Public Assessment Report

Decentralised Procedure

Orlistat Mylan 60 mg capsules, hard

(Orlistat)

Procedure No: UK/H/5278/001/DC

UK Licence No: PL 04569/1359

Generics (UK) Limited (trading as Mylan)
LAY SUMMARY

Orlistat Mylan 60 mg capsules, hard
(orlistat, hard capsules, 60 mg)

This is a summary of the Public Assessment Report (PAR) for Orlistat Mylan 60 mg capsules, hard (PL 04569/1359; UK/H/5278/001/DC). It explains how Orlistat Mylan 60 mg capsules, hard was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Orlistat Mylan 60 mg capsules, hard.

For practical information about using Orlistat Mylan 60 mg capsules, hard, patients should read the package leaflet or contact their doctor or pharmacist.

What are Orlistat Mylan 60 mg capsules, hard and what are they used for?
The application for Orlistat Mylan 60 mg capsules, hard was submitted as a hybrid application. Assessment of the application concluded that the capsules are similar to a reference medicine containing the same active substance (orlistat). The company provided data to demonstrate the safety and efficacy of Orlistat Mylan 60 mg capsules, hard.

The reference medicine for Orlistat Mylan 60 mg capsules, hard is Xenical 120 mg capsules, hard.

Orlistat Mylan 60 mg capsules, hard are used for weight loss in adults aged 18 and over who are overweight, and have a body mass index (BMI) of 28 or above. Orlistat Mylan 60 mg capsules, hard should be used along with a reduced calorie, lower-fat diet.

How do Orlistat Mylan 60 mg capsules, hard, work?
The active ingredient (orlistat) in this medicine is designed to target fat in the patient’s digestive system. It stops about a quarter of the fat in the patient’s meals from being absorbed. This fat will pass out of the body in the patient’s stools. The patient may experience diet-related treatment effects (refer to section 4 of the package leaflet). It is therefore important that the patient commits to a lower-fat diet to manage these effects. If the patient follows this approach, the action of the capsules will assist the patient’s efforts by helping them to lose more weight compared to dieting alone. For every 2 kg (4 lb) the patient loses from dieting alone, Orlistat Mylan 60 mg capsules, hard can help the patient lose 1 kg (2 lb) more.

How are Orlistat Mylan 60 mg capsules, hard, used?
The pharmaceutical form of Orlistat Mylan 60 mg capsules, hard is a hard capsule and the route of administration is oral.

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

Use in adults 18 and over
• The recommended dose is one capsule, three times a day.
• Orlistat Mylan 60 mg capsules, hard should be taken just before, during or up to one hour after meals. This usually means one capsule at breakfast, lunch and dinner. The patient should make sure the three main meals are well balanced, reduced calorie, and lower-fat.
• If the patient misses a meal, or the meal contains no fat, a capsule should not be taken. Orlistat Mylan 60 mg capsules, hard does not work unless there is some fat in the meal.
• The patient should swallow the capsule whole with water.
• The patient must not take more than 3 capsules a day.
• The patient should eat lower-fat meals to reduce the chance of diet-related treatment effects (see section 4 of the package leaflet).
• The patient should try to be more physically active before starting to take the capsules. Physical activity is an important part of a weight loss programme. The patient should check with their doctor first if they have not exercised before.
• The patient should continue to be active while taking Orlistat Mylan 60 mg capsules, hard and after they stop taking it.

How long should Orlistat Mylan 60 mg capsules, hard be taken for?
• Orlistat Mylan 60 mg capsules, hard should not be taken for more than six months.

If the patient does not lose weight after taking Orlistat Mylan 60 mg capsules, hard for 12 weeks, the patient must see their doctor or pharmacist for advice.
The patient may need to stop taking Orlistat Mylan 60 mg capsules, hard.

• Successful weight loss is not just about eating differently for a short period of time, before reverting to the patient’s old habits. People who lose weight and maintain the loss make lifestyle changes, which include changes to what they eat and how active they are.

Orlistat Mylan 60 mg capsules, hard can be obtained without a prescription.

What benefits of Orlistat Mylan 60 mg capsules, hard have been shown in studies?
Because the application for Orlistat Mylan 60 mg capsules, hard was submitted as a hybrid application referring to Xenical 120 mg capsules, hard, results of a clinical study have been provided to support the efficacy of Orlistat Mylan 60 mg capsules, hard. The reference product used for the clinical study was Alli 60 mg capsules, which belongs to the same global marketing authorisation (GMA) as Xenical 120 mg capsules, hard.

What are the possible side effects of Orlistat Mylan 60 mg capsules, hard?
The most common side effects with Orlistat Mylan 60 mg capsules, hard (which may affect more than 1 in 10 people) are wind (flatulence), with or without oily spotting, sudden bowel movements, fatty or oily stools and soft stools.

For the full list of all side effects reported with Orlistat Mylan 60 mg capsules, hard, see section 4 of the package leaflet available on the MHRA website.

Why are Orlistat Mylan 60 mg capsules, hard, approved?
The MHRA decided that the benefits of Orlistat 60 mg capsules, hard are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Orlistat Mylan 60 mg capsules, hard?
A risk management plan (RMP) has been developed to ensure that Orlistat Mylan 60 mg capsules, hard, 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 Mylan 60 mg capsules, hard, 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 Mylan 60 mg capsules, hard.
The marketing authorisation for Orlistat Mylan 60 mg capsules, hard was granted on 03 September 2014.

The full PAR for Orlistat Mylan 60 mg capsules, hard, follows this summary.

For more information about treatment with Orlistat Mylan 60 mg capsules, hard, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in October 2014.
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   IV Overall conclusion and benefit/risk assessment

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### Module 1

#### Information about the initial procedure

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Orlistat Mylan 60 mg capsules, hard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of Application</td>
<td>Hybrid, Article 10 (3)</td>
</tr>
<tr>
<td>Active Substance</td>
<td>Orlistat</td>
</tr>
<tr>
<td>Form</td>
<td>Capsule, hard</td>
</tr>
<tr>
<td>Strength</td>
<td>60 mg</td>
</tr>
<tr>
<td>MA Holder</td>
<td>Generics (UK) Limited (trading as Mylan), Station Close, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States (CMS)</td>
<td>Czech Republic, Germany and Portugal</td>
</tr>
<tr>
<td>Procedure Number</td>
<td>UK/H/5278/001/DC</td>
</tr>
<tr>
<td>Timetable</td>
<td>End of procedure (Day 210) – 06 August 2014</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

The following text is the approved label text for the product. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING LABEL

1. NAME OF THE MEDICINAL PRODUCT

Orlistat 60 mg capsules, hard
orlistat

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule, hard contains 60 mg orlistat.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard
42 capsules, hard
84 capsules, hard
90 capsules, hard
120 capsules, hard

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP.
Once opened, use within 94 days.
9. **SPECIAL STORAGE CONDITIONS**

Do not store above 25°C.
Keep the bottle tightly closed in order to protect from moisture.

10. **SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

11. **NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Mylan, Potters Bar, Hertfordshire, EN6 1TL, United Kingdom

12. **MARKETING AUTHORISATION NUMBER(S)**

PL 04569/1359

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

OTC

15. **INSTRUCTIONS ON USE**

Weight loss aid.

Adults, aged 18 or over, who are overweight (BMI of 28 or above).

16. **INFORMATION IN BRAILLE**

Orlistat 60 mg capsules, hard
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Orlistat 60 mg capsules, hard
orlistat

2. STATEMENT OF ACTIVE SUBSTANCE

Each capsule, hard contains 60 mg orlistat.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Capsule, hard
42 capsules, hard
84 capsules, hard
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Do not store above 25°C.
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PL 04569/1359

13. **BATCH NUMBER**

Lot:

14. **GENERAL CLASSIFICATION FOR SUPPLY**

OTC

15. **INSTRUCTIONS ON USE**

For adults with a BMI of 28 or above.

Weight loss aid.

Can help you lose more weight than dieting alone.
Orlistat is used for weight loss alongside reduced calorie, lower-fat meals in overweight (BMI 28 or above) adults, aged 18 or over.

Orlistat is clinically proven to help you lose more weight than dieting alone. The capsules work only in your digestive system to stop about a quarter of the fat in your meals from being absorbed. This fat passes out of your body and may cause changes to your bowel movements. Eat lower-fat meals to help manage these effects.

To see if your BMI is 28 or above, find your height on the chart. If you weigh less than the weight shown for your height, your BMI is below 28 - do not use Orlistat.
<table>
<thead>
<tr>
<th>Height</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.50 m</td>
<td>63 kg</td>
</tr>
<tr>
<td>1.55 m</td>
<td>67.25 kg</td>
</tr>
<tr>
<td>1.60 m</td>
<td>71.75 kg</td>
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<tr>
<td>1.65 m</td>
<td>76.25 kg</td>
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<td>85.75 kg</td>
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<td>90.75 kg</td>
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<tr>
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<td>95.75 kg</td>
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<tr>
<td>1.90 m</td>
<td>101 kg</td>
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</table>

<table>
<thead>
<tr>
<th>Height</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>4' 10&quot;</td>
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<td>10 st 3 lbs</td>
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<td>11 st 9 lbs</td>
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<td>5' 6&quot;</td>
<td>12 st 5 lbs</td>
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<td>5' 8&quot;</td>
<td>13 st 2 lbs</td>
</tr>
<tr>
<td>5' 10&quot;</td>
<td>13 st 13 lbs</td>
</tr>
<tr>
<td>6' 0&quot;</td>
<td>14 st 10 lbs</td>
</tr>
<tr>
<td>6' 2&quot;</td>
<td>15 st 8 lbs</td>
</tr>
</tbody>
</table>

Being overweight increases your risk of developing several serious health problems such as diabetes and heart disease. You should see your doctor for a check-up.

Do not use:

- if you are under 18 years old.
- if you are pregnant or breast-feeding.
- if you are taking ciclosporin.
- if you are taking warfarin or any other medicines used to thin the blood.
- if you are allergic to orlistat or any of the ingredients.
- if you have cholestasis (condition where the flow of bile from the liver is blocked).
- if you have problems absorbing food (chronic malabsorption syndrome).

Talk to your doctor before taking Orlistat:

- if you are taking amiodarone for heart rhythm problems.
- if you are taking a medicine for diabetes.
- if you are taking a medicine for epilepsy.
- if you have kidney disease.
- if you are taking a thyroid medicine (levothyroxine).
- If you are taking medicines for HIV.

Talk to your doctor or pharmacist when taking Orlistat:

- if you are taking a medicine for high blood pressure.
- if you are taking a medicine for high cholesterol.

How to use

- take one capsule whole with water, three times a day with each main meal containing fat.
- do not take more than three capsules a day.
- you should take a multivitamin (containing vitamins A, D, E and K) once a day, at bedtime.
- you should not take Orlistat for more than six months.

16. INFORMATION IN BRAILLE

Orlistat 60 mg capsules, hard
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Orlistat Mylan 60 mg capsules, hard (PL 04569/1359; UK/H/5278/001/DC) could be approved. The product is a pharmacy (P) medicine available from pharmacies and is indicated for weight loss in adults who are overweight (body mass index, BMI, ≥28 kg/m²) and should be taken in conjunction with a mildly hypocaloric lower-fat diet.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Czech Republic, Germany and Portugal as Concerned Member States (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 capsule hard, which was originally granted a licence on 29 July 1998 to Roche Registration Ltd. The reference product used for the clinical study was Alli 60 mg capsules, which belongs to the same global marketing authorisation (GMA) as Xenical 120 mg capsules, hard.

Orlistat is a non-systemic, anti-obesity medicine which 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.

One multiple-dose bioequivalence study with pharmacodynamic endpoints was submitted to support this application, comparing the test product Orlistat Mylan 60mg capsules, hard (Mylan Laboratories Limited) and the reference product Alli 60 mg capsules (Glaxo Group Limited, France). The bioequivalence study report provides the statement that the study was conducted in accordance with the International Conference on Harmonisation of Technical Requirement for Registration of Pharmaceuticals for Human Use (ICH), Guidance for Good Clinical Practices (GCP), Schedule Y, ICMR guidelines, WMA Declaration of Helsinki and EMA guidelines.

With the exception of the bioequivalence study, no new non-clinical or clinical data were submitted, which is acceptable given that this application was based on the product being shown to be equivalent 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.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 06 August 2014. After a subsequent national phase, a licence was granted in the UK on 03 September 2014.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name(s) of the product in the Reference Member State</th>
<th>Orlistat Mylan 60 mg capsules, hard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (INN)</td>
<td>Orlistat</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antiobesity preparations, excluding diet products, peripherally acting (A08D AB01)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Hard capsule; 60 mg</td>
</tr>
<tr>
<td>Reference number for the Mutual Recognition Procedure</td>
<td>UK/H/5278/001/DC</td>
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<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States</td>
<td>Czech Republic, Germany and Portugal</td>
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<td>Marketing Authorisation Number(s)</td>
<td>PL 04569/1359</td>
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<tr>
<td>Name and address of the authorisation holder</td>
<td>Generics (UK) Limited (trading as Mylan), Station Close, Potters Bar Hertfordshire, EN6 1TL United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Orlistat

Chemical name: L-Leucine, N-formyl, 1-[(3-hexyl-4-oxo-2-oxetanyl)methyl]dodecyl ester, [2S-2α(R*),3β]- N-Formyl-L-leucine, ester with (3S,4S)-3-hexyl-4-[(2S)-2-hydroxy-tridecyl]-2-oxetanone.

Structural formula:

Molecular formula: C_{29}H_{53}NO_{5}
Molecular mass: 495.73
Appearance: White to off white powder or crystalline powder.
Solubility: Freely soluble in chloroform, very soluble in methanol and alcohol and insoluble in water

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.

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.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.

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.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients mannitol (E421), crospovidone, sodium starch glycolate (Type A), sodium laurilsulfate, povidone (K30), talc, Brilliant Blue FCF (E133), erythrosine (E127), titanium dioxide (E171), gelatin and printing ink (comprised of shellac, propylene glycol, black iron oxide (E172) and potassium hydroxide).
P. Medicinal Product
All excipients comply with their respective European Pharmacopoeia monographs with the exception of the colourings Brilliant Blue FCF (E133) and erythrosine (E127) which are controlled to suitable in-house specifications and black iron oxide (E172) which is in compliance with the National Formulary (NF). The colourings Brilliant Blue FCF (E133), erythrosine (E127) and black iron oxide (E172) are in compliance with current EEC directives concerning the use of colouring agents. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

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 minimising the risk of transmission of Bovine Spongiform Encephalopathy/Transmissible Spongiform Encephalopathies (BSE/TSE).

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, stable capsule containing 60 mg orlistat that was comparable in performance to the originator product Alli 60 mg capsules (Glaxo Group Limited, France). A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution and impurity profiles have been provided for the proposed and originator product.

Manufacturing Process
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 pilot scale and shown satisfactory results. The Marketing Authorisation Holder (MAH) has committed to perform process validation on future commercial scale batches.

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.

Container-Closure System
The finished product is packaged in high density polyethylene (HDPE) bottles with polypropylene cap and desiccant containing 42, 84, 90 or 120 capsules.

Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations (Regulation (EU) No. 10/2011) concerning materials in contact with foodstuff.

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 for the unopened bottle which reduces to 94 days once the bottle has been opened.
with the storage conditions ‘Do not store above 25°C. Keep the bottle tightly closed in order to protect from moisture.’

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

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

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labels
The SmPC, PIL and labels are satisfactory from a pharmaceutical perspective.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The leaflet conforms to the requirements. The test shows that the patients/users are able to act upon the information that the leaflet contains.

Marketing Authorisation Application (MAA) Form
The MAA form is satisfactory.

Expert Report (Quality Overall Summary)
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of orlistat are well-known, no new non-clinical studies are required and none have been provided.

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.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application was submitted as a hybrid application referring to an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

There are no objections to the approval of this product from a non-clinical viewpoint.
III.3 CLINICAL ASPECTS
Pharmacokinetics
The clinical pharmacology of orlistat is well-known. No new pharmacodynamic or pharmacokinetic data was required for this application.

In support of this application, the Marketing Authorisation holder has submitted the following bioequivalence study:

A pivotal, open label, crossover, randomised, multiple dose, in vivo bioequivalence study with pharmacodynamic (PD) endpoints to compare the test product Orlistat Mylan 60mg capsules, hard (Mylan Laboratories Limited) versus the reference product Alli 60 mg capsules (Glaxo Group Limited, France) in healthy adult human volunteers under fed conditions.

The subjects were administered a single dose (one 60mg orlistat capsule) of either the test or the reference product with 240 ml of water, three times a day for 9 consecutive days of all the treatment periods.

In each period, subjects were given food on check-in day. Standard breakfast, lunch and dinner at 8:00, 12:00 and 20:00 hours respectively and snacks were given at 16:00 hours during all 5 days of the run-in period and 9 days of the treatment period, during each arm of the study.

In each arm of the study, 20.0 to 11.5 hours before the first day of the 5 days run-in period, the subjects stayed in the facility until 8:00 hours on day 10 of each treatment. The washout period was 10 days.

Subjects were dosed 10 minutes after the first bite of each meal. Two samples of each meal and unconsumed meal by the subjects (breakfast, lunch, snacks and dinner) were taken during the 5 days run-in period and 9 days of the treatment period. Fecal samples were collected on all 5 days of the run-in period and 9 days of the treatment periods. The pharmacokinetic results are presented below:
### Pharmacodynamic Parameters of Orlistat:

<table>
<thead>
<tr>
<th>Pharmacodynamic Parameters</th>
<th>Test Formulation (A)</th>
<th>Reference Formulation (B)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Geometric Mean (%CV)</td>
<td>Arithmetic Mean ± SD</td>
</tr>
<tr>
<td>Fat Ingested (gm) (Day 3 - 5) Run-in period</td>
<td>115.70 (4.37)</td>
<td>116.11 (4.39)</td>
</tr>
<tr>
<td></td>
<td>115.81 ± 5.06</td>
<td>116.22 ± 5.11</td>
</tr>
<tr>
<td>Fat Ingested (gm) (Day 9 - 14) Treatment period</td>
<td>114.48 (1.04)</td>
<td>114.11 (1.61)</td>
</tr>
<tr>
<td></td>
<td>114.49 ± 1.19</td>
<td>114.13 ± 1.84</td>
</tr>
<tr>
<td>Fat Excreted (gm) (Day 3 - 5) Run-in period</td>
<td>- (44.61)</td>
<td>- (42.87)</td>
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<td></td>
<td>20.27 ± 9.04</td>
<td>21.84 ± 9.36</td>
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<tr>
<td>Fat Excreted (gm) (Day 9 - 14) Treatment period</td>
<td>31.16 (35.63)</td>
<td>31.60 (32.65)</td>
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<td>33.38 ± 11.89</td>
<td>33.66 ± 10.99</td>
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<tr>
<td>Fat Excreted After Baseline correction</td>
<td>11.81 (47.69)</td>
<td>- (53.58)</td>
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<td>13.11 ± 6.25</td>
<td>11.83 ± 6.34</td>
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<tr>
<td>%FFE24 (Day 3 - 5) Run-in period</td>
<td>- (45.11)</td>
<td>- (41.66)</td>
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<td>17.63 ± 7.95</td>
<td>18.77 ± 7.82</td>
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<tr>
<td>%FFE24 (Day 9 - 14) Treatment period</td>
<td>27.22 (35.23)</td>
<td>27.77 (32.47)</td>
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<td>29.14 ± 10.27</td>
<td>29.55 ± 9.59</td>
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<tr>
<td>%FFE24 After Baseline correction</td>
<td>10.44 (45.96)</td>
<td>- (51.64)</td>
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<td>11.51 ± 5.29</td>
<td>10.78 ± 5.57</td>
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"-" = Geometric mean could not calculated.

Test formulation (A)  Orlistat Mylan 60 mg capsules, hard (Mylan Laboratories Limited)
Reference formulation (B) Alli 60 mg capsules (Glaxo Group Limited, France).
Intra subject %CV  Intra-subject coefficient of variation
SD  Standard deviation
For the parameter % FFE24, 90% confidence intervals are within the range of 80.00% to 125.00% set by the protocol. Moreover, 90% confidence intervals for the parameter fat ingested and fat excreted are also within the range of 80.00% to 125.00%, except for fat excreted after baseline correction. For fat excreted after baseline correction, the upper limit is 125.99 which is a little outside the upper limit of 125.00%.

The results show that the amount of FFE is within the equivalence limits set by the protocol. However, MHRA advised that it would not be appropriate to extrapolate the use of 90% confidence intervals of 80.00-125.00%, as used in bioequivalence studies to this situation. The marketing authorisation holder (MAH) has justified the use of FFE and also why a bioequivalence model has been used rather than a therapeutic equivalence model with a justified delta. The MAH has also justified why the unadjusted FFE comparison is more appropriate than the baseline adjusted one and also provided baseline corrected data at a 95% confidence interval (refer to summary table below).

The use of an open label study was also advised against by the MHRA; however the MAH has satisfactorily discussed why the use of such a study did not affect the results.
The 95% confidence intervals for %FFE24 (% fecal fat excretion over 24 hours) for test versus reference product for orlistat are within the equivalence limits set by the protocol (80.00-125.00%). Based on the submitted bioequivalence study and after baseline correction, Orlistat Mylan 60mg capsules, hard (Mylan Laboratories Limited) is considered pharmacodynamically equivalent with Alli 60 mg capsules (Glaxo Group Limited, France).

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for an application of this type.

**Efficacy**
No new efficacy data were submitted and none were required for an application of this type.

**Safety**
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for this type of application. No new or unexpected safety issues were highlighted by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPC, PIL and labels are acceptable. The SmPC is consistent with that for the originator product. The PIL is consistent with the SmPC and in line with current guidelines. The labelling is in line with current guidelines.

**MAA Form**
The MAA form is satisfactory.

**Clinical Overview**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for
pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

An acceptable Risk Management Plan has been provided. Routine risk minimisation is provided through the Summary of Product Characteristics and the Patient Information Leaflet and this is sufficient.

Conclusion
There are no objections to the approval of the product from a clinical view-point.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The quality characteristics of Orlistat Mylan 60mg 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 this type of application. The pharmacodynamic, pharmacokinetic and toxicological properties of orlistat are well-known.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for an application of this type.

Based on the submitted bioequivalence study with pharmacodynamic end points, Orlistat Mylan 60mg capsules, hard (Mylan Laboratories Limited) is considered pharmacodynamically equivalent with Alli 60 mg capsules (Glaxo Group Limited, France).

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for this type of application. As the safety profile of orlistat is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product, where appropriate.

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 is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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