SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Beacita 120mg Capsules, hard

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains 120mg orlistat.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule, hard.

The capsule has a blue cap and blue body.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Beacita 120mg Capsules are indicated in conjunction with a mildly hypocaloric diet for the treatment of obese patients with a body mass index (BMI) greater or equal to 30 kg/m², or overweight patients (BMI ≥ 28 kg/m²) with associated risk factors.

Treatment with orlistat should be discontinued after 12 weeks if patients have been unable to lose at least 5% of the body weight as measured at the start of therapy.

4.2 Posology and method of administration

Posology

Adults
The recommended dose of orlistat is one 120 mg capsule taken with water 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 that contains approximately 30% of calories from fat. It is recommended that the diet should be rich in fruit and vegetables. The daily intake of fat, carbohydrate and protein should be distributed over three main meals.

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

Special populations
Paediatric population
The effect of orlistat in children has not been studied.
There is no relevant indication for use of Beacita 120mg Capsules in children.

Elderly (>65 years old) / Patients with hepatic and renal impairment
The effect of orlistat in elderly patients has not been studied.

Patients with hepatic and renal impairment
The effect of orlistat in patients with hepatic and/or renal impairment has not been studied.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1..
- Chronic malabsorption syndrome.
- Cholestasis.
- Breast-feeding.

4.4 Special warnings and precautions for use

In clinical trials, the decrease in bodyweight with orlistat treatment was less in type II diabetic patients than in non-diabetic patients. Antidiabetic medicinal product treatment may have to be closely monitored when taking orlistat.

Co-administration of orlistat with ciclosporin is not recommended (see section 4.5).

Patients should be advised to adhere to the dietary recommendations they are given (see section 4.2).

The possibility of experiencing gastrointestinal adverse reactions (see section 4.8) may increase when orlistat 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 orlistat is taken with a meal very high in fat, the possibility of gastrointestinal adverse reactions may increase.

Cases of rectal bleeding have been reported with orlistat. Prescribers should investigate further in case of severe and/or persistent symptoms.

The use of an additional contraceptive method is recommended to prevent possible failure of oral contraception that could occur in case of severe diarrhoea (see section 4.5).

Coagulation parameters should be monitored in patients treated with concomitant oral anticoagulants (see section 4.5 and 4.8).

The use of orlistat may be associated with hyperoxaluria and oxalate nephropathy leading sometimes to renal failure. This risk is increased in patients with underlying chronic kidney disease and/or volume depletion (see section 4.8).

Rare occurrence of hypothyroidism and/or reduced control of hypothyroidism may occur. The mechanism, although not proven, may involve a decreased absorption of iodine salts and/or levothyroxine (see section 4.5).

Antiepileptic patients: Orlistat may unbalance anticonvulsant treatment by decreasing the absorption of antiepileptic drugs, leading to convulsions (see section 4.5).

Orlistat may potentially reduce the absorption of antiretroviral medicines for HIV and could negatively affect the efficacy of antiretroviral medications for HIV (see section 4.5).

Excipient
Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Ciclosporin
A decrease in ciclosporin plasma levels has been observed in a drug-drug-interaction study and also reported in several cases, when orlistat was administered concomitantly. This can lead to a decrease of immunosuppressive efficacy. Therefore the combination is not recommended (see section 4.4).
However, if such concomitant use is unavoidable, more frequent monitoring of ciclosporin blood levels should be performed both after addition of orlistat and upon discontinuation of orlistat in ciclosporin treated patients. Ciclosporin blood levels should be monitored until stabilised.

Acarbose
In the absence of pharmacokinetic interaction studies, the concomitant administration of orlistat with acarbose should be avoided.

Oral anticoagulants
When warfarin or other anticoagulants are given in combination with orlistat, international normalised ratio (INR) values should be monitored (see section 4.4).

Fat soluble vitamins
Treatment with orlistat may potentially impair the absorption of fat-soluble vitamins (A, D, E and K). The vast majority of patients receiving up to four full years of treatment with orlistat in clinical studies had vitamin A, D, E and K and beta-carotene levels that stayed within 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 and use of a multivitamin supplement could be considered. If a multivitamin supplement is recommended, it should be taken at least two hours after the administration of orlistat or at bedtime.

Amiodarone
A slight decrease in plasma levels of amiodarone, when given as a single dose, has been observed in a limited number of healthy volunteers who received orlistat concomitantly. In patients receiving amiodarone treatment, the clinical relevance of this effect remains unknown but may become clinically relevant in some cases. In patients receiving concomitant amiodarone treatment, reinforcement of clinical and ECG monitoring is warranted.

Antiepileptic medicinal products
Convulsions have been reported in patients treated concomitantly with orlistat and antiepileptic drugs e.g. valproate, lamotrigine, for which a causal relationship to an interaction cannot be excluded. Therefore, these patients should be monitored for possible changes in the frequency and/or severity of convulsions (see section 4.4).

Levothyroxine
Rare occurrence of hypothyroidism and/or reduced control of hypothyroidism may occur when orlistat and levothyroxine are taken at the same time. The mechanism, although not proven, may involve a decreased absorption of iodine salts and/or levothyroxine (see section 4.4).

Antiretrovirals for HIV, antidepressants, antipsychotics and benzodiazepines
There are some case reports of reduced efficacy of antiretroviral HIV medicines, antidepressants, antipsychotics (including lithium) and benzodiazepines coincidental to the initiation of orlistat treatment in previously well-controlled patients. Therefore orlistat treatment should only be initiated after careful consideration of the possible impact in these patients.

Lack of interactions
No interactions with amitriptyline, atorvastatin, biguanides, digoxin, fibrates, fluoxetine, losartan, phenytoin, phentermine, pravastatin, nifedipine Gastrointestinal Therapeutic System (GITS), nifedipine slow release, sibutramine or alcohol have been observed. The absence of these interactions has been demonstrated in specific drug-drug-interaction studies.

The absence of an interaction between oral contraceptives and orlistat has been demonstrated in specific drug-drug interaction studies. However, orlistat may indirectly reduce the availability of oral contraceptives and lead to unexpected pregnancies in some individual cases. An additional contraceptive method is recommended in case of severe diarrhoea (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
For orlistat no clinical data on exposed pregnancies are available.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development (see section 5.3).
Caution should be exercised when prescribing to pregnant women.

Breastfeeding
As it is not known whether orlistat is secreted into human milk, orlistat is contraindicated during breast-feeding.

4.7 Effects on ability to drive and use machines

Orlistat has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions to orlistat are largely gastrointestinal in nature. The incidence of adverse events decreased with prolonged use of orlistat.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and very rare (<1/10,000) including isolated reports.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The following table of undesirable effects (first year of treatment) is based on adverse events that occurred at a frequency of > 2% and with an incidence ≥ 1% above placebo in clinical trials of 1 and 2 years duration:

SYSTEM ORGAN CLASS	**ADVERSE REACTION/EVENT**
Infections and infestations Very common:	Influenza
Metabolism and nutrition disorders Very common:	Hypoglycemia*

Psychiatric disorders Common:	 Anxiety
Nervous system disorders Very common:	 Headache
Respiratory, thoracic and mediastinal disorders Very common: Common:	 Upper respiratory infection Lower respiratory infection
Gastrointestinal disorders Very common: Common:	 Abdominal pain/discomfort Oily spotting from the rectum Flatus with discharge Faecal urgency Fatty/oily stool Flatulence Liquid stools Oily evacuation Increased defecation Rectal pain/discomfort Soft stools Faecal incontinence Abdominal distension* Tooth disorder Gingival disorder
Renal and urinary disorders Common:	 Urinary tract infection
Reproductive system and breast disorders Common:	 Menstrual irregularity
General disorders and administration site conditions Common:	 Fatigue

* only unique treatment adverse events that occurred at a frequency of > 2% and with an incidence ≥ 1% above placebo in obese type 2 diabetic patients.

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 four year period.

The following table of undesirable effects is based on post-marketing spontaneous reports, and therefore the frequency remains unknown:

SYSTEM ORGAN CLASS	ADVERSE REACTION
Immune system disorders	Hypersensitivity (e.g. pruritus, rash, urticaria, angioedema, bronchospasm and anaphylaxis)

Gastrointestinal disorders	Rectal bleeding (see section 4.4) Diverticulitis Pancreatitis
Hepatobiliary disorders	Cholelithiasis Hepatitis that may be serious. Some fatal cases or cases requiring liver transplantation have been reported.
Skin and subcutaneous tissue disorders	Bullous eruptions
Renal and urinary disorders	Oxalate nephropathy that may lead to renal failure.
Investigations	Increase in liver transaminases and in alkaline phosphatase. Decreased prothrombin, increased INR and unbalanced anticoagulant treatment resulting in variations of haemostatic parameters have been reported in patients treated with anticoagulants in association with orlistat (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Single doses of 800 mg orlistat and multiple doses of up to 400 mg three times daily for 15 days have been studied in normal weight and obese subjects without significant adverse findings. In addition, doses of 240 mg three times daily have been administered to obese patients for 6 months. The majority of 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 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiobesity preparations, excl. diet products; peripherally acting antiobesity agent, ATC code A08AB01.

Orlistat is a potent, specific and 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 active serine site of the gastric and pancreatic lipases. The inactivated enzyme is thus unavailable to hydrolyse dietary fat, in the form of triglycerides, into absorbable free fatty acids and monoglycerides.

In the 2-year studies and the 4-year study, a hypocaloric diet was used in association with treatment in both the orlistat and the placebo treated groups.

Pooled data from five 2 year studies with orlistat and a hypocaloric diet showed that 37% of orlistat patients and 19% of placebo patients demonstrated a loss of at least 5% of their baseline body weight after 12 weeks of treatment. Of these, 49% of orlistat treated patients and 40% of placebo treated patients went on to lose ≥ 10% of their baseline body weight at one year. Conversely, of patients failing to demonstrate a loss of 5% of their baseline body weight after 12 weeks of treatment, only 5% of orlistat treated patients and 2% of placebo treated patients went on to lose ≥ 10% of their baseline body weight at one year. Overall, after one year of treatment, the percentage of patients taking 120 mg orlistat who lost 10% or more of their body weight was 20% with orlistat 120 mg compared to 8% of patients taking placebo. The mean difference in weight loss with the drug compared to placebo was 3.2 kg.

Data from the 4-year XENDOS clinical trial showed that 60% of orlistat patients and 35% of placebo patients demonstrated a loss of at least 5% of their baseline body weight after 12 weeks of treatment.
Of these, 62% of orlistat treated patients and 52% of placebo treated patients went on to lose ≥ 10% of their baseline body weight at one year. Conversely, of patients failing to demonstrate a loss of 5% of their baseline body weight after 12 weeks of treatment, only 5% of orlistat treated patients and 4% of placebo treated patients went on to lose ≥ 10% of their baseline body weight at one year. After 1 year of treatment, 41% of the orlistat treated patients versus 21% of placebo treated patients lost ≥ 10% of body weight with a mean difference of 4.4 kg between the two groups. After 4 years of treatment 21% of the orlistat treated patients compared to 10% of the placebo treated patients had lost ≥ 10% of body weight, with a mean difference of 2.7 kg.

More patients on orlistat or placebo lost baseline body weight of at least 5% at 12 weeks or 10% at one year in the XENDOS study than in the five 2-year studies. The reason for this difference is that the five 2-year studies included a 4-week diet and placebo lead-in period during which patients lost on average 2.6 kg prior to commencing treatment.

Data from the 4-year clinical trial also suggested that weight loss achieved with orlistat delayed the development of type 2 diabetes during the study (cumulative diabetes cases incidences: 3.4% in the orlistat group compared to 5.4% in the placebo-treated group). The great majority of diabetes cases came from the subgroup of patients with impaired glucose tolerance at baseline, which represented 21% of the randomised patients. It is not known whether these findings translate into long-term clinical benefits.

In obese type 2 diabetic patients insufficiently controlled by antidiabetic agents, data from four one-year clinical trials showed that the percentage of responders (≥ 10% of body weight loss) was 11.3% with orlistat as compared to 4.5% with placebo. In orlistat-treated patients, the mean difference from placebo in weight loss was 1.83 kg to 3.06 kg and the mean difference from placebo in HbA1c reduction was 0.18% to 0.55%. It has not been demonstrated that the effect on HbA1c is independent from weight reduction.

In a multi-centre (US, Canada), parallel-group, double-blind, placebo-controlled study, 539 obese adolescent patients were randomised to receive either 120 mg orlistat (n=357) or placebo (n=182) three times daily as an adjunct to a hypocaloric diet and exercise for 52 weeks. Both populations received multivitamin supplements. The primary endpoint was the change in body mass index (BMI) from baseline to the end of the study.

The results were significantly superior in the orlistat group (difference in BMI of 0.86 kg/m^2 in favour of orlistat). 9.5% of the orlistat treated patients versus 3.3% of the placebo treated patients lost ≥ 10% of body weight after 1 year with a mean difference of 2.6 kg between the two groups. The difference was driven by the outcome in the group of patients with ≥ 5% weight loss after 12 weeks of treatment with orlistat representing 19% of the initial population. The side effects were generally similar to those observed in adults. However, there was an unexplained increase in the incidence of bone fractures (6% versus 2.8% in the orlistat and placebo groups, respectively).

5.2 Pharmacokinetic properties

Absorption

Studies in normal weight and obese volunteers have shown that the extent of absorption of orlistat was minimal. Plasma concentrations of intact orlistat were non-measurable (< 5 ng/ml) eight hours following oral administration of orlistat.

In general, at therapeutic doses, detection of intact orlistat in plasma was sporadic and concentrations were extremely low (< 10 ng/ml or 0.02 μmol), with no evidence of accumulation, which is consistent with minimal absorption.

Distribution

The volume of distribution cannot be determined because the drug is minimally absorbed and has no defined systemic pharmacokinetics. *In vitro* orlistat is > 99% bound to plasma proteins (lipoproteins and albumin were the major binding proteins). Orlistat minimally partitions into erythrocytes.

Metabolism
Based on animal data, it is likely that the metabolism of orlistat occurs mainly within the gastrointestinal wall. Based on a study in obese patients, of the minimal fraction of the dose that was absorbed systemically, two major metabolites, M1 (4-member lactone ring hydrolysed) and M3 (M1 with N-formyl leucine moiety cleaved), accounted for approximately 42% of the total plasma concentration.

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 therapeutic doses (average of 26 ng/ml and 108 ng/ml respectively), these metabolites are considered to be pharmacologically inconsequential.

Elimination
Studies in normal weight and obese subjects have shown that faecal excretion of the unabsorbed drug was the major route of elimination. Approximately 97% of the administered dose was excreted in faeces 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 (faecal plus urinary) was 3 to 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.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to reproduction.

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. To date, active substances responsible for malformations in man have been found teratogenic in animals when well-conducted studies were performed in two species.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule filling:

Cellulose, microcrystalline PH112

Sodium starch glycollate (type A)

Colloidal anhydrous silica

Sodium lauryl sulphate

Capsule shell:

Gelatine

Indigo carmine (E132)

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.
Store in original package in order to protect from light and moisture.

6.5 Nature and contents of container

Al/PVC/PVDC blisters containing 21, 42, 84 and 90 hard capsules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER(S)

PL 30306/0380

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/09/2012

10 DATE OF REVISION OF THE TEXT

29/10/2020