Public Assessment Report

Decentralised Procedure

Orlistat 120 mg hard capsules

(Orlistat)

Procedure No: UK/H/6016/001/DC

UK Licence No: PL 42357/0172

Amneal Pharma Europe Ltd.
LAY SUMMARY

Orlistat 120 mg hard capsules 
(Orlistat, hard capsule, 120 mg).

This is a summary of the Public Assessment Report (PAR) for Orlistat 120 mg hard capsules (PL 42357/0172; UK/H/6016/001/DC). It explains how Orlistat 120 mg hard capsules, were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use Orlistat 120 mg hard capsules.

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

The product will be referred to as Orlistat throughout the remainder of this PAR.

What is Orlistat and what is it used for?
Orlistat is a ‘hybrid generic medicine’. This means that it is similar to a ‘reference medicine’ containing the same active substance, already authorised in the European Union (EU), called Xenical 120 mg capsules, hard (Roche Registration Limited, UK).

Orlistat is indicated in the treatment of obesity in conjunction with a low calorie intake diet.

How does Orlistat work?
This medicine contains the active substance orlistat. It works in the patient’s digestive system to block about one-third of the fat in the food they eat from being digested.

Orlistat attaches to the enzymes in the digestive system (lipases) and blocks them from breaking down some of the fat the patient has eaten during their meal. The undigested fat cannot be absorbed and is eliminated by the body.

How is Orlistat used?
The pharmaceutical form of this medicine is a hard capsule and the route of administration is oral (by mouth).

The patient must always use this medicine exactly as their doctor has told them. The patient must check with their doctor or pharmacist if they are not sure.

The usual dose of Orlistat 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 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. This means the patient will usually take one capsule at breakfast time, one capsule at lunch time and one capsule at dinner time. To gain optimal benefit, the patient should avoid the intake of food containing fat between meals, such as biscuits, chocolate and savoury snacks.

Orlistat only works in the presence of dietary fat. Therefore, if the patient misses a main meal or if they have a meal containing no fat, Orlistat should not be taken.
The patient should tell their doctor if, for any reason, they have not taken their medicine exactly as prescribed. Otherwise, the patient’s doctor may think that it was not effective or well tolerated and may change their treatment unnecessarily.

The patient’s doctor will discontinue the treatment with Orlistat after 12 weeks if they have not lost at least 5% of their body weight as measured at the start of treatment with Orlistat.

Orlistat has been studied in long-term clinical studies of up to 4 years duration.

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

This medicine can only be obtained with a prescription.

**What benefits of Orlistat have been shown in studies?**

As Orlistat is 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.

**What are the possible side effects of Orlistat?**

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

The patient should tell their doctor or pharmacist as soon as possible if they do not feel well while they are taking Orlistat.

The majority of unwanted effects related to the use of Orlistat 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 their recommended diet.

**Very common side effects** (may affect more than 1 in 10 people):

- headache
- abdominal pain/discomfort
- urgent or increased need to open the bowels
- flatulence (wind) with or without discharge
- oily discharge, oily or fatty stools
- liquid stools
- low blood sugar levels (experienced by some people with type 2 diabetes)
- upper respiratory infections
- flu (influenza)

**Common** (may affect up to 1 in 10 people):

- rectal pain/discomfort
- soft stools
- incontinence (stools)
- bloating (experienced by some people with type 2 diabetes)
- tooth/gum disorder
- irregularity of menstrual cycle
- tiredness
- anxiety
- lower respiratory infections
- urinary tract infections

For the full list of all side effects reported with Orlistat, see section 4 of the package leaflet available on the MHRA website.

For the full list of restrictions, see the package leaflet.

**Why was Orlistat approved?**
The MHRA decided that the benefits of Orlistat outweigh the identified risks and it was recommended that it be approved for use.

**What measures are being taken to ensure the safe and effective use of Orlistat?**
A risk management plan (RMP) has been developed to ensure that Orlistat is 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 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**
Spain and the UK agreed to grant a Marketing Authorisation for Orlistat on 01 June 2016. A Marketing Authorisation was granted in the UK on 21 June 2016.

The full PAR for Orlistat follows this summary.

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

This summary was last updated in October 2016.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Orlistat (PL 42357/0172; UK/H/6016/001/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.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Spain as Concerned Member State (CMS). The application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, as a hybrid application. The reference medicinal product for this application is 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.

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.

To support the application, a single pharmacodynamics study using faecal fat excretion as a surrogate parameter to demonstrate therapeutic equivalence of Orlistat 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 a hybrid application for a product similar to 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 manufacturer 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 on 01 June 2016. After a subsequent national phase, a licence was granted in the UK on 21 June 2016.
II QUALITY ASPECTS

II.1 Introduction
Each hard capsule contains 120 mg orlistat. Other ingredients consist of the pharmaceutical excipients:

Capsule content:
Cellulose, microcrystalline PH 112 (E460), sodium starch glycolate (type A), colloidal anhydrous silica and sodium laurilsulfate.

Capsule shell:
Gelatin, titanium dioxide (E171) and indigo carmine (E132).

Orlistat is available in aluminium (Al)/polyvinyl chloride (PVC)/ polyvinylidene chloride (PVdC) blisters in pack sizes of 21, 42 and 84 hard capsules. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
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

Structural formula:

![Structural formula of Orlistat](image)

Molecular formula: $C_{29}H_{53}NO_5$
Molecular mass: 495.73 g/mol
Appearance: 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.

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 for the active substance. 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 analyses data are provided that comply with the proposed specification. 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 food.

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.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. 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. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Do not store above 25°C. Store in the original package in order to protect from light and moisture.’

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.
III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of orlistat are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant’s non-clinical expert report 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 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Orlistat is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary. However an environmental risk assessment has been provided. The conclusion was that Orlistat is unlikely to pose a risk to the environment.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted or necessary for this type of application.

There are no objections to the approval of this application from a non-clinical viewpoint.

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 a weak lipase inhibitory activity and low plasma levels at therapeutic doses; they are considered to be pharmacologically inconsequential. The applicant measured plasma levels of orlistat and M1 to determine systemic exposure as a component of the safety assessment. The levels of the metabolite M3 are reported to be marginally higher than M1 (108ng/ml and 26ng/ml respectively). The data presented is acceptable.

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 \( \Delta \text{FFE}_{\text{treatment}} \), 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 \( \Delta \text{FFE} \)-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 summarised below:

Results

Primary objective:

Table 1: Mean pharmacodynamic parameters of baseline corrected faecal fat excretion \(\Delta \text{FFE [g/24h]}\) obtained on day 7

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Test (\Delta \text{FFE [g/24h]}) (n=20)</th>
<th>Reference (\Delta \text{FFE [g/24h]}) (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arithmetic Mean (SD)</td>
<td>27.59 (5.58)</td>
<td>27.62 (4.69)</td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>28.50 (17.30, 36.30)</td>
<td>26.85 (18.50, 35.10)</td>
</tr>
<tr>
<td>Geometric Mean (CV%)</td>
<td>27.01 (21.85)</td>
<td>27.23 (17.62)</td>
</tr>
</tbody>
</table>

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 \(\Delta \text{FFE}\) Treatment; Test vs. Reference

<table>
<thead>
<tr>
<th>(\Delta \text{FFE}_{\text{TREATMENT}})</th>
<th>Point estimate (%)</th>
<th>95% Confidence interval (%)</th>
<th>CV\text{ANOVA} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>99</td>
<td>91-108</td>
<td>12.4</td>
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</table>

With a CV\text{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. \(C_{\text{max}}\) values were very low but similar for both products (geometric mean \(C_{\text{max}}\) 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)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>(\text{AUC}_{0-t}) ng/ml/h</th>
<th>(C_{\text{max}}) ng/ml</th>
<th>(C_{\text{last}}) ng/ml</th>
<th>(t_{\text{max}}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (n=20)</td>
<td>212.90 (73.44)</td>
<td>48.16 (15.78)</td>
<td>36.92 (13.31)</td>
<td>0.00 (0.00, 6.00)</td>
</tr>
<tr>
<td>Reference (n=20)</td>
<td>195.91 (63.29)</td>
<td>45.47 (14.02)</td>
<td>35.17 (13.10)</td>
<td>4.00 (0.00, 6.08)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>108 (97-120)</td>
<td>105 (95-117)</td>
<td></td>
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</tbody>
</table>

\(\text{AUC}_{0-t}\) Area under the plasma concentration curve from administration to last observed concentration at time \(t\).

\(C_{\text{max}}\) Maximum plasma concentration

\(C_{\text{last}}\) Last observed concentration at time \(t\)

\(t_{\text{max}}\) Time until \(C_{\text{max}}\) is reached

*ln-transformed values
Geometric mean $C_{\text{max}}$ 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$_{0-\text{tlast}}$ 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 $C_{\text{max}}$] 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 $\lambda_z$ 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 (RMP)**
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Gastrointestinal events</th>
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<tbody>
<tr>
<td></td>
<td>Hypersensitivity reactions</td>
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<td></td>
<td>Hepatobiliary events</td>
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<td>Effect on coagulation parameters</td>
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<td></td>
<td>Hypoglycaemia</td>
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<td></td>
<td>Pancreatitis</td>
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<td></td>
<td>Oxalate nephropathy and renal insufficiency</td>
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<td></td>
<td>Hypothyroidism / reduced control of hypothyroidism</td>
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<tr>
<td></td>
<td>Convulsions / reduced control of epilepsy</td>
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<tr>
<td></td>
<td>Drug interactions with ciclosporin, acarbose, amiodarone, fat soluble vitamins, and anti-retrovirals</td>
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<thead>
<tr>
<th>Important potential risks</th>
<th>Failure of oral contraception</th>
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<tr>
<td></td>
<td>Drug interactions with anticoagulants, antiepileptic drugs, levothyroxine/iodine salts, and antidepressant and antipsychotic drugs.</td>
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<tr>
<th>Missing information</th>
<th>Use in patients with hepatic impairment</th>
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<tr>
<td></td>
<td>Use in patients with renal impairment</td>
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<tr>
<td></td>
<td>Use during pregnancy</td>
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<td></td>
<td>Use during lactation</td>
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<td></td>
<td>Use in children less than 12 years of age</td>
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</table>

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

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V User consultation

The 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 PIL 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

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 is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
<table>
<thead>
<tr>
<th>PAR Orlistat 120 mg hard capsules</th>
<th>UK/H/6016/001/DC</th>
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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 II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
</table>
