Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Orlistat 120 mg Capsules, hard

(orlistat)

Procedure No: UK/H/5945/001/DC

UK Licence No: PL 30322/0011

Alissa Healthcare Research Limited

LAY SUMMARY

Orlistat 120 mg Capsules, hard
(orlistat)

This is a summary of the Public Assessment Report (PAR) for Orlistat 120 mg Capsules, hard (PL 30322/0011; UK/H/5945/001/DC). It explains how the application for Orlistat 120 mg Capsules, hard was assessed and its authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Orlistat 120 mg Capsules, hard.

For practical information about using Orlistat 120 mg Capsules, hard, patients should read the package leaflet or contact their doctor or pharmacist.

The product may be referred to as 'Orlistat Capsules' in this report.

What are Orlistat Capsules and what are they used for?

Orlistat Capsules are a 'hybrid medicine'. This means that Orlistat Capsules are similar to a 'reference medicine' already authorised in the European Union (EU) called Xenical 120 mg capsules, hard (Roche Registration Limited, UK), which was first authorised in the EU on 29 July 1998.

Orlistat Capsules are used to treat obesity in conjunction with a low calorie intake diet.

How do Orlistat Capsules work?

Orlistat Capsules contain the active substance orlistat. It works in the digestive system to block about one-third of the fat in eaten food from being digested. Orlistat attaches to the enzymes in the digestive system (lipases) and blocks them from breaking down some of the fat that has been eaten during a meal. The undigested fat cannot be absorbed and is eliminated by the body.

How are Orlistat Capsules used?

Orlistat Capsules are available as hard capsules and are taken by mouth. This medicine should always be taken exactly as advised by the patient's doctor. The patient should check with his/her doctor or pharmacist if he/she is not sure.

The usual dose of Orlistat Capsules is one 120 mg capsule taken with each of the three main meals per day. It can be taken immediately before, during a meal or up to one hour after a meal. The capsule should be swallowed with water.

Orlistat Capsules should be taken with a well-balanced, calorie controlled diet that is rich in fruit and vegetables and contains an average of 30 % of the calories from fat. The patient's daily intake of fat, carbohydrate and protein should be distributed over three meals.

Orlistat Capsules only work in the presence of dietary fat. Therefore, if the patient misses a main meal or has a meal that contains no fat, an Orlistat capsule should not be taken.

Orlistat Capsules are not intended to be used in children.

Please read Section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

Orlistat Capsules can only be obtained with a prescription.

What benefits of Orlistat Capsules have been shown in studies?

As Orlistat Capsules are a hybrid medicine, studies in patients have been limited to tests to determine that the medicine is therapeutically equivalent to the reference medicine, Xenical 120 mg capsules, hard (Roche Registration Limited, UK). Two medicines are therapeutically equivalent when they produce the same measure of therapeutic effect in the body.

In addition, the company (Alissa Healthcare Research Limited) provided data from the published literature on orlistat.

What are the possible side effects of Orlistat Capsules?

Like all medicines Orlistat Capsules can cause side effects, although not everybody gets them.

The majority of unwanted effects related to the use of Orlistat Capsules result from its local action in the digestive system. These symptoms are generally mild, occur at the beginning of treatment and are particularly experienced after meals containing high levels of fat. Normally, these symptoms disappear if the patient continues treatment and keeps to his/her recommended diet.

Very Common side effects (affects more than 1 user in 10):

- headache
- abdominal pain/discomfort, urgent or increased need to open the bowels, flatulence (wind) with discharge, oily discharge, oily or fatty stools, liquid stools, low blood sugar levels (experienced by some people with type 2 diabetes).

Common side effects (affects 1 to 10 users in 100)

- Rectal pain/discomfort, soft stools, incontinence (stools), bloating (experienced by some people with type 2 diabetes)
- Tooth/gum disorder
- Irregularity of menstrual cycle
- Tiredness.

For the full list of all side effects reported with Orlistat Capsules, see section 4 of the package leaflet.

For the full list of restrictions, see the package leaflet for Orlistat Capsules.

Why are Orlistat Capsules approved?

It was concluded that, in accordance with EU requirements, Orlistat Capsules have been shown to have comparable quality and be therapeutically equivalent to Xenical 120 mg capsules, hard (Roche Registration Limited, UK). Therefore, the view was that, as for Xenical 120 mg capsules, hard (Roche Registration Limited, UK)), the benefits outweigh the identified risks and it was recommended that Orlistat Capsules can be approved for use.

What measures are being taken to ensure the safe and effective use of Orlistat Capsules?

A Risk Management Plan has been developed to ensure that Orlistat Capsules are used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Orlistat Capsules, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Orlistat 120 mg Capsules.

Ireland and the UK agreed to grant a Marketing Authorisation for Orlistat Capsules on 27 November 2015. A Marketing Authorisation was granted in the UK to Alissa Healthcare Research Limited on 04 December 2015.

The full PAR for Orlistat Capsules follows this summary.

For more information about treatment with Orlistat Capsules, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in January 2016.

SCIENTIFIC DISCUSSION

TABLE OF CONTENTS

Scientific discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK and Ireland considered that the application for Orlistat 120 mg Capsules, hard (PL 30322/0011; UK/H/5945/001/DC) could be approved. The product is a Prescription Only Medicine (POM) and 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 > 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.

This application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS). The application for Orlistat 120 mg Capsules was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application and cross-refers to Xenical 120 mg capsules, hard (Roche Registration Limited, UK), which was first authorised in the European community via the Centralised Procedure on 29 July 1998.

The active substance, orlistat is a peripherally acting anti-obesity agent (ATC code A08AB01). It is a semi-synthetic derivative of lipstatin and is a long-acting inhibitor of gastrointestinal lipases. It forms a covalent bond with the active serine site of gastric and pancreatic lipases in the lumen of the stomach and small intestine. The inactivated enzyme is unable to hydrolyse dietary fat (triglycerides) into absorbable free fatty acids and monoglycerides, leading to a decrease in triglyceride absorption.

To support the application, a single pharmacodynamic study using faecal fat excretion as a surrogate parameter to demonstrate therapeutic equivalence of Orlistat 120 mg Capsules to the reference product Xenical 120 mg Capsules, hard (Roche Registration Limited, UK) was submitted.

With the exception of the therapeutic equivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been in clinical use for over 10 years.

The RMS has been assured that acceptable standards of good manufacturing practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 208) on 27 November 2015. After a subsequent national phase, a licence was granted in the UK on 04 December 2015.

II QUALITY ASPECTS

II.1 Introduction

The application is submitted in accordance with Article 10(3) of Directive 2001/83/EC, as amended.

The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

The product is available as a blue hard capsule.

Each capsule contains 120 mg of orlistat.

The other ingredients consist of the pharmaceutical excipients in the capsule filling and capsule shell namely, microcrystalline cellulose PH 112, sodium starch glycolate (type A), colloidal anhydrous silica, sodium laurilsulfate, gelatin, indigo carmine (E132) and titanium dioxide (E171). Appropriate justification for the inclusion of each excipient has been provided.

The product is supplied in aluminium/polyvinylchloride/polyvinylidene chloride blisters containing 21, 42 and 84 hard capsules.

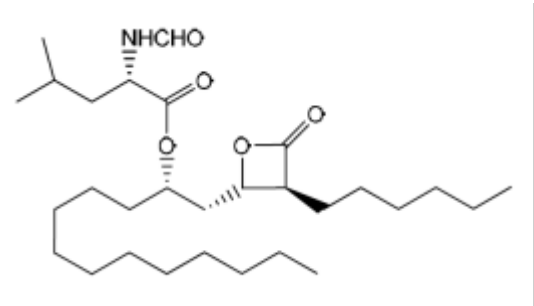
Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for the primary packaging material have been provided. All primary packaging is controlled to European Pharmacopoeia standards that comply with guidance concerning materials in contact with food.

II.2 Drug Substance

Orlistat

International Non-proprietary Name (INN):	Orlistat
Chemical name:	N-Formyl-L-leucine(1S)-1-[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl] dodecyl ester; N-formyl-L-leucine ester with (3S,4S)-3-hexyl-4- [(2S)-2-hydroxytridecyl]-2-oxetanone
Molecular formula:	$C_{29}H_{53}NO_5$
Mr: 495.73	
Structural formula:	



Polymorphism	Z-isomer
Description:	A white or almost white crystalline powder
Solubility:	It is freely soluble in ethanol, methanol, acetone and chloroform. It is slightly soluble in n-heptane and practically insoluble in water and 0.1M hydrochloric acid.
Isomerism	Orlistat exhibits chirality

Polymorphism	Orlistat is known to exist in two polymorphic forms which can be distinguished by X-ray powder diffraction

Orlistat is not the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Appropriate proof-of-structure data have been supplied. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data that comply with the proposed specification are provided.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with foodstuff.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, stable, immediate release hard capsule containing 120 mg of orlistat that was comparable in performance to the reference medicinal product Xenical 120mg capsules, hard (Roche Registration Limited, UK). Suitable pharmaceutical development data have been provided for this application.

Comparative *in-vitro* dissolution profiles have been provided for this product and the originator product, Xenical 120mg capsules, hard (Roche Registration Limited, UK).

With the exception of indigo carmine (E132), all excipients comply with their respective European Pharmacopoeia monographs. Indigo carmine (E132) is controlled to a suitable in-house specification, which is also in compliance with the current EU Directive concerning the use of colouring agents. Satisfactory Certificates of Analysis have been provided for all excipients showing compliance with their proposed specifications.

With the exception of gelatin, none of the excipients contain materials of animal or human origin. The suppliers of gelatin have provided Certificates of Suitability from the European Directorate for the Quality of Medicines and Healthcare (EDQM) to show that it is manufactured in line with current European guidelines concerning the minimising of risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacturing Process
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated with pilot-scale batches and has shown satisfactory results. The Marketing Authorisation Holder has committed to performing process validation studies on the first three full-scale production batches.

Control of Finished Product
The finished product specification is acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years, with the special storage conditions 'Store below 25 °C. Store in original package and keep the blister in the outer carton in order to protect from light and moisture.' has been accepted.

Suitable post approval stability commitments have been provided.

Bioequivalence/Bioavailability
A traditional pharmacokinetic study to measure bioequivalence was not appropriate because the therapeutic activity of orlistat is within the gastrointestinal tract, i.e. outside the body compartment usually measured. Accordingly, a pharmacodynamic study was conducted, using faecal fat excretion as a surrogate parameter to demonstrate therapeutic equivalence of Orlistat 120 mg Capsules to the reference product Xenical 120 mg Capsules, hard (Roche Registration Limited, UK).

Satisfactory Certificates of Analysis have been provided for the test and reference batches used in the therapeutic equivalence study. The therapeutic equivalence study is discussed in Section III.3, Clinical Aspects.

II.4 Conclusion
It is recommended that a Marketing Authorisation is granted for this application for Orlistat 120 mg Capsules.

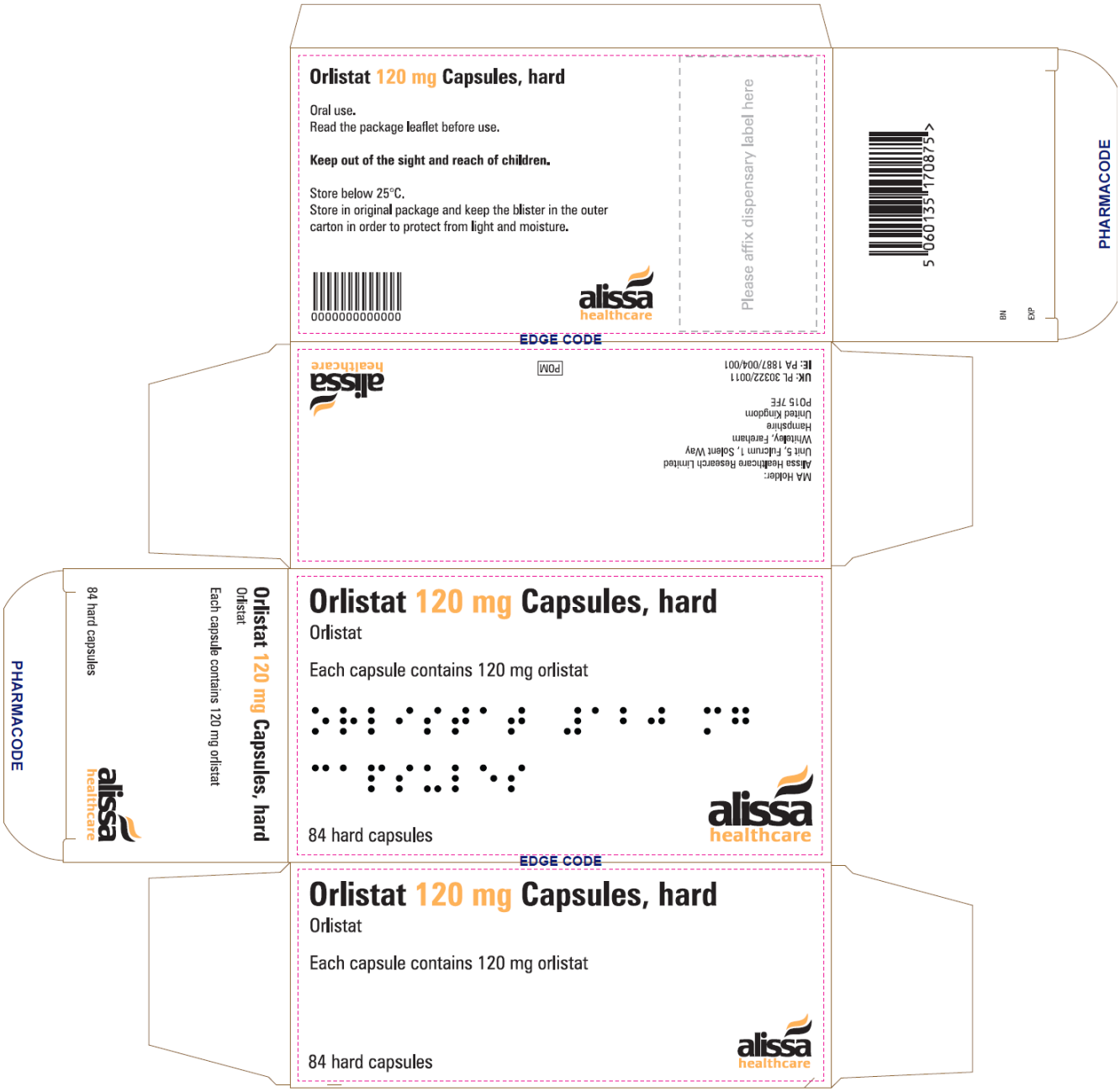
II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labelling are satisfactory and, where appropriate, in line with current guidance.

In accordance with Directive 2010/84/EU, the current version of the SmPC and PIL are available on the MHRA website. The current labelling is presented below:


EXP
BN


Orlistat 120 mg Capsules, hard
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C.
Store in original package and keep the blister in the outer carton in order to protect from light and moisture.
0000000000000
alissa healthcare
Please affix dispensary label here
BN
EXP
POM
UK: PL 30322/0011
IE: PA 1887/004/001
MA Holder:
Alissa Healthcare Research Limited
Unit 5, Fulcrum 1, Solent Way
Whiteley, Fareham
Hampshire
United Kingdom
PO15 7FE
Orlistat 120 mg Capsules, hard
Orlistat
Each capsule contains 120 mg orlistat
21 hard capsules
Orlistat 120 mg Capsules, hard
Orlistat
Each capsule contains 120 mg orlistat
21 hard capsules
Orlistat 120 mg Capsules, hard
Orlistat
Each capsule contains 120 mg orlistat
21 hard capsules


Orlistat 120 mg Capsules, hard
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C.
Store in original package and keep the blister in the outer carton in order to protect from light and moisture.
0000000000000
alissa healthcare
Please affix dispensary label here
BN
EXP
MA Holder:
Alissa Healthcare Research Limited
Unit 5, Fulcrum 1, Solent Way
Whiteley, Fareham
Hampshire
United Kingdom
PO15 7FE
UK: PL 30322/0011
IE: PA 1887/004/001
POM
Orlistat 120 mg Capsules, hard
Orlistat
Each capsule contains 120 mg orlistat
42 hard capsules
Orlistat 120 mg Capsules, hard
Orlistat
Each capsule contains 120 mg orlistat
42 hard capsules
Orlistat 120 mg Capsules, hard
Orlistat
Each capsule contains 120 mg orlistat
42 hard capsules


Orlistat 120 mg Capsules, hard
Oral use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store below 25°C.
Store in original package and keep the blister in the outer carton in order to protect from light and moisture.
0000000000000
alissa healthcare
Please affix dispensary label here
5 060135 1708757
BN
EXP
PHARMACODE
EDGE CODE
PDM
UK: PL 30322/0011
IE: PA 1887/004/001
MA Holder:
Alissa Healthcare Research Limited
Unit 5, Fulcrum 1, Solent Way
Whiteley, Fareham
Hampshire
United Kingdom
PO15 7FE
Orlistat 120 mg Capsules, hard
Orlistat
Each capsule contains 120 mg orlistat
84 hard capsules
PHARMACODE
Orlistat 120 mg Capsules, hard
Orlistat
Each capsule contains 120 mg orlistat
84 hard capsules
EDGE CODE
Orlistat 120 mg Capsules, hard
Orlistat
Each capsule contains 120 mg orlistat
84 hard capsules

III NON-CLINICAL ASPECTS

III.1 Introduction

The pharmacodynamic, pharmacokinetic and toxicological properties of orlistat are well known and are adequately described in the applicant's non-clinical overview. No new non-clinical data were submitted and none are required for an application of this type.

The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacokinetics

The pharmacokinetic properties of orlistat are well known and adequately described in the applicant's non-clinical overview.

III.3 Pharmacodynamics

The pharmacodynamic properties of orlistat are well known and are adequately described in the applicant's non-clinical overview.

III.4 Toxicology

The toxicological properties of orlistat are well known and are adequately described in the applicant's non-clinical overview.

III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP/4447/00 corr 2*], the applicant submitted an Environmental Risk Assessment (ERA) for orlistat.

In the Phase I assessment, the Predicted Environmental Concentration in surface water ($PEC_{surfacewater}$) for orlistat (0.84 µg/L) exceeded the action limit of 0.01 µg/L at which a Phase II assessment is necessary. The log n-octanol/water partition coefficient ($logK_{ow}$) value for orlistat (8.19) exceeds the threshold (4.5) for screening for persistence, bioaccumulation and toxicity.

However, the applicant has provided suitable justification for not submitting a Phase II assessment. The applicant has referred to the reference product's ERA in their presented ERA, including referencing of the Alli EPAR published on the EMA website. The active substance is the same and the finding from this publicly available source provides supportive evidence in the Applicant's completion of this ERA.

The applicant's justification that generic orlistat will take the place of innovator is acceptable, and it is agreed that there is no unknown environmental risk associated with orlistat and the ERA submitted is now acceptable.

III.6 Discussion on the non-clinical aspects

It is recommended that a Marketing Authorisation is granted for Orlistat 120 mg Capsules, hard from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a hybrid application as defined by Article 10(3) of Directive 2001/83/EC, as amended, with the reference product Xenical 120mg capsules, hard (Roche Registration Limited, UK).

Orlistat 120 mg Capsules are considered to be a locally applied, locally acting product within the gastrointestinal tract. With consideration of the note for Guidance on the clinical requirements for

locally applied, locally acting products containing known constituents (CPMP/EWP/239/95 final), the Applicant conducted a therapeutic equivalence study, using faecal fat excretion as a surrogate parameter.

The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

No new pharmacokinetic data were submitted and none are required for an application of this type. The pharmacokinetic properties of orlistat are well known and are adequately described in the applicant's clinical overview and are summarised below.

Orlistat is a highly lipophilic compound with extremely low solubility in water. Absorption is minimal and bioavailability is less than 1%. The drug has no defined systemic pharmacokinetics. Therefore, an assessment of bioequivalence would not be possible and the absence of a bioequivalence study is accepted.

Of the minimal fraction of orlistat that is systemically absorbed, two major metabolites, M1 and M3, account for approximately 42% of the plasma concentration. These metabolites have low plasma levels at therapeutic doses, weak lipase inhibitory activity, and are considered to be pharmacologically inconsequential. M3 levels are reported to be marginally higher than M1 (108ng/ml and 26ng/ml respectively). M1 represents the primary metabolite (hydrolysis of beta-lactone ring), whilst M3 is a product of further M1 metabolism, formed by cleavage of the N-formyl leucine side-chain of M1.

The half-life of orlistat is less than 3 hours, M1 approximately 3 hours and M3 approximately 13.5 hours.

A study in adolescents suggested no saturation of M1 plasma concentrations after 21 days of treatment with 120 mg Xenical, three times a day. In a dose-ranging study, the concentration of the M1 metabolite was reported to increase with dose in a less than proportional manner. Conversely, it was stated in the Xenical NDA (20-766/S-018) that in the target population of obese patients the steady state plasma levels of M1 increased in proportion to orlistat dose.

Therefore, the applicant measured plasma levels of the M1 (but not the M3 metabolite) and orlistat to determine formulation-related effects on systemic exposure as a component of the safety assessment.

It is accepted that the plasma levels of M1 will adequately reflect systemic exposure to orlistat and that formation of the M1 metabolite is unlikely to be saturated during each 7 day study period (see therapeutic equivalence study discussed below in Section IV.3, Pharmacodynamic).

IV.3 Pharmacodynamics

The clinical pharmacodynamics properties of orlistat are well-known.

To support the application, the Marketing Authorisation Holder submitted the therapeutic equivalence study detailed below. With the exception of the data presented from the therapeutic equivalence study, no new pharmacodynamic data are provided or required for this application.

A single centre, controlled, open-label, randomised (sequence of treatments), multiple dose (3 x 120 mg capsule daily) two-period cross-over study to demonstrate therapeutic equivalence of the applicant's test product Orlistat 120 mg capsule versus the reference product Xenical 120 mg capsules (Roche Registration Limited, UK). It was performed in a 2-period cross-over design with Test and Reference products and preceding baseline assessment.

Primary Objective:
To demonstrate therapeutic equivalence, after multiple dose administration, between the test and reference product in faecal fat excretion based on average baseline –corrected 24-hour faecal fat excretion as a direct surrogate parameter for the therapeutic effect.

The primary pharmacodynamic parameter was the difference in average faecal fat excretion of active treatment (Test and Reference) and baseline [$\Delta FFE_{treatment}$, g/24h]. Decision in favour of equivalence was accepted if the 95% confidence intervals did not exceed the limits of 0.8 and 1.25 for the ratio of ΔFFE-values. The acceptance range of 80.00-125.00% has been used in previous trials of the therapeutic equivalence of orlistat. A 95% confidence interval is considered by CHMP to be the standard approach for therapeutic equivalence trials (Scientific Advice EMEA/CHMP/SAWP/717352/2009).

Secondary objectives included:
- Characterisation of systemic exposure by quantitation of orlistat and M1 plasma concentrations
- Descriptive characterisation of overall safety and tolerability of test and reference products in the study population
- Characterisation of the effect of orlistat on postprandial serum concentrations of triglycerides.

Brief description of study
The product was administered (3 x 120mg capsule daily) for seven days during each of two treatment periods (I and II), which were each preceded by a five day treatment-free pre-phase (TFPP) during which the subjects adhered to a standardised diet. The TFPP prior to treatment period II served as the wash-out for the previous treatment period. Five days was considered sufficient to clear the drug from the preceding treatment period (given the half-life of orlistat and its principle metabolites [M1 and M3]) and ensure that the faecal fat excretion returned to the non-treatment baseline; this normally occurs within 48 to 72 hours. The TFPP was observed prior to the baseline assessment period (BAP) and treatment period I in order to create analogous conditions. Both preparations were administered mid-meal and the content, timing and duration of meals was specified. Twenty-four hour faecal samples were collected for the last 5 days of each 7 day assessment period and analysed for fat content. The results of the study are summarized below:

Results
Primary objective:

Table 1: Mean pharmacodynamic parameters of baseline corrected faecal fat excretion (ΔFFE [g/24h]) obtained on day 7

	Test ΔFFE [g/24h] (n=20)	**Reference ΔFFE [g/24h] (n=20)**
Arithmetic Mean (SD)	27.59 (5.58)	27.62 (4.69)
Median (min, max)	28.50 (17.30, 36.30)	26.85 (18.50, 35.10)
Geometric Mean (CV%)	27.01 (21.85)	27.23 (17.62)

The similarity of both treatment effects was confirmed by the statistical evaluation which resulted in a point estimate of 99% and a 95% confidence interval of 91 to 108% for the comparison of Test vs. Reference [Table 2].

Table 2: Parametric point estimates and 95% confidence intervals determined for ΔFFE Treatment; Test vs. Reference

	Point estimate (%)	**95% Confidence interval (%)**	**CV_{ANOVA} (%)**
$\Delta FFE_{TREATMENT}$	99	91-108	12.4

With a CV_{ANOVA} of 12.4% a low intra-individual variability was determined.

Secondary Objectives:
Measurable plasma concentrations of orlistat were determined in 12 (10%) out of 120 of the Test and Reference samples. Most subjects had only one sample with quantifiable plasma concentrations of orlistat so no statistical evaluation was performed. C_{max} values were very low but similar for both products (geometric mean C_{max} 0.26ng/ml after Test and 0.31ng/ml after Reference).

Measurable plasma concentrations of the M1 metabolite were detected in all available plasma samples - 120 (100%) for the Test and 120 (100%) for the Reference formulation and a pharmacokinetic evaluation could be performed [Table 3].

Table 3: Pharmacokinetic parameters for M1 obtained on day 7 after oral multiple dose administration (non-transformed values; arithmetic mean ± standard deviation)

Treatment	**AUC_{0-t}** ng/ml/h	**C_{max}** ng/ml	**C_{last}** ng/ml	**t_{max}** h
Test (n=20)	212.90 (73.44)	48.16 (15.78)	36.92 (13.31)	0.00 (0.00, 6.00)
Reference (n=20)	195.91 (63.29)	45.47 (14.02)	35.17 (13.10)	4.00 (0.00, 6.08)
***Ratio (90% CI)**	108 (97-120)	105 (95-117)		

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
C_{max} Maximum plasma concentration
C_{last} Last observed concentration at time t
t_{max} Time until Cmax is reached
**ln-transformed values*

Geometric mean C_{max} values were comparable for both products with 45.57ng/ml for Test and 43.34ng/ml for Reference. This resulted in a point estimate of 105% (90% confidence interval 95% to 117%). The result was similar for $AUC_{0-tlast}$ with geometric mean values of 201.02h*ng/ml (Test) and 186.38h*ng/ml (Reference); the point estimate was 108% (90% CI 97 to 120%). Systemic exposure determined by M1 plasma concentrations fell within the common acceptance criteria for bioequivalence decisions. The measured difference in plasma M1 exposure [M1 T/R ratio (90% CI) for AUC=108% (97-120); 105% (95-117) for C_{max}] is unlikely to result in an increased incidence or severity of adverse events.

The mean plasma concentration versus time profiles for M1 showed that, within the dosing interval, the terminal elimination phase was not reached and, therefore, all PK parameters based on λ_z were not calculated.

Triglyceride serum concentrations vs. time curves were similar for both treatments and differed from the baseline period over the course of a single day.

All 20 volunteers (100%) reported a total of 115 adverse events (AEs) during the study which resolved completely, 57 during Test and 58 during Reference treatment. All 115 AEs (100%) were considered study drug related and 104 (90%) were within the gastrointestinal disorders System Order Class. No serious adverse events were reported. The safety and tolerability of the Test and Reference products were very similar.

IV.4 Clinical Efficacy

The clinical efficacy of orlistat is well-known. With the exception of the data from the above study, no new clinical efficacy data were submitted and none were required.

IV.5 Clinical Safety

With the exception of the data from the therapeutic equivalence study, no new clinical safety data were submitted and none were required. The safety data collected during the study showed that the test and reference product had a comparable tolerability. No new or unexpected safety concerns arose during the study. The proposed product has shown equivalence to the reference product such that the safety can be expected to be equivalent to the marketed Xenical 120mg capsules, hard (Roche Registration Limited, UK).

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Orlistat 120 mg Capsules, hard.

The MAH identified the following as safety concerns:

Summary of safety concerns	
Important identified risks	• Pancreatitis • Oxalate nephropathy • Gastrointestinal events • Hypersensitivity reactions • Hypoglycaemia • Drug interactions with anticoagulants, ciclosporin, amiodarone, fat soluble vitamins and acarbose • Hepatobiliary events
Important potential risks	• Misuse/off-label use in patients with BMI<28kg/m^2, children, and in patients with eating disorders • Drug interactions with levothyroxine, anticonvulsants and antiretrovirals • Failure of oral contraception
Missing information	• Hepatic and renal impairment • Use during pregnancy • Children less than 12 years of age and elderly patients • Exposure of infants through lactation

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns. This is satisfactory.

IV.7 Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

V. USER CONSULTATION

A package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the pack leaflet was English.

The results show that the package leaflet meets the criteria for readability as set out in the guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Orlistat 120 mg Capsules, hard are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type. As the pharmacokinetics, pharmacodynamics and toxicology of orlistat are well-known, no additional data were required.

EFFICACY
With the exception of the data submitted in the therapeutic equivalence study, no new clinical data were submitted and none are required for this type of application.

Therapeutic equivalence has been demonstrated between the proposed product Orlistat 120 mg Capsules, hard and the reference product Xenical 120 mg capsules, hard (Roche Registration Limited, UK).

SAFETY
The safety profile of orlistat is well-known. With the exception of the safety data generated during the therapeutic study, no new safety data were submitted and none are required for this application. No new or unexpected safety issues arose during the study. The proposed product has shown equivalence to the reference product such that the safety can be expected to be equivalent to the already licensed and marketed Xenical 120mg capsules, hard (Roche Registration Limited, UK).

BENEFIT/RISK ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with orlistat is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is therefore considered to be positive.

RECOMMENDATION
The grant of a Marketing Authorisation is recommended.

Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

(Type IB/II variations, PSURs, commitments)

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)