IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Atorvastatin 20 mg Film-Coated Tablets
Atorvastatin Calcium Trihydrate
PA0281/236/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/4483/1-4/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 09/08/2018 under procedure number IE/H/0606/001-004/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/236/001-004
Marketing Authorisation Holder: Pinewood Laboratories Ltd

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Ireland and the UK considered that the applications for Atorvastatin 10mg, 20mg, 40mg and 80mg Film-Coated Tablets (PL 29831/0467-70; UK/H/4483/001-4/DC) could be approved.

Atorvastatin 10mg, 20mg, 40mg and 80mg Film-Coated Tablets are prescription only medicines (POM) and are indicated for:

- Hypercholesterolaemia

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), LDL-cholesterol (LDL-C), apolipoprotein B, and triglycerides in adults, adolescents and children aged 10 years or older 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 nonpharmacological measures is inadequate.
Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable.

- Prevention of cardiovascular disease

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

These applications for Atorvastatin 10mg, 20mg, 40mg and 80mg Film-Coated Tablets were submitted according to Article 10(1) of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Lipitor 10mg, 20mg, 40mg and 80mg Film-Coated Tablets, originally granted in the UK to Parke Davis & Company Limited on 7th November 1996 (PL 00018/0240-2, 10mg, 20mg and 40mg only). The 80mg dose was originally granted to Pfizer Manufacturing Ireland on 15th August 2000.

These licences then underwent two changes of ownership, to Pfizer Manufacturing Ireland on 12th September 2011 (PL 16051/0001-3, 10mg, 20mg and 40mg only) and Pfizer Ireland Pharmaceuticals on 12th September 2011 (PL 39933/0001-4).

Atorvastatin is an established HMG co-A reductate inhibitor, a "statin" used for reduction of cholesterol and for reduction of risk of coronary events. The brand leader (Lipitor) was authorised in the EU a number of years ago. The mean dose-response relationship has been shown to be log-linear for atorvastatin, but plasma concentrations of atorvastatin acid and its metabolites do not correlate with LDL-cholesterol reduction at a given dose. The clinical dosage range for atorvastatin is 10–80 mg/day, and it is given in the acid form.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for these applications as the pharmacology of atorvastatin is well-established.

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.

II. QUALITY ASPECTS

III SCIENTIFIC OVERVIEW AND DISCUSSION

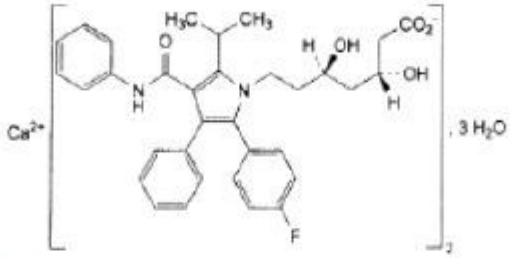
III.1 QUALITY ASPECTS

S. Active substance

INN/Ph.Eur name: Atorvastatin (atorvastatin calcium trihydrate)

Chemical name:
Calcium (3R5R)-7-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoate trihydrate.

Structure:



Physical form: White or almost white powder.
Solubility: Very slightly soluble in water, slightly soluble in ethanol, soluble in dimethylsulfoxide (DMSO) freely soluble in methanol, and practically insoluble in methylene chloride.

Molecular formula: $C_{66}H_{68}CaF_2N_4O_{10}.3H_2O$
Molecular weight: 1209

The source of atorvastatin used in the product complies with the European Pharmacopoeia monograph for atorvastatin.

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 analysis data are provided and 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.

Stability studies have been performed with the active substance and no significant changes of the parameters were observed. On the basis of the results, a suitable re-test period could be approved.

P. Medicinal Product

Other Ingredients

Other ingredients in the tablet core consist of pharmaceutical excipients sodium lauryl sulphate, colloidal anhydrous silica, anhydrous sodium carbonate, mannitol, butylhydroxyanisole, microcrystalline cellulose, croscarmellose sodium and magnesium stearate. The ingredients of the film-coating are hypromellose, microcrystalline cellulose and stearic acid.

All excipients comply with their respective European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin. Confirmation has been provided that the magnesium stearate used is of vegetable origin.

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

Pharmaceutical Development

The objective of the development programme was to produce safe, efficacious products containing atorvastatin that could be considered generic medicinal products of Lipitor 10mg, 20mg, 40mg and 80mg Film-Coated Tablets.

The applicant has provided suitable product development sections. Valid justifications for the use and amounts of each excipient have been provided.

Comparative *in vitro* dissolution profiles have been provided for the proposed and reference products. A comparative *in vitro* impurity profile was provided for the 80mg proposed and reference products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches of each strength have been provided and are satisfactory. The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification

The finished product specifications are acceptable. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container-Closure System

These products are packaged in aluminium blisters placed into cardboard boxes. Each pack contains 28 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with the relevant EU directives and EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished products in the packaging proposed for marketing and in accordance with current guidelines. These data support an adequate shelf-life of 18 months with with no special storage instructions.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are pharmaceutically acceptable. The UK approved SmPCs, PIL and labelling are included in modules 2, 3 and 4 of this report.

User testing results have not been submitted for the PIL for this product. A satisfactory bridging report to a PIL for a previously approved product has been provided. As both PILs are adequately similar, no specific user testing results for the proposed PIL is required.

MAA forms
The MAA forms are pharmaceutically satisfactory.

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

Conclusion
From a quality point of view, it is recommended that Marketing Authorisations are granted for these applications.

III. NON-CLINICAL ASPECTS

III.2 NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of atorvastatin are well-known. As atorvastatin is a widely used, well-known active substance, the applicant has not provided any new non-clinical data and none are required. An overview based on literature is therefore appropriate.

Non-Clinical Overview
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Environmental Risk Assessment
A satisfactory justification has been provided for the absence of an Environmental Risk Assessment.

Conclusion
From a non-clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.

IV. CLINICAL ASPECTS

III.3 CLINICAL ASPECTS

Clinical Pharmacology

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with these applications and none were required.

Pharmacokinetics

Bioequivalence study

A randomised, open-label, two-treatment, three sequence, three period, single dose, reference replicated, crossover study to compare the pharmacokinetics of the test product Atorvastatin 80mg Film-Coated Tablets versus the reference product Lipitor 80mg Film-Coated Tablets (atorvastatin) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 48 hours post dose. The washout period between each treatment period was 10 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for atorvastatin are presented below as log-tranformed values for geometric means:

Atorvastatin

Treatment	AUC_{0-t} (µg/mL/h)	$AUC_{0-\infty}$ (µg/mL/h)	C_{max} (µg/mL)
Test (T)	181.257 (47.27)	189.419 (46.19)	39.397 (52.69)
Reference (R)	165.573 (47.42)	172.560 (46.02)	38.086 (49.89)
T/R Ratio (90% CI)	110.85 (105.54 – 116.42)		105.24 (96.69 – 114.55)

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration

Pharmacokinetic parameters were also measured for the atorvastatin metabolites, *o*-hydroxy atorvastatin and *p*-hydroxy atorvastatin, however as per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), the bioequivalence of the parent compound is of critical value, while that of the metabolites is not crucial to demonstrate bioequivalence of the proposed product against the reference product.

The 90% CI for AUCinf has not been calculated in the study report, but this is not mandatory. As per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence, if AUC_t and C_{max} fulfil the criteria for acceptance that would be sufficient to demonstrate bioequivalence.

The results for the primary variables indicated that the 90% confidence intervals test/reference ratio of geometric means for AUC_{0-t} and C_{max} for atorvastatin lie within acceptable limits (80-125%). Thus, bioequivalence has been shown between the test and reference products in this study.

As the product range meet all the criteria as specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1) for a

biowaiver for the other strengths, the results and conclusions of the bioequivalence study on the 80mg strength can be extrapolated to Atorvastatin 10mg, 20mg and 40mg Film-Coated Tablets.

Efficacy
No new efficacy data were submitted with these generic applications and none were required.

Safety
With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with these generic applications and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

The Pharmacovigilance System and Risk Management Plan
The RMS considers that 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.

A satisfactory justification has been provided for the absence of a Risk Management Plan.

Summary of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and Labelling
The SmPCs, PIL and labelling are clinically satisfactory and consistent with those for the reference products, where appropriate.

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.

MAA Forms
The MAA forms are clinically satisfactory.

Conclusions
From a clinical point of view, it is recommended that Marketing Authorisations are granted for these applications.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Atorvastatin 10mg, 20mg, 40mg and 80mg 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 80mg Film-Coated Tablets and the reference product Lipitor 80mg Film-Coated Tablets. These bioequivalence study results and conclusions can be extrapolated to Atorvastatin 10mg, 20mg and 40mg Film-Coated Tablets.

No new or unexpected safety concerns arose from the bioequivalence study.

The SmPCs, PIL and labelling are satisfactory and consistent with those for the reference products.

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

VI. REVISION DATE

02/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/4483/1-4/DC to IE/H/0606/001-004/DC			
MAH transfer				04/01/2021