Indications and potential uses

Adults

Refit is indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) ≥ 30 kg/m² and overweight patients (BMI ≥ 28 kg/m²) with associated risk factors such as type II diabetes, hyperlipidemia and hypertension.

In patients who fail to respond adequately to suitable weight-reducing measures, orlistat can be used as an adjunct to a hypocaloric diet and physical measures in the treatment of dietary overweight.

Treatment with orlistat should be discontinued after 12 weeks in patients who have not lost at least 5% of their body weight as measured at the start of drug therapy.

Adolescents

Obese adolescents should be treated with orlistat only if measures carried out in a therapeutic program over 6 months, including a balanced diet appropriate to the age of the patient and a program of physical activity aimed at modifying the patient's behavior, are not successful. Treatment with orlistat should be considered in particular if complications of obesity are present.

Dosage and administration

The recommended dose of orlistat is one 120mg capsule to be taken immediately before, during, or up to one hour after each main meal. If a meal is missed or contains no fat, the dose of orlistat should be omitted.

The patient should be on a nutritionally balanced, mildly hypocaloric diet in which approximately 30% of the calories are from fat. The diet should be rich in fruit and vegetables. The daily intake of fat, carbohydrate, and protein should be distributed between three main meals.

Doses of orlistat above 120mg three times daily have not been shown to provide additional benefit.
The effect of **Refit** results in an increase in fecal fat 24-48 hours after dosing. Upon discontinuation of therapy, fecal fat content usually returns to pretreatment levels within 48-72 hours.

Safety and efficacy were investigated in clinical studies lasting up to 4 years.

In adolescents treatment with orlistat should be initiated only if an adequate reduction of body weight cannot be achieved by means of diet and increased physical activity. Treatment should be given only if accompanied by determinations of vitamin levels and as part of an overall care program.

Obese adolescents should be treated with orlistat only if their BMI is above the level indicated in the following table:

**International definition of obesity as per Cole:**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>BMI male</th>
<th>BMI femal</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>26.02</td>
<td>26.67</td>
</tr>
<tr>
<td>12.5</td>
<td>26.43</td>
<td>27.24</td>
</tr>
<tr>
<td>13</td>
<td>26.84</td>
<td>27.76</td>
</tr>
<tr>
<td>13.5</td>
<td>27.25</td>
<td>28.20</td>
</tr>
<tr>
<td>14</td>
<td>27.63</td>
<td>28.57</td>
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<tr>
<td>14.5</td>
<td>27.98</td>
<td>28.87</td>
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<tr>
<td>15</td>
<td>28.30</td>
<td>29.11</td>
</tr>
<tr>
<td>15.5</td>
<td>28.60</td>
<td>29.29</td>
</tr>
<tr>
<td>16</td>
<td>28.88</td>
<td>29.43</td>
</tr>
<tr>
<td>16.5</td>
<td>29.14</td>
<td>29.56</td>
</tr>
<tr>
<td>17</td>
<td>29.41</td>
<td>29.69</td>
</tr>
<tr>
<td>17.5</td>
<td>29.70</td>
<td>29.84</td>
</tr>
</tbody>
</table>

The duration of treatment should be limited to a year in adolescents, since no experience is available with long-term treatment. Adolescents should take a multivitamin preparation daily during treatment with orlistat in order to prevent vitamin deficiency during puberty and the extended growth phase. The multivitamin preparation should be taken at least two hours after the ingestion of orlistat or at bedtime.

*Special dosage instructions*
The tolerability and efficacy of Refit have not been studied in children under 12 years of age, elderly patients, or patients with hepatic and/or renal impairment.

Orlistat is not intended for the treatment of children under 12 year of age.

**Contraindications**

Refit is contraindicated in patients with chronic malabsorption syndrome, in patients with cholestasis, during breastfeeding, and in patients who are hypersensitive to orlistat or to any of the other ingredients of the capsules.

**Warnings and precautions**

Patients should be informed of the possibility that gastrointestinal side effects may occur and of how these can best be managed, e.g. by paying attention to the composition, in particular the fat content, of their diet. Ingestion of low-fast food reduces the probability of gastrointestinal side effects. This can help patients to pay attention to and regulate their fat intake.

Patients should be advised to adhere to the dietary recommendations. The probability of occurrence of gastrointestinal side effects may increase when orlistat is taken with a fatty meal (e.g. in a 2000 kcal/day diet, > 30% of calories from fat is equivalent to > 67 g of fat). The daily intake of fat should be distributed between three main meals.

Use of doses above the recommended dose of 120mg three times daily results in no detectable increase in effect, but can increase the occurrence of gastrointestinal side effects.

In clinical trials, the decrease in body weight with orlistat therapy was less in type 2 diabetic patients than in non-diabetic patients. Antidiabetic drug treatment should be closely monitored during orlistat therapy.

Because of the improvement in glycemic control, the dose of oral antidiabetics or of insulin may need to be adjusted.

Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E, K).

In most patients who received up to 4 years of treatment with orlistat in clinical studies, levels of vitamin A, D, E, and K and beta-carotene remained within the normal range. In order to ensure adequate nutrition, patients on a weight-control diet should be advised to have a diet rich in fruit and vegetables. Use of a multivitamin supplement can be considered. If a multivitamin supplement is
recommended, it should be taken at least 2 hours after the ingestion of orlistat or at bedtime.

Co-administration of Refit and cyclosporine A led to a reduction in the cyclosporine A plasma concentration. Accordingly, when orlistat is co-administered with cyclosporine A, cyclosporine A plasma levels should be monitored more frequently than is usually the case. An interval of three hours between ingestion of the two medications is recommended (see Interactions).

Adolescents should undergo a medical review after the start of treatment, after 6 weeks, and thereafter at three-monthly intervals. Weight loss should be monitored, since massive weight loss during adolescence can negatively influence growth.

Treatment should be stopped after three months if no reduction of BMI has occurred or if significant side effects occur. In the event of rapid weight loss the treating physician should consider the potential side effects on growth and puberty and on the occurrence of gallstones in order to decide whether treatment should be interrupted.

Treatment with orlistat is not indicated in nonobese adolescents.

**Interactions**

A decrease in cyclosporine A plasma levels was observed in a drug interaction study and also reported in several cases in which orlistat was administered concomitantly. This can lead to a reduction in immunosuppressive effect. Therefore, this combination is not recommended. Patients treated with cyclosporine A must be monitored more frequently after initiation and cessation of treatment with orlistat. Cyclosporine A plasma levels should be monitored until stabilized.

In the absence of pharmacokinetic or pharmacodynamic interaction studies, concomitant administration of orlistat with acarbose, thiazolidinediones (glitazones), glinides or anorectic drugs is not recommended.

When warfarin or other anticoagulants are given in combination with orlistat (high-dose or long-term therapy), international normalized ratio (INR) values (Quick test results) should be monitored.

Olistat can impair the absorption of fat-soluble vitamins (A, D, E, and K). Most patients who received up to four years of treatment with orlistat in clinical studies had vitamin A, D, E, and K and beta-carotene levels within the normal range. In order to ensure adequate vitamin intake, patients following a diet
should be advised to have a diet rich in fruit and vegetables and use of a multivitamin supplement could be recommended.

When indicated, multivitamin supplements should be taken at least two hours after taking Refitor before going to bed.

A pharmacokinetic study in which amiodarone was administered orally during treatment with orlistat showed a 25-30% reduction in systemic exposure to amiodarone and desethylamiodarone.

Due to the complex pharmacokinetics of amiodarone, the clinical significance of this finding is unclear. The effect of commencing orlistat treatment in patients on stable amiodarone therapy has not been studied, however a reduced therapeutic effect of amiodarone is possible.

No interactions
No interaction have been observed with amitriptyline, atorvastatin, biguanides, glibenclamide, digoxin, fibrates, fluoxetine, losartan, furosemide, captopril, atenolol, phenytoin, oral contraceptives, phentermine, pravastatin, nifedipine, sibutramine, or alcohol. Special drug interaction studies have confirmed that no interactions occur with these substances.

Pregnancy and lactation
No clinical data are available on pregnancies exposed to orlistat.

Animal studies do not indicate direct or indirect harmful effects on pregnancy, embryofetal development, parturition or postnatal development.

As it is not know whether orlistat is excreted in breast milk, orlistat should not be used during breastfeeding.

Effects on ability to drive and use machines
It is not to be expected that Refit would impair the ability to drive or to use machines.

Undesirable effects
Side effects of orlistat are largely gastrointestinal in nature and related to pharmacologic effect of the drug on preventing the absorption of ingested fat. Commonly observed effects are oily spotting from the rectum (27%), flatulence with defecation (24%), fecal urgency (22%), oily or fatty stool (20%), increased defecation (11%) and fecal incontinence (8%). The higher the fat content of the
diet, the higher is the incidence of these undesirable effects. Abdominal pain (20.5%) and watery stools (15.8%) can also occur.

In clinical studies these pharmacologic effects were generally mild and transient and did not lead to cessation of treatment. Gastrointestinal side effects occurred within the first 3 months of treatment and most patients experienced only one episode.

Only 3% of patients experienced more than two episodes of any one of the side effects referred to here.

**Immune system:** common: influenza.
**Psychiatric disturbances:** common: anxiety.
**Nervous system:** common: headache.
**Respiratory organs:** common: upper airway infections, lower airway infections.
**Gastrointestinal tract:** very common: abdominal pain/discomfort (21%), flatulence (24%), liquid and soft stool (16%); common: involuntary defecation, rectal pain/discomfort, dental symptoms, gingival symptoms.
**Liver:** occasional: hepatitis, elevated transaminases and alkaline phosphatase.
**Skin/hypersensitivity reactions:** rare: hypersensitivity reactions: pruritus, rash, urticaria, bullous rash, angioedema, anaphylaxis.
**Kidneys and urinary tract:** common: urinary tract infection.
**Reproductive system:** common: irregularity of menstruation.
**General:** common: fatigue.

### Overdosage
The cases of orlistat overdosage reported showed either no adverse events or adverse events similar to those reported with the recommended dose.

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.

### Preclinical data
Preclinical data obtained in conventional studies of tolerability, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive toxicity reveal no special hazard for humans.

No teratogenic effect was observed in animal reproductive studies. In the absence of a teratogenic effect in animals, no malformations are to be expected in humans. To date, drugs responsible for malformatins in humans have also
been found to be teratogenic in animals when carefully conducted studies are performed in two species.

**Conditions**
Do not store above 25°C and protect from moisture.

**Presentation**
**ReflitCapsule:** Orlistat 120mg/capsule
(available in a pack of 45 capsules).