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Xenical®

Orlistat

1. DESCRIPTION

1.1 Therapeutic / Pharmacological Class of Drug

Peripherally 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 indicated for treatment of obese patients or 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.
The daily intake of fat, carbohydrate and protein should be distributed over three main meals.
Doses above 120 mg three times daily have not been shown to provide additional benefit.

2.2.2 Special Dosage Instructions

Clinical investigations in patients with hepatic and/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 medical 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 cyclosporine plasma levels when Xenical is co-administered (see section 2.4.3, Interactions with other Medicinal Products and other Forms of Interaction).
The majority of patients in long-term studies of up to 4 years of treatment had vitamin A, D, E and K and beta-carotene levels within normal range. In order to ensure adequate nutrition, the use of a multivitamin supplement should be considered.
Patients should be advised to adhere to dietary guidelines (see section 2.2, Dosage and Administration). The possibility of experiencing gastrointestinal events (see section 2.6, Undesirable Effects) may increase when Xenical is taken with a diet high in fat (e.g. in a 2000 kcal/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 Xenical is taken with any one meal very high in fat, the possibility of gastrointestinal effects may increase. 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 (e.g. sulfonylureas).

2.4.2 Laboratory Tests

Coagulation parameters, such as international normalised ratio (INR) values, should be monitored in patients treated with concomitant oral anticoagulants.

2.4.3 Interactions with other Medicinal Products and other Forms of Interaction

Decreases in the absorption of vitamin D, E and ß-carotene 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). 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.
No interactions based on specific drug-drug-interaction studies with amitriptyline, atorvastatin, biguanides, digoxin, fibrates, fluoxetine, losartan, phenytoin, oral contraceptives, phentermine, pravastatin, warfarin, nifedipine Gastrointestinal Therapeutic System (GITS), nifedipine slow release, sibutramine or alcohol have been observed. However, when warfarin or other oral anticoagulants are given in combination with orlistat, international normalised ratio (INR) values should be monitored.

2.5 Use in Special Populations

2.5.1 Pregnancy

In animal reproductive studies, no embryotoxic or teratogenic effects were observed with orlistat. In absence of a teratogenic effect in animals, no malformative effect is expected in human beings. 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.

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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 Undesirable Effects
2.6.1 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 evacuation, increased defecation and fecal 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. Consumption of 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 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 Xenical were: abdominal pain/discomfort, flatulence, liquid stools, soft stools, rectal pain/discomfort, tooth disorder, gingival disorder.
Other events observed rarely were: upper respiratory infection, lower respiratory infection; influenza; headache; menstrual irregularity; anxiety; fatigue; urinary tract infection.
Unique treatment 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 year 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, bronchspasm and anaphylaxis.
Very rare cases of bullous eruption, increase in liver transaminases and in alkaline phosphatase and exceptional cases of severe liver injury resulting in liver transplant or death, have been reported. No causal relationship or physiopathological mechanism between liver injury and orlistat 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 (see section 2.4.3, Interactions with other Medicinal Products and other Forms of Interaction).
Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic drugs (see section 2.4.3, Interactions with other Medicinal Products and other Forms of Interaction).
Cases of hyperoxaluria and oxalate nephropathy have been reported.

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 normal-weight and obese subjects without significant adverse findings.
In addition, doses of 240 mg t.i.d. 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.
Should a significant overdose of Xenical 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
3.1.1 Mechanism of action
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 gastric and pancreatic lipases. The inactivated enzyme is thus unable to hydrolyse dietary fat, in the form of triglycerides, into absorbable free fatty acids and monoglycerides. As undigested triglycerides are not absorbed, the resulting caloric 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 individuals who failed to respond to dieting alone. Over 2 years, statistically significant improvements in metabolic risk factors associated with obesity were observed. Furthermore, significant improvements in body fat were observed in comparison to placebo. Orlistat was also effective in prevention of 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 lose weight.

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

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baseline was even more marked, at approximately 45%. Additionally, weight loss was significantly greater in the orlistat group than in the placebo group, and was maintained throughout the 4-year study period. Furthermore, orlistat-treated patients showed significant reductions in metabolic risk factors compared to placebo.

Obese Adolescents
A clinical trial conducted over 1 year showed that obese adolescents treated with orlistat had a decreased BMI, compared to those in the placebo group, who had an increased BMI. Furthermore, those in the orlistat group had significantly decreased fat mass and waist and hip circumference compared to those in the placebo group. Diastolic blood pressure was also significantly reduced in the orlistat group compared to placebo.

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

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

3.2.3 Metabolism
Based on animal data, it is likely that the metabolism of orlistat occurs mainly presystemically. Two major metabolites, (M1 and M3) accounted for approximately 42% of the total radioactivity in plasma resulting from the minute fraction of the dose that was absorbed systemically in obese 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.

3.2.4 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, M1 and M3 are all subject to biliary excretion.

3.2.5 Pharmacokinetics in Special Populations
Plasma concentrations of orlistat and its metabolites M1 and M3 were similar in pediatric patients compared 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.

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. PACKS
Capsules 120 mg 9, 21, 42, 84

Medicine: keep out of reach of children

Current at July 2017

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CHEPLAPHARM Arzneimittel GmbH, Germany
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