SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion for the approval of Xenical. This scientific discussion has been updated until 1 November 2003. For information on changes after this date please refer to module 8B.

1. Introduction

Obesity is a disease characterised by an excess body fat. It is often measured by calculation of the body mass index (BMI), i.e. the body weight in kg divided by body surface area in m^2. Individuals may be regarded as obese with a BMI >25-27 kg/m² (depending on age). A number of concomitant pathological processes and diseases are associated with obesity including coronary heart disease, hypertension, stroke, non-insulin dependent diabetes mellitus and certain forms of cancer. Besides changes in diet, behaviour and physical activities, obesity may be treated by surgery or pharmacological therapy. All currently available medicinal products for obesity treatment are appetite suppressants (amphetamine-like products) that act via the central nervous system (CNS). However, they may not be prescribed during longer periods than 3 months, due to the potential risk of abuse. Thus, there is a need for medicinal products that can be used in chronic treatment together with dietary and behavioural modifications.

Orlistat belongs to a new class of pharmacological agents. It inhibits the action of gastrointestinal lipases and thereby impairs the metabolism of lipids in the intestinal lumen leading to a prevention of lipid absorption.

Xenical is 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 $\geq$ 28 kg/m²) with associated risk factors. The treatment should only be started if diet alone has previously produced a weight loss of at least 2.5 kg over a period of 4 consecutive weeks. 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 drug therapy. The recommended dose of orlistat is one 120 mg capsule three times daily, which should be taken immediately before, during or up to one hour after each main meal.

2. Chemical, pharmaceutical and biological aspects

Orlistat, a hydrogenated derivative of lipstatin and an inhibitor of gastrointestinal lipases produced by chemical synthesis, is presented as Xenical 120 mg capsules in different pack sizes.

Composition

Xenical is presented as a conventional hard gelatin capsule (size 1) containing pellets with an active substance concentration of 50%. The excipients cellulose microcrystalline (as diluent and extrusion/spheronisation aid), sodium starch glycollate (as desintegrant), sodium lauryl sulphate (as wetting agent), povidone K30 (as binder and stabiliser), and talc is added (for lubrication) to the pellets before encapsulation.

Different clinical trial formulae and dosage strengths were used during Phase I-III studies. Bioequivalence was demonstrated between the formulations and strengths used in the Phase I-III studies and those proposed for marketing.

The different steps in the development of the marketing formulation are well described: satisfactory details have been provided to justify and to optimise the retained form (hard gelatin capsules which fulfil the various demands, i.e. drug load, technology and compliance), the formulation (the selected concentration of each excipients are correctly fixed). Process development has also been well described and studied.

Method of preparation

The manufacturing process involves granulation, extrusion and spheronisation, drying, lubrication and encapsulation.

All operating procedures comply with GMP. The choice of in-process controls and frequency of testing ensure that the process is controlled, particularly with regard to the critical parameters. It is considered that the manufacturing process has been fully validated on both pilot and full scale batches, and is reproducible.

Control of starting materials

Orlistat is a white to off-white crystalline powder. It is a lipophilic substance with very low solubility in water within the physiological pH range. Two polymorphic forms have been found, A and B, but only B is produced by the current synthetic route as defined in Part II of the dossier. Sixteen stereoisomers are possible in theory, because of the four chiral centres.

In the early phase of the development, the synthetic route evolved from an "alpha-pyrone" synthesis to a "delta-lactone" synthesis. Pre-clinical studies were performed with orlistat obtained by these prototype routes. Finally orlistat, as intended for marketing, is synthesised in a 5-step process using a controlled stereoselective route (i.e. "the dihydropyrone" synthesis) ensuring consistent production of only one of the possible stereoisomers in the desired physical form, B. The preclinical toxicity programme showed there were no significant differences between the two polymorphs. Four intermediates are isolated and controlled in this process.

Starting material specifications, in-process control of the key intermediates and release specifications ensures the quality and the stereospecificity of synthesis. The chromatograms referring to the three synthetic routes showed that the level of impurities in the chromatogram of "the dihydropyrone" synthesis appears lower as compared to the other routes of synthesis. All raw materials and synthesis intermediates are controlled according to suitable specifications and using specific and validated methods, which are chirally selective where necessary.

Active substance

Orlistat is tested and released according to an in-house monograph. The active substance specification includes tests for characterisation, identity, purity, assay, residual solvents, water, sulphated ash, heavy metals and others. All potential organic impurities are detected using the combined chromatographic systems, HPLC/GC/TLC. The validation of the analytical methods used is acceptable in relation to ICH recommendations. The proposed specification limits are based on data arising from 50 pilot-scale and 50 clinical batches made by the dihydropyrone synthesis, and on safety studies. Results of these batches confirm their consistent quality.

Other ingredients

All excipients comply with Ph. Eur. requirements. The capsule shells contain commonly used excipients. The excipients and colouring agents in the capsule shell comply with the EEC requirements.

The proposed standard containers are PVC/PE/PVDC/Alu blister packs, and amber glass bottles fitted with a plastic screw closure and containing a desiccant unit. Essential verifications have been performed for all materials and test results are satisfactory.

Control tests on the finished product

The specification includes standard tests for appearance, identification of the active substance (IR and HPLC), assay, determination of degradation impurities (HPLC-system I), dissolution test, and a periodic microbial test performed according to the Ph. Eur. requirements. The dissolution specification limit is 75% (Q) after 45 minutes. The limits for the total of all degradation products are set up to ≤ 0.5% at release and 2.0% at shelf life. The proposed specification for the control of the finished product is suitable for assessing batch-to-batch consistency. Certificates of analysis for 3 pilot-scale and 1 full-scale production batches demonstrate consistent quality of the finished product when manufactured according to the process defined in the dossier.

Stability of the product

The stability of the active substance, orlistat, obtained from different sources has been investigated under stressed conditions as well as under accelerated and long-term conditions. The stability results show that a three year re-test period is acceptable when samples are stored below 30°C in perforated low density polyethylene (LDPE) bags in closed metal drums gassed with nitrogen.

However, long-term stability studies up to 3 years duration, without gassing, are on going. Until the results are available, orlistat is stored in LDPE bags inside closed steel drums gassed with nitrogen.

Stability of the finished product has been studied on 4 batches stored in both blister packs and amber glass bottles for up to 18 months at 25°C/60%RH and up to 12 months at 30°C/75%RH; both pilot and production scale batches were included. In addition, supportive stability data with clinical batches, up to 3 years in both packaging and up to 3 years in blisters, were provided. Appearance, impurities, assay and dissolution test were monitored using stability-indicating methods. For the whole shelf-life period, the assay limits of orlistat are maintained at 95-105% of the theoretical value, and the total impurity limit should be set at 2.0% at shelf life.

The results showed no change in the capsules' appearance and in dissolution rate after 45 minutes. However, available stability data showed that the degradation products increased when the storage is carried out at 30°C/75%RH, as expected. Degradation was less in glass bottles than in blisters, and a higher storage temperature is therefore possible.

These results support the shelf-life and storage conditions for Xenical capsules as defined in the SPC, i.e. three years when keep in a dry place and stored below 25°C in blister packs, and below 30°C in glass bottles with desiccant.

3. Toxico-pharmacological aspects

All pivotal preclinical studies were conducted in compliance with GLP and when applicable, in accordance with internationally accepted guidelines.

Orlistat can exist in two crystalline forms, polymorphs A and B, which have similar physico-chemical properties. Polymorph B is the more thermodynamically stable of the two polymorphs. It is the only form used in the clinical development and is the form intended for marketing. Both forms were used in the preclinical toxicity programme, and there were no significant differences between the two polymorphs.

Pharmacodynamics

The pharmacodynamic action of orlistat has been studied *in vitro* and *in vivo*. Studies using different *in vitro* enzyme preparations of mammalian source showed that orlistat was a specific, long lasting inhibitor of a wide range of tri- and di-acylglycerol lipases. However, it had weak or no inhibitory effects on other hydrolytic enzymes (e.g. acetylcholine esterase, liver carboxylesterase, α-amylase, trypsin, chymotrypsin, phospholipase A_2) and it had only marginal effects on subsequent steps of fat absorption. In the presence of emulsified triglycerides as substrate, inhibition was mainly determined by the concentration of the drug in the lipid phase. After orlistat withdrawal, the lipase activity was rapidly restored due to a continuous secretion of enzymes.

Using *in vivo* animal models, a dose dependent and rapidly reversible inhibition of triglyceride absorption was demonstrated, with IC_{50} ranging from 1.4 (dog) to 67 (mouse) mg/kg body weight or 0.8 (dog) to 2.9 (mouse) mg/g dietary fat. The highest inhibitory effect was seen when the drug was dissolved in dietary fat. The magnitude of inhibition did not change during long-term administration. Effects on plasma and hepatic lipids varied between species, and a biphasic dose response was observed, with hypolipidaemia at low doses (effects on intestinal absorption) and hyperlipidemia at higher doses (systemic effects).

Studies in animal models of obesity showed dose dependent reductions of body weight and body fat (e.g. genetically obese mice: 17% (weight), 21% (body fat) after 114 mg/kg/d for 43 days, genetically obese rats 15% (weight), 24% (body fat) after 42 mg/kg/d for 77 days). However, the predictability of these data for clinical efficacy and safety was regarded to be limited, since animals compensated partially for the loss of dietary fat by increased food intake.

Orlistat administration resulted in a non-physiologic phase of unabsorbed lipids in the intestine. Consequently, absorption of apolar lipids was reduced (e.g. lipid soluble vitamins, carotenoids and cholesterol) while polar lipids (fatty acids, bile acids, phospholipids and retinol) were not affected.

In vitro studies with the two main human metabolites (M1, M3) indicated that they had very weak lipase inhibitory effects.

The general pharmacology program did not indicate adverse effects on the central nervous, cardiovascular, gastrointestinal- or immune systems or on systemic lipase metabolism after doses that were considered to be therapeutically relevant.

Pharmacokinetics

The pharmacokinetics of orlistat was studied in mouse, rat, rabbit and dog, the main species used in the preclinical program. In all species, absorption after oral administration of C^{14}-labelled orlistat was low (1-22% depending on formulation and feeding state). Binding to albumin and lipoproteins was high (>99%) in all species including humans. Distribution studies in rats given oral doses of radiolabelled orlistat, showed the highest tissue levels of drug-related radioactivity in the liver and kidney after a single dose. After 30 days repeated oral administration, a 3-5 fold tissue accumulation was observed in liver, kidney and fat. In pregnant rats, no placental transfer of drug-related radioactivity to foetal tissues was observed. Excretion into milk has not been studied. The low absorption of orlistat together with the occurrence of first pass metabolism resulted in a very low oral bioavailability (<1%), and thus only minor amounts of unchanged orlistat reaching the systemic circulation.

The fraction of orlistat that is absorbed undergoes extensive metabolism, with similar metabolic patterns in the animal species studied and in humans. The major part of an oral C^{14}-orlistat dose was excreted in faeces (85-99% in rats and dogs). The remaining part of the dose was excreted in approximately equal amounts via urine and bile. The excretion balance was similar after 2 years administration of unlabelled orlistat to rats.

Overall, the pharmacokinetic profile of orlistat was similar in the animal species used for safety assessment and in humans. Toxicokinetic data from animals given high doses in the toxicity studies showed that the systemic exposure to orlistat and the two main human metabolites (M1 and M3) were higher than that of humans given therapeutic doses.

Toxicology

Single dose toxicity of orlistat after oral administration was studied in mice, rats, young rats and dogs. The acute toxicity was considered to be low, with no signs of toxicity after doses of 1000 mg/kg (dog, given pyramiding doses from 50-1000 mg/kg), 2000 mg/kg (2 week old rat) and 5000 mg/kg (rat, mouse).

Repeated dose toxicity of orlistat after oral administration was studied in mice (3 months duration), rats and dogs (up to 12 months duration). In all species, signs of toxicity were related to exaggerated pharmacodynamic responses to orlistat i.e. inhibition of gastrointestinal lipases and at high doses, inhibition of systemic lipases. Both rodents and dogs showed increased food intake without concomitant increase in body weight gain. In rats given doses > 500 mg/kg/d, disturbances in the lipid metabolism were evident, e.g. hypertriglyceridemia, hyperbilirubinemia and hypocholesterolemia and histopathology showed lipidic infiltration in liver, heart, bone marrow and adrenal glands. A reduced absorption of liposoluble vitamins (A, D3, E) was also evident in all species. The 24 months carcinogenicity study in rats showed a similar pattern of toxicity together with an increased turnover of red blood cells possibly due to lipemia-induced hemolysis. In rats and dogs, the non-toxic dose levels after 12 months administration, were 125 and 300 mg/kg/d, respectively. In rats, 25 mg/kg/d for 12 months did not affect lipid metabolism.

Reproductive toxicity of orlistat was studied in standard segment II, III studies and I with doses up to 400 mg/kg/d (I, III) and 800 mg/kg/d (II). Fertility studies in rats did not indicate impairment of male or female reproductive functions. After administration of orlistat to rats and rabbits during the organogenetic period, no teratogenicity or embryotoxicity were observed. Peri-post natal exposure of dams and follow-up of offspring did not reveal any concern.

In a standard battery of *in vitro* and *in vivo* genotoxicity tests, orlistat lacked genotoxic potential.

Carcinogenicity was studied in mice and rats following 2 years of administration. In these studies, there was no indication of drug-related neoplastic potential. Using a Proliferating Cell Nuclear Antigen test, a dose and time dependent proliferation of rectal cells (rats at 500 mg/kg/d) and of

colonic cells (male mice at 25 mg/kg/d, female mice 750 mg/kg/d) was revealed. Additional studies in rats fed a high fat and low calcium diet, revealed colonic mucosal proliferation without neoplastic changes after up to 1-month administration. However, there were no orlistat-related changes in the colonic mucosa after 3, 6 or 9 months administration.

A number of special toxicity studies did not reveal cause for concern with respect to local tolerance or antigenicity.

Summary and conclusion on preclinical pharmacology and toxicology

The pharmacological activity of orlistat results in partial inhibition of triglyceride absorption by reducing hydrolysis and production of absorbable unesterified fatty acids and monoglycerides. Due to structural similarities with triglycerides, orlistat interacts with the lipases in a substrate like manner. Studies in animal models of obesity showed dose dependent reductions of body weight and body fat although the predictability of these data for clinical efficacy and safety was considered to be limited.

The pharmacokinetic properties of orlistat were similar in the animal species used for safety assessment and in humans. Overall, the toxicology program revealed effects mainly related to the pharmacodynamic action of orlistat, i.e. inhibition of lipases leading to fatty faeces, reduction of body weight gain, changes in triglycerides, bilirubin and cholesterol, and reduction of absorption of liposoluble vitamins. No abnormalities were seen in reproductive toxicity or genotoxicity studies. Carcinogenicity studies revealed proliferation of rectal or colonic mucosa, without any indication of drug-related neoplastic potential.

4. Clinical aspects

The marketing application is supported by adequately designed clinical studies, conducted and analysed according to current GCP recommendations.

The core dossier consists of seven long-term (1 to 2 years) clinical trials**. They were double blind, comparative (vs. placebo and different dosages), randomised, multicentre trials aimed at evaluating the efficacy of orlistat combined with a hypocaloric diet in weight reduction and prevention of weight regain. The effects on obesity risk factors (lipids, blood pressure, fasting glucose, and insulin), vitamin levels and faecal fat excretion were explored as secondary efficacy criteria.

The main characteristics of these studies are presented below:

Number of studies	Phase	Treatments and dose schedule	Sample size	Design
51	I	orlistat: from 50 to 360 mg	1004 subjects	single dose, open, pharmacokinetics
19	I	orlistat: from 10 to 400 mg t.i.d.	308 subjects	repeated dose, versus PL, 5- to 42 days duration
10	II	10, 60, 120 mg (3 mos) 30, 60, 120, 240 mg (6 mos) 80, 160 mg (2 mos) 10, 30, 60, 120 mg (2 mos)	1421 patients	dose-ranging
7	III	PL run-in (1 to 6 mos), then PL or 30*, 60 or 120 mg t.i.d.	4188 patients	DB, R, PG, PL, 1-yr or 2-yr duration

DB= double blind; R= randomised; PG= parallel group; PL= placebo; t.i.d.= *tris in die*

* only one study

** BM14119B, NM 14302, NM14161, BM14149, NM14185, BM14119C and NM14336 (in diabetic patients)

Clinical pharmacology

Pharmacodynamics

Orlistat belongs to a new class of pharmacological agents. Its mechanism of action is through the inhibition of action of gastrointestinal lipase, impairing the metabolism of lipids in the intestinal lumen and preventing absorption. Nineteen phase I trials have been carried out in order to elucidate the mechanism of action in humans.

The degree of inhibition of dietary fat absorption was measured using faecal fat excretion in a retrospective population-based meta-analysis. The activity is dose-dependent, with about 30% of inhibition at the 120 mg dosage which plateaus at about 35% inhibition after doses greater than 400 mg t.i.d..

In clinical trials, fat excretion was approximately 2.6 g/24 h at day 1 compared to 23 g/24 h after 1-year treatment with orlistat 120 mg t.i.d.. The mean change in 72-hour fat excretion from randomisation to the end of week 52 was 15.4 ± 12.1 g and 20.9 ± 15.1 g, after orlistat 60 mg and 120 mg t.i.d., respectively.

The effect of the drug on the colon, due to the excess of fat in faeces, was investigated in 12 obese patients during 6 weeks of treatment with 120 mg t.i.d. and no increase in cell proliferation was observed.

Hepatobiliary physiology was extensively studied in phase I trials since the drug has been detected in the bile even in small amounts. It was not affected by orlistat.

As in animal experiments the systemic absorption of orlistat is 10% or more when the drug is taken with food, food interaction was investigated in faze I clinical trials in healthy volunteers. No increase in orlistat absorption was shown when the drug was taken with food. In addition, it was shown that orlistat has no effect on systemic lipase activities.

An effect on intracellular lipases, which would in turn affect autacoids production and could hinder the digestion, was also ruled out because orlistat is minimally absorbed from the gastrointestinal tract and its metabolites have poor lipase inhibitory activity.

Pharmacokinetics

Pharmacokinetics was investigated in 31 clinical studies and in other additional Phase I, II and III studies, in which orlistat concentrations were measured.

The drug is absorbed to a minimal extent, with a C_{max} in blood < 5 ng/ml. The drug is extensively bound to plasma proteins, > 99%. Absolute bioavailability was not calculated because of the lack of an acceptable intravenous formulation for human use. The drug is poorly excreted in urine (1.1 –4.1% of the dose) and extensively in faeces (> 96% of the dose total and 83% of the dose unchanged). Biliary concentrations of orlistat up to 43 ng/ml i.e. much higher than plasma concentrations show that this drug is partially excreted in the bile and may be subject to enterohepatic cycling. Two major metabolites have been identified in plasma, M1 and M3, which are 1000- and 2500-fold less potent than orlistat, respectively. The elimination half-life for orlistat, although not accurately measured because of the low plasma concentrations, was estimated to be <2 h; more than 95% of the administered dose was eliminated within 2-3 days.

The effect of orlistat in special populations (paediatric, elderly, hepatic and renal insufficiency) was not investigated because of the low systemic exposure of orlistat. No data on secretion in human milk were provided and, therefore, this lipophilic drug should be contraindicated in nursing mothers.

Interaction studies

Many drug interaction studies were undertaken to investigate the possible effect of orlistat treatment on the pharmacokinetics of drugs with a narrow range therapeutic window and likely to be administered concomitantly to orlistat.

Orlistat was shown not to alter the pharmacokinetics of digoxin, fibrates, phenytoin, warfarin, nifedipine, alcohol and vitamin A. No interaction was noted with oral contraceptives.

Pilot studies were performed to investigate the interaction of orlistat with furosemide, captopril, atenolol and glyburide and no pharmacokinetic alteration was seen. It has to be underlined that orlistat was not given at the proposed therapeutic dose and therefore no conclusions could be drawn.

Co-administration of orlistat with pravastatin increases after 10 days of administration by 26% the C_{max} and by 33% the AUC of pravastatin, which may result in an enhancement of dose related adverse drug reactions. In absence of pharmacokinetic interaction studies, the concomitant administration of orlistat with fibrate, acarbose, biguanide and anorectic drugs is not recommended.

The impairment of the absorption of fat-soluble vitamins was investigated. It showed a non statistically significant decrease in fat-soluble vitamins; therefore the risk of deficiency in vitamin A during long-term treatment with orlistat was not considered to be relevant. On the contrary, vitamins D, E and β-carotene showed a statistically significant decrease after long-term treatment with the drug in combination with a diet. A slight decrease in vitamin K absorption might affect the prothrombin time and might be detrimental to some patients. This is mentioned in the special warnings and precautions for use section of the SPC.

An interaction study was performed with cyclosporin, which showed reductions in cyclosporin plasma levels when combined with orlistat. Monitoring of cyclosporin plasma levels until stabilisation is therefore recommended in the section 4.4 of the SPC as well as in the package leaflet.

In January 2000, the section 4.4 of the SPC was updated regarding the interaction with cyclosporin giving a recommendation to monitor cyclosporin plasma levels more frequently than usual when orlistat is co-administered and to continue this monitoring when orlistat is discontinued

In November 2002, information was added to the section 4.5 of the SPC regarding interactions with other products. No interaction with amitriptyline, atorvastatin, biguanides, digoxin, fibrates, fluoxetine, losartan, phenytoin, oral contraceptives, phentermine, pravastatin, and nifedipine GITS, nifedipine slow release, sibutramine or alcohol have been observed. However, when given as a single dose, a small decrease in plasma levels of amiodarone has been observed in a limited number of healthy volunteers who received orlistat concomitantly. The clinical relevance of this effect in patients receiving amiodarone treatment remains unknown but may be of minor relevance, in patients receiving concomitant amiodarone treatment, reinforcement of clinical and ECG monitoring is warranted.

Clinical efficacy

Dose-response studies and main clinical studies

The efficacy of orlistat was investigated in 4 dose-ranging studies (phase II clinical trials) of 2- to 6-months duration, comparing different doses, from 10 to 240 mg t.i.d., and in 7 long-term (1- to 2-years duration) phase III clinical trials. The latter were double blind, randomised, multicentre, comparing doses of 30, 60 and 120 mg t.i.d. versus placebo, aimed at evaluating the efficacy of orlistat combined with hypocaloric or eucaloric diet. All the studies were preceded by a 1-month run-in placebo period (except study NM 14336 with a 5 week run-in period and study NM 14302: 6-month run-in placebo) and were performed according to the same protocol:

- **Inclusion criteria** - BMI value between 28 and 43 kg/m^2.
- **Efficacy criteria** - The primary efficacy criterion was change in body weight (weight reduction after a 1-year treatment and prevention of weight regain during the 2^{nd} year of treatment). The secondary efficacy criteria were related to obesity risk factors: lipids (total, LDL, HDL and VLDL cholesterol; triglycerides); lipoprotein a, apoproteins A-1 and B; blood pressure, insulin and glucose; anthropometric measurements, such as waist circumference, and quality of life.
- **Safety criteria** - Undesirable effects related to its pharmacological effect: decreased systemic absorption of lipophilic substances, e.g. fat-soluble vitamins; impairment of calcium and bone metabolism; enhanced faecal fat excretion with increased amounts of fat in the colon. Laboratory assessments of routine test of organs' function.
- **Diet** - A mild hypocaloric diet (<1500 kcal/day), containing approximately 30% of calories from fat, was prescribed during the run-in period and the first year of treatment (except for

study NM14302 where an eucaloric diet was given during the 1-year treatment period), then an eucaloric diet was prescribed during the second year.

1. Results - Primary efficacy criteria

After randomisation, the placebo-treated patients lost 2.6 kg, compared to 6.1 kg for the orlistat-treated patients (refer to the table below on Primary efficacy criteria in pooled studies over 1 year). The difference, calculated as least square mean difference (LSM, adjusted means on factors included in the model: centre; stratum for weight loss after the run-in period or percentage of weight loss; interaction centre×stratum, centre×treatment and treatment×stratum) was –3.2 kg, and it was statistically significant (p< 0.001).

Primary efficacy criteria in pooled studies over 1 year:			
	Orlistat 60 mg (n=452)	**Orlistat 120 mg (n=1561)**	**Placebo (n=1119)**
Initial body weight at randomisation (kg)	97.3	97.0	97.1
Mean weight loss		-6.1	-2.6
LSM of difference (kg)	-2.6	-3.2	
p value	<0.001	<0.001	

The clinical relevance of such a modest effect was questioned. After a formal request from the CPMP and according to the "Note for guidance on clinical investigation of drugs used in weight control", the company was requested to provide the percentage of the responders, i.e. ≥ 10% loss in body weight.

After 1 year of drug treatment (excluding the 4-weeks run-in period), 8.3% of the patients in the placebo and 20.2% in the orlistat 120 mg group had a body weight loss ≥10%, which was statistically significant.

The frequency of distribution of weight loss (≥ 5% and ≥ 10%), after 1-year orlistat therapy in comparison with placebo, is reported below (meta-analysis of 5 studies of the core dossier, excluding the study in diabetic patients). The calculations were performed comparing the data after 1-year treatment versus the baseline after the run-in period.

% of weight loss	**Placebo (N= 1119)**	**Orlistat 120 mg (N= 1561)**	**p-value**
All studies (except study in diabetics)			
• ≥ 5%	23.4%	45.3%	< 0.001
• ≥ 10%	8.3%	20.2%	< 0.001
Study in diabetics			
• ≥ 5%	13.2%	30.2%	< 0.001
• ≥ 10%	4.4%	9.3%	=0.09

No clinically relevant difference was seen between the 60 and the 120-mg dosages (16.6% versus 20.2% weight loss ≥ 10%), although the absolute difference in weight loss of 0.6 kg was close to statistical significance (p< 0.10).

In type II diabetic patients, the percentage of responders (≥ 10% of bodyweight loss in addition to the diet run-in period) was 9% with orlistat as compared to 4% with placebo. The mean difference in weight loss with the drug compared to placebo was – 2.1 kg in these patients.

The meta-analysis of mean change (LSM) in body weight (kg) from the second-year baseline to week 104 (weight regain during the second-year therapy without diet; studies NM14161, BM14149, NM14185, BM14119C) showed that the patients in the placebo group gained +2.5 (± 4.3) kg, those in orlistat 60 mg t.i.d. +3.2 (± 4.3) kg and those in orlistat 120 mg gained +2.9 (± 4.5) kg. No difference between groups was observed. After a 6-month period of diet alone where a 10 kg-loss was observed, patients regained 3.0 kg with orlistat 120 mg and 5.1 kg with placebo respectively in the following year without diet (study NM14302).

In order to select those patients likely to respond, as well as not to unduly expose patients to the drug, the CPMP requested a two-step selection of patients. The patients who, despite an appropriate

hypocaloric diet, were unable to lose more than 2.5 kg during 4 consecutive weeks should not be treated (negative predictive value=0.90, sensitivity=0.52 and specificity=0.61). After 12 weeks of treatment, if the patient did not lose at least 5% of his/her body weight as measured at the start of drug therapy, then the drug should be discontinued. These criteria (of losing at least 5% of body weight after 12 weeks of therapy) have a positive predictive value=0.48, sensitivity=0.83 and specificity=0.77.

2. Results - Secondary efficacy criteria

The effect of 1-year treatment with orlistat on obesity-associated risk factors was analysed combining all the core dossier studies (meta-analysis); the sub-group of responders (body weight loss ≥ 10%) was also analysed. The data are summarised below:

	Placebo *		**Orlistat ****		**diff.′**	**p-value**
	Initial value	Mean change	Initial value	Mean change		
Total cholesterol (mmol/l)						
- global	5.2	+ 0.2 (± 0.6)	5.1	- 0.1 (± 0.7)	- 0.3	< 0.001
- body weight loss ≥ 10%	4.8	+ 0.1 (± 0.7)	5.0	- 0.3 (± 0.7)	- 0.3	< 0.001
LDL (mmol/l)						
- global	3.4	+ 0.1 (± 0.5)	3.3	- 0.2 (± 0.6)	- 0.3	< 0.001
- body weight loss ≥ 10%	3.1	- 0.04 (± 0.6)	3.3	- 0.3 (± 0.6)	- 0.3	< 0.001
HDL (mmol/l)						
- global	1.2	+ 0.1 (± 0.2)	1.2	+ 0.1 (± 0.2)	- 0.03	< 0.001
- body weight loss ≥ 10%	1.1	+ 0.3 (± 0.2)	1.1	+ 0.2 (± 0.2)	- 0.1	< 0.001
Triglycerides (mmol/l)						
- global	1.6	- 0.03 (± 0.7)	1.5	- 0.05 (± 0.8)	-0.02	0.37
- body weight loss ≥ 10%	1.3	- 0.2 (± 0.5)	1.5	- 0.3 (± 1.1)	+ 0.08	0.08
Systolic (mm Hg)						
- global	123.7	+ 0.6 (± 13.7)	122.6	- 1.0 (± 13.6)	- 1.0	0.021
- body weight loss ≥ 10%	120.0	- 3.0 (± 14.0)	122.5	- 3.8 (± 12.5)	+ 1.0	0.44
Diastolic (mm Hg)						
- global	79.2	+ 0.5 (± 9.4)	78.7	- 1.2 (± 9.2)	- 1.5	0.001
- body weight loss ≥ 10%	77.1	- 1.6 (± 9.5)	78.7	- 4.2 (± 9.1)	- 1.5	0.13
glucose (mmol/l)						
- global	5.7	0.0 (± 0.6)	5.6	- 0.04 (± 0.6)	- 0.07	0.001
- body weight loss ≥ 10%	5.4	- 0.1 (± 0.5)	5.6	- 0.2 (± 0.5)	- 0.03	0.48
insulin (mmol/l)						
- global	95.5	+ 24.0 (± 129.4)	92.2	- 18.6 (± 66.5)	- 9.6	0.002
- body weight loss ≥ 10%	83.1	- 14.6 (± 53.1)	82.0	- 18.6 (± 66.5)	- 3.7	0.37

* placebo N.~900 (global); N.~90 (body weight loss ≥ 10%)

** orlistat 120 mg t.i.d. N.~1300 (global); N= 300 (body weight loss ≥ 10%)

′ figures have been rounded up

Mean change in obesity-related risk factors was also analysed in a subgroup of patients with abnormal initial values (all the patients and a subgroup of responders). The results are presented below:

	Placebo *		Orlistat **		diff. ′	p-value
	Initial value	Mean change	Initial value	Mean change		
LDL (≥ 3.362 mmol/l) - global - body weight loss ≥ 10%	 4.1 4.0	 + 0.02 (± 0.6) - 0.2 (± 0.8)	 4.1 4.0	 - 0.3 (± 0.6) - 0.6 (± 0.6)	 - 0.3 - 0.3	 < 0.001 = 0.005
HDL (<0.905 mmol/l) - global - body weight loss ≥ 10%	 0.8 0.8	 + 0.2 (± 0.1) + 0.2 (± 0.1)	 0.8 0.8	 + 0.1 (± 0.1) + 0.2 (± 0.1)	 0.0 - 0.01	 = 0.87 = 0.79
Triglycerides (≥ 2.54 mmol/l) - global - body weight loss ≥ 10%	 3.5 3.4	 - 0.7 (± 1.6) - 1.7 (± 0.4)	 3.6 4.5	 - 0.6 (± 2.0) - 2.5 (± 4.4)	 + 0.2 - 0.3	 = 0.16 = 0.28
Diastolic (≥ 90 mm Hg) - global - body weight loss ≥ 10%	 94.0 92.1	 - 5.4 (± 9.1) - 11.0 (± 9.1)	 93.7 94.0	 - 7.9 (± 8.2) - 11.0 (± 7.6)	 - 1.9 + 2.3	 = 0.06 = 0.43
insulin (≥ 90 mmol/l) - global - body weight loss ≥ 10%	 146.2 141.5	 - 6.4 (± 118.5) - 25.8 (± 90.2)	 144.4 132.3	 - 23.8 (± 142.9) - 42.9 (± 106.4)	 - 19.7 - 7.3	 = 0.02 = 0.42

* Total number of patient with abnormal values in the placebo group: LDL (N= 506), HDL (N= 213), triglycerides (N= 105), diastolic blood pressure (N= 197) and insulin (N= 392)

** Total number of patient with abnormal values in the orlistat group: LDL (N= 648), HDL (N= 294), triglycerides (N= 138), diastolic blood pressure (N= 222) and insulin (N= 560)

* Number of patient responders (body weight loss ≥ 10%) with abnormal values in the placebo group: LDL (N= 32), HDL (N= 20), triglycerides (N= 4), diastolic blood pressure (N= 13) and insulin (N= 30)

** Number of patient responders (body weight loss ≥ 10%) with abnormal values in the orlistat group: LDL (N= 138), HDL (N= 76), triglycerides (N= 15), diastolic blood pressure (N= 38) and insulin (N= 99)

′ figures have been rounded up.

Clinical studies in special populations

No specific effect of orlistat on obesity-related risk factors was shown other than that due to body weight loss. In the study in diabetic patients (subgroup of responders), the obesity-related risk factors were not modified by treatment: glucose decreased by 1.3 (± 1.2) mmol/l and 0.8 (± 1.3) mmol/l after 1 year treatment with placebo and orlistat 120 t.i.d., respectively. Insulin decreased by 72.9 (±82.4) pmol/l after 1 year treatment with placebo and by 56.9 (± 57.7) pmol/l after 1 year treatment with orlistat 120 t.i.d.. No statistically significant difference between groups was detected.

Supportive studies

The clinical benefit, in terms of cardiovascular parameters, was not clearly demonstrated in the responders, although a slight improvement was observed in systolic and diastolic blood pressure: -3.8 and – 4.2 mm Hg, respectively.

The quality of life, although subjective and difficult to interpret, seemed to improve after 1 year 120 mg t.i.d orlistat treatment. Overweight distress, depression, satisfaction with treatment and self-regard improved in comparison with placebo (at least $p < 0.04$).

Clinical safety

Patient exposure

The safety assessment was based on over 4800 patients receiving at least one dose of orlistat. Approximately 2150 patients received orlistat for at least one year and 880 for two years. The total percentage of premature withdrawals over the first year, whatever the reason, was 35.3% in the placebo group, 25.3% in the orlistat 30-mg t.i.d., 26.0% in the orlistat 60-mg t.i.d. and 29.1% in the orlistat 120 mg t.i.d.. The highest number of patients who dropped out as treatment failure and were lost to follow-up was recorded in the placebo group, while the orlistat group(s) had the highest incidence of patients withdrawn for adverse drug events:

Reason for withdrawal	**Placebo (N= 1466)**	**Orlistat 30 mg t.i.d. (N= 186)**	**Orlistat 60 mg t.i.d. (N= 623)**	**Orlistat 120 mg t.i.d. (N= 1913)**
Adverse events	4.9%	9.7%	6.9%	8.8%
Treatment failure	2.6%	1.1%	1.6%	1.0%
Lost to follow-up	9.8%	5.4%	6.1%	7.7%
Other	18.0%	9.2%	11.4%	11.6%
Total	35.3%	25.3%	26.0%	29.1%

Adverse events and serious adverse events/deaths

In the phase III studies, approximately 6% of the patients (total number = 2722) reported serious adverse events (AE) over one year in both orlistat (all tested dose schedules) and placebo groups. The body systems showing the most serious AEs were: reproductive female disorders, body as a whole, gastrointestinal system disorders and musculo-skeletal system disorders. Hypersensitivity reactions have been reported post marketing.

According to the mechanism of action of the drug, the major safety concern is the gastrointestinal tolerability of the drug, notably oily spotting from the rectum, flatus with discharge, faecal urgency, fatty/oil stool, oil stool, oily evacuation, increased defecation and faecal incontinence. Although they were rarely serious and a cause for premature discontinuation from the study, they were 10- to 20-fold more frequent with orlistat than with placebo. The respective percentages of oily spotting from the rectum were: 18.8% with orlistat 60 mg t.i.d., 26.6% with orlistat 120 mg t.i.d. and 1.3% with placebo; the respective percentages of flatus with discharge were: 18.85% with orlistat 60 mg t.i.d., 23.9% with orlistat 120 mg t.i.d. and 1.4% with placebo. Faecal urgency was 3 times higher in the orlistat groups: 20.2% with orlistat 60 mg t.i.d., 22.1% with orlistat 120 mg t.i.d. and 6.7% with placebo. These adverse drug reactions (ADR) were dose-dependent, higher and more severe in comparison with placebo.

During the second year of treatment, however, the frequency of oily spotting from the rectum, flatus with discharge and faecal urgency decreased from about 20.0% of the patients to about 4%. About 15% of the patients experienced gastrointestinal ADRs which lasted for more than 4 weeks; the data collected and analysed according to the protocol do not provide sufficient information to judge whether the ADRs were truly continuous or if they were individual episodes occurring on a weekly basis.

Overall, the gastrointestinal ADRs remain the most common ADRs. As far as the other adverse events recorded during the clinical trials are concerned, no difference in the safety profile between orlistat and placebo was detected and no AE seemed to be dose-related. The biological tolerability of the drug, tested by the routine laboratory examinations was good and no difference versus placebo was observed with all the dose schedules tested.

Ten cases of breast cancer in the orlistat groups (60 and 120 mg t.i.d. doses) versus one in the placebo were reported. During the evaluation phase, a follow-up survey found two new cases in the 120 mg group and one in the placebo group. The data provided by the company were also analysed by a panel of experts appointed by the company. The observed cases were not evenly distributed across studies and the histological types were different. No predictive elements have been found in the preclinical studies. In addition, the occurrence was too early in some cases (36 to 38 days from the beginning of treatment) and the timing necessary to development of the tumor was not consistent with drug exposure. Furthermore, direct toxicity is unlikely since the drug is negligibly absorbed. A detection

bias was ruled out: women with breast cancer were not found having lost more weight than those without tumors. However to rule out any promoting effect of the drug on the tumoral growth, additional data will be produced from an ongoing 2-year study in Sweden, which is expected to produce data on 3350 patients (estimate end in the year 2000). The protocol foresees a mammography at entry, at one year, and at the end of the study.

The possibility of colonic cancer was raised in the view of increased lipid content in the colonic fecal content and current epidemiological data linking human colon cancer and increased fat intake. The review of recent available epidemiological evidence showed that the relationship between fat intake and colon cancer is doubtful. Increased energy intake was incriminated as the main risk factor whereas fat intake could be a confounding factor, taking into account the fact that the drug is neither genotoxic, nor carcinogenic and that clinical data in the exposed population did not indicate a risk of colon cancer.

Laboratory findings

The following table presents the mean changes in the absorption of fat-soluble vitamins in the trials with the non-US patients after 2-year treatment with orlistat 120 mg t.i.d.:

	Placebo		**Orlistat 120mg**		**diff.**	**p-value**
Vitamins (reference interval)	Initial value	Mean change	Initial value	Mean change		
vitamin A (1.58-3.97 µmol/l)	2.4	- 0.01 (± 0.5)	2.5	- 0.1 (± 0.5)	- 0.07	= 0.10
β-carotene (0.09-1.06 µmol/l)	0.4	+ 0.04 (± 0.3)	0.4	- 0. 1 (± 0.4)	- 0.1	< 0.001
vitamin D (18-121 nmol/l)	60.1	+ 4.4 (± 20.7)	60.3	- 4.5 (± 21.9)	- 8.2	< 0.001
vitamin E (18.1-50.6 µmol/l)	27.6	+ 3.1 (± 4.5)	28.4	- 0.7 (± 7.0)	- 3.0	< 0.001

The decreases observed were clinically relevant for β-carotene, vitamin E, and vitamin D. The decline in 25-OH-D resulted in no detectable changes in calcium or bone metabolism. In a subgroup of patients plasma calcium and parathyroid hormone levels showed no change (total and ionised calcium) or a slight decrease (parathyroid hormone), from 33.2 to 31.5 ng/l, in comparison with placebo, from 32.5 to 31.9, remaining, however, in the reference interval (13.3-60.2 ng/l). Another evidence of the absence of metabolic and clinical consequences on calcium and bone metabolism was offered by the data on bone mineral content and density performed in 40 patients (14 with placebo and 16 with orlistat 120 mg t.i.d.), which did show any difference between day 1 and day 52 neither intra- nor between group. Due to these changes in vitamin D, E, and β-carotene levels, the SPC mentions that multivitamin supplementation may be considered.

Safety in special populations

Analysis of estrogen levels resulting from 80 postmenopausal women indicated no significant difference in estrogen changes from baseline for orlistat group or placebo.

Efficacy and safety discussion

After 1-year treatment with orlistat (120 mg t.i.d.) in association with a mild hypocaloric diet, a modest effect of orlistat on body weight was observed. The mean effect at one year was –3.2 kg weight loss as compared to placebo. Patients who lose more than 10% of their body weight were considered responders. Responder rates were 8% in the placebo group as compared to 20% in orlistat 120 mg group. During the second year, orlistat associated with a eucaloric diet did not prevent weight regain. The drug was less effective in type II diabetes. No specific effect of orlistat on obesity related risk factors was shown.

The gastrointestinal ADRs remain the most common ADRs. Due to the changes in vitamin D, E, and β-carotene levels, the SPC mentions that multivitamin supplementation may be considered. Breast cancer occurrence was likely to be a chance finding. To rule out any promoting effect of orlistat on the

tumour growth, additional data are requested to the company from the ongoing 2-year study in Sweden.

Moreover, in order to select those patients likely to respond, as well as not to unduly expose patients to the medicinal product, the CPMP requested a two-step selection of patients. The patients who, despite an appropriate hypocaloric diet, were unable to lose more than 2.5 kg over a period of 4 consecutive weeks should not be treated. After 12 weeks of treatment, if the patient does not lose at least 5% of his/her body weight as measured at the start of drug therapy, then the treatment with orlistat should be discontinued. As there are no safety and efficacy data beyond 2 years, the maximal duration of treatment should not be longer than 2 years.

The majority of CPMP agreed that the mean effect of orlistat is modest. Some CPMP members held a divergent view. They considered the therapeutic effect of Xenical too small to be clinically relevant, whereas the adverse events are incompletely understood, especially concerning breast cancer. However, the majority of the CPMP considered that, although modest, this effect is clinically relevant, and it was also recognised that currently there is no safe medicinal product for long-term treatment of obesity available.

In July 1999, the section 4.8 of the SPC was updated to with information that rare cases of hypersensitivity have been reported and that main clinical symptoms are pruritus, rash, urticaria, angioedema and anaphylaxis.

In January 2001, the section 4.8 of the SPC was updated to include information on that in very rare cases an increase in liver transaminases and in alkaline phophatase have been reported during the post marketing phase.

In June 2001, the section 4.8 of the SPC was updated with information that very rare cases of bullous eruptions having been reported during post marketing phase.

In March 2002, the section 5.1 of the SPC was updated to include information on obese type 2 diabetic patients insufficiently controlled by antidiabetics. 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.

5. Overall conclusions and benefit/risk assessment

Benefit/risk assessment

The quality of orlistat 120 mg capsules, as demonstrated in the chemical and pharmaceutical documentation is considered acceptable.

The pharmacological activity of orlistat has been shown in animals and man to inhibit, proportionally with the dose, the action of gastrointestinal lipase, impairing the metabolism of lipids in the intestinal lumen and preventing absorption.

The clinical data provided showed, in obese patients with an initial body weight of about 100 kg, a modest effect of orlistat on body weight after 1-year treatment in association with a mild hypocaloric diet, and no specific effects on obesity-associated risk factors. At one year, the mean effect was –3.2 kg weight loss as compared to placebo. The percentage of patients losing at least 10% of their initial body weight after the start of medicinal treatment was 20.2% and 8.3% in the orlistat 120 mg and placebo-treated groups, respectively. During the second year orlistat associated with a eucaloric diet did not prevent weight regain. The overall safety issues have been adequately addressed and appropriate warnings and precautions have been included in the SPC. With regards to the occurrence of breast cancer, it was likely to be a chance finding.

In order to select those patients likely to respond, as well as not to unduly expose patients to orlistat, the patients who, despite an appropriate hypocaloric diet, were unable to lose more than 2.5 kg over a period of 4 consecutive weeks should not be treated. After 12 weeks of treatment, if the patient does not lose at least 5% of his/her body weight as measured at the start of drug therapy, and then the

treatment with orlistat should be discontinued. The maximal duration of treatment should not be longer than 2 years. Moreover, to rule out any promoting effect of the medicinal product on the tumour growth, additional data from the ongoing 2-years study in Sweden are requested from the company.

CPMP recommendation

Therefore, the CPMP considered the benefit to risk assessment positive and the granting of a Marketing Authorisation was recommended for this medicinal product. At the time of the 5-year renewal, the CPMP considered that the benefit/risk profile of Xenical continued to be favourable and recommended the renewal of the Community Marketing Authorisation on 26 June 2003.