Public Assessment Report

Decentralised Procedure

Atorvastatin 10 mg film-coated Tablets
Atorvastatin 20 mg film-coated Tablets
Atorvastatin 40 mg film-coated Tablets
Atorvastatin 80 mg film-coated Tablets

(atorvastatin calcium)

UK/H/1919, 2370, 2380/001-04/DC

UK licence numbers: PL 08553/0336-0339, 0365-0368, 0369-0372

Dr. Reddy’s Laboratories (UK) Limited
LAY SUMMARY
Atorvastatin 10 mg, 20 mg 40 mg and 80 mg film-coated Tablets
(atorvastatin calcium)

This is a summary of the public assessment report (PAR) for Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets (UK/H/1919/001-04/DC; PL 08553/0336-0339). The Marketing Authorisations for Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets (PL 08553/0365-0368 and 0369-0372; UK/H/2370 & 2380/001-04/DC) were cancelled on 18th August 2014 and 28th November 2012 respectively. These medicinal products will be referred to as Atorvastatin Tablets in the remainder of this summary, for ease of reading.

This summary explains how Atorvastatin Tablets were assessed and their authorisations recommended as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

For practical information about Atorvastatin Tablets, patients should read the package leaflets or contact their doctor or pharmacist.

What are Atorvastatin Tablets and what are they used for?
Atorvastatin Tablets are ‘generic medicines’. This means that Atorvastatin Tablets are similar to ‘reference medicines’ already authorised in the UK called Lipitor® 10 mg, 20 mg, 40 mg and 80 mg Tablets (Pfizer Ireland Pharmaceuticals; PL 16051/0001-0003 and 0005).

Atorvastatin Tablets are used to lower lipids known as cholesterol and triglycerides in the blood when a low fat diet and life style changes on their own have failed. Atorvastatin Tablets can also be used if a patient is at an increased risk of heart disease, even if the cholesterol levels are normal. Patients should maintain a standard cholesterol lowering diet during treatment.

How are Atorvastatin Tablets used?
Atorvastatin Tablets are taken by mouth. A whole tablet should be swallowed with water, and can be taken at any time of the day, with or without food.

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

Before starting treatment, the patient’s doctor will place the patient on a low-cholesterol diet, which should be maintained also during therapy with this medicine. The usual starting dose is 10 mg of atorvastatin once a day in adults and children aged 10 years or older. This may be increased if necessary by the patient’s doctor until the patient is taking the amount they need. The patient’s doctor will adapt the dose at intervals of 4 weeks or more. The maximum dose of atorvastatin is 80 mg once daily for adults and 20 mg once daily for children.

Atorvastatin Tablets can only be obtained on prescription from a doctor.
For further information on how Atorvastatin Tablets are used, refer to the Summaries of Product Characteristics or package leaflets available on the MHRA website.

**How do Atorvastatin Tablets work?**
Atorvastatin Tablets belong to a group of medicines called statins, which are lipid (fat) regulating medicines. Statins lower blood cholesterol (and triglycerides).

**How have Atorvastatin Tablets been studied?**
Because Atorvastatin Tablets are generic medicines, studies in patients have been limited to tests to determine that they are bioequivalent to the reference medicines, Lipitor® 10 mg, 20 mg, 40 mg and 80 mg Tablets. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

**What are the benefits and risks of Atorvastatin Tablets?**
As Atorvastatin Tablets are generic medicines that are bioequivalent to Lipitor® 10 mg, 20 mg, 40 mg and 80 mg Tablets, their benefits and risks are taken as being the same as those for Lipitor® 10 mg, 20 mg, 40 mg and 80 mg Tablets.

**Why are Atorvastatin Tablets approved?**
It was concluded that, in accordance with EU requirements, Atorvastatin Tablets have been shown to have comparable quality and are bioequivalent to Lipitor® 10 mg, 20 mg, 40 mg and 80 mg Tablets. Therefore, the view was that, as for Lipitor® 10 mg, 20 mg, 40 mg and 80 mg Tablets the benefit outweighs the identified risk.

**What measures are being taken to ensure the safe and effective use of Atorvastatin Tablets?**
A satisfactory pharmacovigilance system has been provided to ensure that Atorvastatin Tablets are used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics and the package leaflets for Atorvastatin Tablets, including the appropriate precautions to be followed by healthcare professionals and patients.

**Other information about Atorvastatin Tablets**
Germany, Italy, Romania and the UK agreed to grant Marketing Authorisations for Atorvastatin Tablets (PL 08553/0336-0339; UK/H/1919/001-04/DC) on 11th August 2010. Marketing Authorisations were granted in the UK on 9th September 2010.

The full PAR for Atorvastatin Tablets follows this summary. For more information about treatment with Atorvastatin Tablets, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in June 2015.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Dr. Reddy’s Laboratories (UK) Limited Marketing Authorisations for the medicinal products Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets (PL 08553/0336-9, 0365-0368 and 0369-0372, UK/H/1919, 2370, 2380/001-04/DC) on 9th September 2010. The Marketing Authorisations for Atorvastatin Tablets (PL 08553/0365-0368 and 0369-0372; UK/H/2370 & 2380/001-04/DC) were cancelled on 18th August 2014 and 28th November 2012 respectively.

The products are prescription-only medicines (POM).

These are generic applications for Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets, four strengths of atorvastatin, submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applications refer to the UK reference products, Lipitor® 10 mg, 20 mg, 40 mg and 80 mg Tablets (PL 16051/0001-3 and 0005 respectively), authorised to Pfizer Ireland Pharmaceuticals on 8th September 1997 (PL 16051/0001-3) and 15th August 2000 (PL 16051/0005). Lipitor® 10 mg, 20 mg and 40 mg Tablets are the innovator products. Lipitor® 10 mg, 20 mg, 40 mg and 80 mg Tablets have been authorised in the UK for more than 10 years; thus the period of data exclusivity has expired.

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase (ATC code: C10A A05), the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into VLDL and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolised primarily through the high affinity LDL receptor. Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets are indicated for hypercholesterolaemia and for the prevention of cardiovascular disease, as described below:

Hypercholesterolaemia:

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non-pharmacological measures is inadequate.

Atorvastatin is also indicated to reduce total C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.
Prevention cardiovascular disease

Prevention of cardiovascular events in patients estimated to have a high risk for a first cardiovascular event (see section 5.1 of SmPC), as an adjunct to correction of other risk factors.

No new non-clinical or clinical efficacy studies were conducted for these applications, which is acceptable given that the applications were for generic versions of products that have been licensed for over 10 years.

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profile of the test product, Atorvastatin 80 mg film-coated Tablets, to that of the reference product, Lipitor® 80 mg Tablets (PL 16051/0005, Pfizer Ireland Pharmaceuticals). The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture and assembly of these products. Evidence of compliance with GMP has been provided for the named manufacturing and assembly sites. 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 or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS considers that the pharmacovigilance system as described by the Marketing Authorisation Holder (MAH) fulfils the requirements and provides adequate evidence that the MAH has the services of a Qualified Person (QP) 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.

The Marketing Authorisation Holder has provided adequate justification for not submitting a Risk Management Plan (RMP). As the applications are for generic versions of already authorised reference products, for which safety concerns requiring additional risk minimisation have not been identified, a risk minimisation system is not considered necessary. The reference products have been in use for many years and the safety profile of the active is well-established.

The Marketing Authorisation Holder has provided adequate justification for not submitting an Environmental Risk Assessment (ERA). These were applications for generic products and there is no reason to conclude that marketing of these products will change the overall use pattern of the existing market. The products are not of genetic modification and neither have any of their excipients been genetically modified. There are no environmental concerns associated with the method of manufacture or formulation of the products.
II QUALITY ASPECTS
II.1 DRUG SUBSTANCE
Atorvastatin calcium (amorphous)

Nomenclature:
INN: Atorvastatin calcium
Chemical name: \([R-(R^*, R^*)]-2-(4-Fluorophenyl)-\beta,\delta,\text{-dihydroxy-5-(1-methylethyl)-3 phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt(2:1)}\)

Structure:

Molecular formula: \(C_{66}H_{68}CaF_2N_4O_{10}\)
Molecular weight: 1155.36 g/mol
CAS No: 134523-03-8
Physical form: White or off white powder.
Solubility: Soluble in dimethyl sulphoxide.
Polymorphism: Atorvastatin calcium exhibits polymorphism.

The active substance, atorvastatin calcium, is not the subject of a European Pharmacopoeia (Ph. Eur.) or British Pharmacopoeia (B.P.) 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 specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin.

Appropriate specifications have been provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specifications. Satisfactory Certificates of Analysis have been provided for any reference standards used by the active substance manufacturer during validation studies.

The active substance is stored in appropriate packaging. Specifications and Certificates of Analysis have been provided for the packaging materials used. The primary packaging, a low-density polyethylene (LDPE) bag, in direct contact with the active substance satisfies Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.
Appropriate stability data have been generated by the active substance manufacturer for active substance stored in the proposed commercial packaging. Based on the data, a retest period of 5 years has been set, and is satisfactory.

II.2 Medicinal Product Description and Composition
Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets are presented as white, oblong, film-coated tablets containing 10 mg, 20 mg, 40 mg, or 80 mg of the active ingredient atorvastatin, as atorvastatin calcium. Full descriptions of the markings of the individual tablets may be found by referring to the SmPCs or patient information leaflets.

Other ingredients consist of pharmaceutical excipients, namely butyl hydroxyanisole, ‘Prosolve SMCC90’ (consisting of microcrystalline cellulose and colloidal anhydrous silica), lactose monohydrate, sodium laurilsulfate, sodium hydrogen carbonate, crospovidone (Type A), magnesium stearate, and ‘Sinespum C’ (consisting of dimethicone 400, sucrose, sorbitan tristearate, macrogol 40 stearate, and 2-bromo-2-nitropropane-1,3-diol) making up the tablet core; and ‘Opadry OYL-28900 White’ making up the film-coating. Opadry OYL-28900 White consists of lactose monohydrate, hydroxypropyl methylcellulose (hypromellose 15 CP), titanium dioxide (E171) and macrogol/PEG 4000. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs, with the exception of Prosolve SMCC90, Sinespum C and Opadry OYL-28900 White, which comply with satisfactory in-house specifications. Satisfactory Certificates of Analysis have been provided for all excipients.

The magnesium stearate is of vegetable origin. The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption. None of the excipients are sourced from genetically modified organisms.

There were no novel excipients used and no overages.

Pharmaceutical development
Details of the pharmaceutical development of the medicinal products have been supplied and are satisfactory. The aim was to develop medicinal products bioequivalent and pharmaceutically equivalent to the reference products, Lipitor® 10 mg, 20 mg, 40 mg and 80 mg Tablets (PL 16051/0001-3 and 0005, Pfizer Ireland Pharmaceuticals).

Comparative dissolution and impurity data were provided for batches of the test products and appropriate reference products. The dissolution and impurity profiles were satisfactory.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the products and the method of manufacture. Process validation studies were conducted and validation data provided for all the product strengths and were satisfactory.

**Finished product specifications**

The finished product specifications are provided for both release and shelf-life and are satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. The test methods have been described and have been adequately validated, as appropriate. Satisfactory batch analysis data are provided for all strengths of the medicinal product. The data demonstrate that the batches are compliant with the proposed specifications. Certificates of Analysis have been provided for any reference standards used.

**Container Closure System**

The medicinal products are licensed for marketing in polyvinylchloride (PVC) / aluminium / polyamide / aluminium blister strips, which are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons in pack sizes of 10, 14, 28, 30, 50, 56 and 100 film-coated tablets (see SmPC for licensed pack sizes for individual licences). The MAH has stated that not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis for all packaging components used have been provided. All primary product packaging complies with EU legislation, Directive 2002/72/EC (as amended), and is suitable for contact with foodstuffs.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 2 years has been set, which is satisfactory. Storage instructions are ‘Store below 25°C’.

**Bioequivalence Study**

A bioequivalence study was presented comparing the test product, Atorvastatin 80 mg film-coated Tablets, to the reference product, Lipitor® 80 mg Tablets (PL 16051/0005, Pfizer Ireland Pharmaceuticals).

An evaluation of the bioequivalence study is found in the Clinical Aspects section.

**Quality Overall Summary**

A satisfactory quality overview is provided, and has been prepared by an appropriately qualified expert. The CV of the expert has been supplied.

**Product Information**

The approved Summaries of Product Characteristics (SmPCs), and Patient Information Leaflets (PILs) and labelling are satisfactory. The PIL user testing report has been evaluated and is accepted.
II.3 Discussion on chemical, pharmaceutical and biological aspects

All pharmaceutical issues have been resolved and the quality grounds for these applications are considered adequate. There are no objections to approval of Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets from a pharmaceutical point of view.
III NON-CLINICAL ASPECTS
Specific non-clinical studies have not been performed, which is acceptable considering that these are applications for generic versions of products that have been licensed for more than 10 years. The non-clinical overview provides a satisfactory review of the pharmacodynamic, pharmacokinetic, and toxicological properties of atorvastatin calcium, a widely used and well-known active substance. The CV of the non-clinical expert has been supplied. For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator medicinal products, Lipitor® 10 mg, 20 mg and 40 mg Tablets (Pfizer Ireland Pharmaceuticals).

There are no objections to approval of Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets from a non-clinical point of view.
IV CLINICAL ASPECTS

Hypercholesterolaemia:

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in patients with primary hypercholesterolaemia including familial hypercholesterolaemia (heterozygous variant) or combined (mixed) hyperlipidaemia (corresponding to Types IIa and IIb of the Fredrickson classification) when response to diet and other non-pharmacological measures is inadequate.

Atorvastatin is also indicated to reduce total C and LDL-C in patients with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

Prevention cardiovascular disease

Prevention of cardiovascular events in patients estimated to have a high risk for a first cardiovascular event (see section 5.1 of SmPC), as an adjunct to correction of other risk factors.

The indications are consistent with those for the reference products and are satisfactory.

POSOLOGY AND METHOD OF ADMINISTRATION

Full details concerning the posology are provided in the SmPCs. The posology is consistent with that for the reference products and is satisfactory.

TOXICOLOGY

The toxicology of atorvastatin calcium is well known. No new data have been submitted and none are required for applications of this type.

CLINICAL PHARMACOLOGY

The clinical pharmacology of atorvastatin calcium is well known. With the exception of the bioequivalence study, no new pharmacodynamic or pharmacokinetic data are supplied and none are required for these applications.

Pharmacokinetics – bioequivalence study

The applications are supported by the bioequivalence study presented by the applicant comparing the pharmacokinetic profiles of Atorvastatin 80 mg film-coated Tablets (test) and Lipitor® 80 mg film-coated tablets - Pfizer Ireland Pharmaceuticals (reference). The study was of an appropriate design and was conducted to principles of Good Clinical Practice (GCP). Certificates of Analysis have been provided for the test and reference products. The use of the 80 mg strength only for the bioequivalence study has been adequately justified.

This was a comparative, controlled, balanced, randomised, two-period, two sequence, two-way, single-dose crossover bioequivalence study conducted in 72 healthy adult
human subjects under fasting conditions. Following an overnight fast of 10 hours, a single dose of the investigational products was administered orally, with water, to each subject in each period. A satisfactory washout period of 14 days was maintained between the two dosing days in each group.

Blood samples were taken pre-dose (0.0) and at specified time points up to 72.0 hours after administration of test or reference product. Plasma levels of atorvastatin were detected by a validated HPLC-MS/MS analytical method.

The primary pharmacokinetic parameters for this study were \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \). Bioequivalence of the test product versus the reference product was concluded if the 90% Confidence Intervals (CI) fell within the acceptance range, 0.80-1.25 (80.00%-125.00%), for log-transformed \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \).

Results:
72 subjects were enrolled in the study, and all 72 completed the study and were included in the pharmacokinetic evaluation and statistical analysis.

Safety - 9 adverse events (headache, nausea, fever and muscle pain) were reported during the study in 6 subjects. None was serious: eight were classified as ‘moderate’ and one was classified as ‘mild’. Only 2 instances of headache and one of nausea were considered to be ‘possibly related’ to the study medication. All events resolved by the end of the study period. The adverse events that were reported were similar in the test and reference product arms of the study and are consistent with known data on atorvastatin. There were no deaths or serious or significant adverse events.

The summary of the results of the bioequivalence study are tabulated below:

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**Conclusion on Bioequivalence**

The results of the bioequivalence study show that the 80 mg strength test and reference products are bioequivalent, under fasting conditions, as the confidence intervals for \( C_{\text{max}} \), \( \text{AUC}_{0-t} \), and \( \text{AUC}_{0-\infty} \) fall within the acceptance criteria ranges of 80.00-125.00% in line with current guidelines.

Satisfactory justification is provided for a bio-waiver for Atorvastatin 10 mg, 20 mg and 40 mg film-coated Tablets. As Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr**), the results and
conclusions of the bioequivalence study on the 80 mg strength can be extrapolated to the 10 mg, 20 mg and 40 mg strength tablets.

Clinical efficacy
No new data have been submitted and none are required. The UK reference products are established and the applications depend upon the ability to demonstrate bioequivalence. Efficacy is reviewed in the clinical overview. The efficacy of atorvastatin calcium is well-established from its extensive use in clinical practice.

Clinical safety
No new data have been submitted and none are required for applications of this type. No new or unexpected safety concerns arose from these applications. Safety is reviewed in the clinical overview. The safety profile of atorvastatin calcium is well-known.

PRODUCT INFORMATION:

Summary of Product Characteristics (SmPC)
The approved SmPCs are consistent with those for the reference products, and are acceptable.

Patient Information Leaflet
The final PIL is in line with the approved SmPCs and are satisfactory.

Labelling
The labelling are satisfactory.

Clinical overview
A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. The CV of the clinical expert has been supplied.

CONCLUSION
For generic applications of this nature, the need for repetitive tests on animals and humans is avoided. Reference is made to the innovator medicinal products, Lipitor® 10 mg, 20 mg and 40 mg Tablets (Pfizer Ireland Pharmaceuticals).

Sufficient clinical information has been submitted to support these applications. The benefit-risk of the products is considered favourable from a clinical perspective. The grant of Marketing Authorisations was, therefore, recommended on medical grounds.

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, as amended. The language used for the purpose of user testing the package leaflet was English.

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 AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

QUALITY
The important quality characteristics of Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets 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 applications of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Atorvastatin 80 mg film-coated Tablets, and the reference product, Lipitor® 80 mg Tablets (PL 16051/0005, Pfizer Ireland Pharmaceuticals).

As the proposed products, Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets, meet the criteria specified in the “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 rev. 1/Corr**), the results and conclusions of the bioequivalence study on the 80 mg strength were extrapolated to the 10 mg, 20 mg and 40 mg strength tablets, and omission of further bioequivalence studies on the other strengths can be accepted.

No new or unexpected safety concerns arise from these applications.

PRODUCT LITERATURE
The approved SmPCs are consistent with those for the UK reference products and are satisfactory.

The final PIL is in line with the SmPCs. The 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 results show that the leaflet meet 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.

The approved labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical concerns have been identified. The bioequivalence study and its conclusions support the claim that the applicant’s products, Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets, and their respective reference products, Lipitor® 10 mg, 20 mg, 40 mg and 80 mg Tablets (Pfizer Ireland Pharmaceuticals), are interchangeable. Extensive clinical experience with atorvastatin calcium is considered to have demonstrated the therapeutic value of the active substance. The benefit: risk ratio is considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.

LABELLING
Each tablet contains 20 mg atorvastatin as atorvastatin calcium. Tablets also contain lactose and sucrose. For oral use. Swallow the tablets whole with a drink of water. Read the package leaflet before use. Take as directed by your doctor.

Store below 25°C.
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Steps taken after the initial procedure with an influence on the Public Assessment Report

The following table lists a non-safety update to the Marketing Authorisation for these products that has been approved by the MHRA since the products were first licensed. The table includes an update that is detailed in the annex to this PAR. This is not a complete list of the post-authorisation change that has been made to these Marketing Authorisations.

Please note this update only applies to Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets (UK/H/1919/001-04/DC; PL 08553/0336-0339). The Marketing Authorisations for Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated Tablets (PL 08553/0365-0368 and 0369-0372; UK/H/2370 & 2380/001-04/DC) were cancelled on 18th August 2014 and 28th November 2012 respectively.

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<td>Licence cancellation</td>
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</tbody>
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Annex 1

Reference: PL 08553/0336-0010; PL 08553/0337-0009; PL 08553/0338-0009; PL 08553/0339-0009

Product: Atorvastatin 10, 20 40 and 80 mg film-coated Tablets

MAH: Dr. Reddy’s Laboratories (UK) Limited

Active Ingredient: Atorvastatin calcium

Reason:
To update the SmPCs and PIL to bring in line with the Brand Leader Lipitor (Pfizer) SmPCs and PIL.

Supporting evidence
The applicant has submitted updated SmPCs and the leaflet.

Evaluation
The amended SmPCs and the leaflet mock-up are satisfactory.

Conclusion
The variation was approved on 27th April 2015 and the updated SmPCs and the PIL have been incorporated into these Marketing Authorisations. The proposed changes are acceptable.
SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) Updated

Following approval of the variation on 27\textsuperscript{th} April 2015 the SmPCs were updated. In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
PATIENT INFORMATION LEAFLET (PIL) - Updated

Following approval of the variation on 27th April 2015 the PIL was updated. In accordance with Directive 2010/84/EU the Patient Information Leaflet (PIL) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.