsule filling: microcrystalline cellulose, sodium starch glycollate, povidone, sodium lauryl sulphate and talc. Capsule shell: gelatine, indigo carmine (E132) and titanium dioxide (E171).

2. CLINICAL PARTICULARS

2.1 Therapeutic Indication(s)

Xenical, in conjunction with a mildly hypocaloric diet, is used for treatment of overweight patients with associated comorbidities.

2.2 Dosage and Administration

2.2.1 Standard Dosage

The recommended dose of Xenical is one 120 mg 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 Xenical may be omitted.

The patient should be on a nutritionally balanced, mildly hypocaloric, diet that contains approximately 30% of calories from fat.

2.2.2 Special Dosage Instructions

Clinical investigations in patients with hepatic or renal impairment and children under the age of 12 have not been undertaken.

2.3 Contraindications

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

2.4 Warnings and Precautions

2.4.1 General

A reduction in cyclosporine plasma levels has been observed when Xenical is co-administered. Therefore it is recommended to monitor more frequently than usual the cyclosporin plasma levels when Xenical is co-administered (see section 2.4.1, Warnings and Precautions, General). In a PK study 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 reduced therapeutic effect of amiodarone is possible. Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic drugs. A causal relationship has not been established; however, patients should be monitored for possible changes in the frequency and/or severity of convulsions.

2.4.2 Interactions with other Medicinal Products and other Forms of Interaction

Decreases in the absorption of vitamin D, E and carotenoids have been observed when co-administered with Xenical. If a multivitamin supplement is recommended, it should be taken at least two hours after the administration of Xenical or at bedtime. A reduction in cyclosporin plasma levels has been observed when Xenical is co-administered (see section 2.4.1, Warnings and Precautions, General).

2.5 Use in Special Populations

2.5.1 Pregnancy

In animal reproductive studies, no malformative effect is expected in animals, no malformative effect is expected in humans. However, Xenical is not recommended for use during pregnancy in the absence of clinical data.

2.5.2 Nursing Mothers

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

2.5.3 Children

No data are available on the safety and efficacy of Xenical in children.

2.5.4 Other Special Populations

No special precautions are required for patients using Xenical.
2.5.3 Pediatric Use
Clinical investigations in children under the age of 12 have not been undertaken.

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

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

2.6.1 Unintended Effects
2.6.1.1 Clinical trials
Adverse reactions to Xenical are largely gastrointestinal in nature and related to the 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 stool, oily evanescence, increased defecation, flatulence and rectal incontinence. The incidence of these increases the higher the fat content of the diet. Patients should be counselled 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. Control of an over a diet low in fat will decrease the likelihood of experiencing adverse gastrointestinal events and this may help patients monitor and regulate their fat intake. These adverse gastrointestinal reactions are generally mild to moderate and transient. They occurred early in treatment (within 3 months) and most patients experienced only one episode. Treatment-emergent G4 adverse events that occurred commonly among patients treated with Xenical were: abdominal pain/discomfort, flatulence, liquid stools, soft stools, rectal pain/diarrhoea; tooth disorder, gingival disorder. Other events observed rarely were: upper respiratory infection, lower respiratory infection; influenza; headache; menorrhagia; anxiety; fatigue; urinary tract infection.

2.6.1.2 Drug interaction
Unwanted adverse events observed in obese type 2 diabetic patients were hypoglycemia (very common) and abdominal distension (common). Weight loss induced by Xenical is accompanied by improved metabolic control in type 2 diabetics which might allow or require reduction in the dose of hypoglycemic medication (see section 2.4, Warnings and Precautions). In a 4-year clinical trial, the general pattern of adverse event distribution was similar to that reported for the 1 and 2 years with studies with the total incidence of gastrointestinal related adverse events occurring in year 1 decreasing year on year over the 4-year period.

2.6.2 Post-Marketing
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 rash, urticaria, angioedema, bronchospasm and anaphylaxis. Very rare cases of bullous eruption, increase in rash, urticaria, angioedema, bronchospasm and anaphylaxis.

2.7 Overdose
Single doses of 800 mg Xenical and multiple doses of up to 400 mg t.i.d. for 15 days have been studied in obese subjects without significant adverse findings. Doses of 240 mg t.i.d. have been administered to obese patients for 6 months without significant increase of adverse findings. Orlistat overdos cases received either no adverse events or adverse events that are similar to those reported with recommended dose. Should a significant overdose 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.

3. PHARMACOLOGICAL PROPERTIES AND EFFECTS
3.1 Pharmacodynamic Properties
Xenical 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 pancreatic and intestinal lipases. The inactivated enzyme is thus unable to hydrolyse dietary fat, thus in form of triglyceride into absorbable free fatty acids and monoglycerides. As undegraded triacylglycerides are not absorbed, the resulting calorie deficit has a positive effect on weight control. Based on fecal fat measurements, the effect of Xenical is seen as soon as 24-48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to pre-treatment levels, within 48-72 hours.

3.1.2 Efficacy/Clinical studies
Obese Adults
Clinical trials have demonstrated that orlistat promotes weight loss, exceeding that achieved with diet alone. Weight loss was apparent within 2 weeks of initiation of treatment and continued for a duration of 6 to 12 months, even in patients who had failed to lose weight after dieting alone. Over 2 years, statistically significant improvements in metabolic risk factors associated with obesity were observed. Furthermore, significant improvements in weight regain, with approximately half of the patients regaining no more than 25% of lost weight and about half of these regaining no weight or even continuing to lost weight. Xenical were: abdominal pain/discomfort, flatulence, liquid stools, soft stools, rectal pain/diarrhoea; tooth disorder, gingival disorder. Other events observed rarely were: upper respiratory infection, lower respiratory infection; influenza; headache; menorrhagia; anxiety; fatigue; urinary tract infection.

Obese Patients with Type 2 Diabetes
Clinical trials conducted over a period of 6 months to one year showed that overweight or obese patients with type 2 diabetes had greater weight loss compared to dieting alone. It was also demonstrated that the weight loss was primarily due to decreased body fat. Additionally, despite receiving anti-diabetic medication, the average patient had poor glycemic control prior to study entry, but showed statistically significant (and clinically meaningful) improvements in glycemic control following treatment with orlistat. Furthermore, anti-diabetic medication usage decreased, insulin levels were lower and decreased insulin resistance was apparent. Delay in Onset of Type 2 Diabetes in Obese Patients
A clinical trial conducted over a 4-year period showed that orlistat significantly reduced the risk of onset of type 2 diabetes, with the risk decreased by approximately 37%, compared to the placebo group. The decrease in risk for patients with impaired glucose tolerance at
3.3 Preclinical Safety
Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

3.3.1 Carcinogenicity
See section 3.3, Preclinical Safety.

3.3.2 Mutagenicity
See section 3.3, Preclinical Safety.

3.3.3 Impairment of Fertility
See section 3.3, Preclinical Safety.

3.3.4 Teratogenicity
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.

4. Pharmaceutical particulars
4.1 Storage
This medicine should not be used after the expiry date (EXP) shown on the pack. Do not store above 25°C. Store in original package and keep the blister in the outer carton, in order to protect from light and moisture.

5. Pack
Capsules 120 mg

9, 21, 42, 84

Medicine: keep out of reach of children

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by Roche S.p.A., Via Morelli, 2, 20090 Segrate (MI), Italy
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