IPAR

PUBLIC ASSESSMENT REPORT FOR A MEDICINAL PRODUCT FOR HUMAN USE

Scientific discussion

Atorvastatin 10mg, 20mg, 40mg & 80mg Film-coated Tablets
Atorvastatin
PA 0688/021/001–004

The Public Assessment Report reflects the scientific conclusion reached by the Irish Medicines Board (IMB) 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 IMB 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 IMB leading to the approval of the medicinal product for marketing in Ireland.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the IMB has granted a marketing authorisation for Atorvastatin 10mg, 20mg, 40mg & 80mg film-coated tablets, from Chanelle Medical for the following indications:<? xml:namespace prefix = "o" ns = "urn:schemas-microsoft-com:office:office" />

Hypercholesterolaemia

Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol, LDL-cholesterol, apolipoprotein B, and triglycerides in adults 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 adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (eg. LDL apheresis) or if such treatments are unavailable.

Atorvastatin also raises HDL-cholesterol and lowers the LDL/HDL and total cholesterol/HDL ratios.

Prevention of Cardiovascular Disease

Prevention of cardiovascular events in 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.

This application for Atorvastatin 10mg, 20mg, 40mg & 80mg film-coated tablets were submitted as a New National generic application in accordance with Article 10(1) of Directive 2001/83/EC as amended.

The Summary of Product Characteristics for (SPC) for this medicinal product is available on the IMB's website at http://www.imb.ie/

Name of the product	Atorvastatin 10mg, 20mg, 40mg & 80mg film-coated tablets
Name(s) of the active substance(s) (INN)	Atorvastatin calcium trihydrate
Pharmacotherapeutic classification (ATC code)	C10A A05
Pharmaceutical form and strength(s)	Film-coated tablets 10mg, 20mg, 40mg & 80mg of atorvastatin as atorvastatin calcium trihydrate
Marketing Authorisation Number(s) in Ireland (PA)	PA 688/21/1-4
Marketing Authorisation Holder	Chanelle Medical Ireland

II QUALITY ASPECTS

II.1. Introduction<?xml:namespace prefix = "o" ns = "urn:schemas-microsoft-com:office:office" />

This application is for Atorvastatin 10mg, 20mg, 40mg & 80mg film-coated tablets

II.2 Drug substance

The active substance is Atrovastatin calcium trihydrate, an established active substance, manufactured in accordance with the principles of Good Manufacturing Proactive (GMP)

The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Brief description of the dosage form

Name of Active substance	**Quality**	**Unit**
Atorvastatin (as calcium trihydrate)	10, 20, 40, 80	mg

Name of excipients

Tablet Core:-
Calcium carbonate, E170
Microcrystalline cellulose, E460
Lactose monohydrate
Croscarmellose Sodium
Polysorbate 80, E433
Hydroxypropyl cellulose, E463
Magnesium stearate E572

Coating
Hypromellose (E464)
Titanium Dioxide (E171)
Macrogol 400

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances)*

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The product is presented in aluminium blisters.

Evidence has been provided that Blister complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product
Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines demonstrating the stability of the product for 3 years with no special storage conditions.

Compliance with the Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products has been satisfactorily demonstrated.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Atorvastatin 10mg, 20mg, 40mg & 80mg film-coated tablets.

III NON-CLINICAL ASPECTS

III.1 Introduction

This active substance has been available on the European/Irish market for more than 10 years. No new preclinical data have been submitted as preclinical data have been superseded by clinical experience and therefore no preclinical assessment report is available.

IV CLINICAL ASPECTS

IV.1 Introduction

Atorvastatin is a well known active substance with established efficacy and tolerability.

This medicinal product is the same as Lipitor on the European market . The content of the SPC approved during the national procedure is in accordance with that accepted for the reference product Lipitor marketed by Pfizer.

For this generic application, the applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the test product is compared with the pharmacokinetic profile of the reference product.

Based on the pharmacokinetic parameters of the active substance, the reference tablet and test tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The IMB has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption: Atorvastatin is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to atorvastatin dose. Atorvastatin tablets are 95% to 99% bioavailable compared to solutions. The absolute bioavailability of atorvastatin is approximately 12% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism.

Distribution: Mean volume of distribution of atorvastatin is approximately 381 L. Atorvastatin is 98% bound to plasma proteins.

Metabolism: Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products. Apart from other pathways these products are further metabolised via glucuronidation. In vitro, inhibition of HMG-CoA reductase by ortho- and parahydroxylated metabolites is equivalent to that of

atorvastatin. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites.

Excretion: Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, the drug does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

Special Populations

Geriatric: Plasma concentrations of atorvastatin and its active metabolites are higher in healthy elderly subjects than in young adults while the lipid effects were comparable to those seen in younger patient populations.

Paediatric: Pharmacokinetic data in the paediatric population are not available.

Gender: Concentrations of atorvastatin and its active metabolites in women differ (approximately 20% higher for Cmax and 10% lower for AUC) from those in men. These differences were of no clinical significance, resulting in no clinically significant differences in lipid effects among men and women.

Renal Insufficiency: Renal disease has no influence on the plasma concentrations or lipid effects of atorvastatin and its active metabolites.

Hepatic Insufficiency: Plasma concentrations of atorvastatin and its active metabolites are markedly increased (approximately 16-fold in Cmax and 11-fold in AUC) in patients with chronic alcoholic liver disease (Childs-Pugh B).

IV.3 Pharmacodynamics

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, 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 catabolized primarily through the high affinity LDL receptor.

Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

Atorvastatin reduces LDL production and the number of LDL particles. Atorvastatin produces a profound and sustained increase in LDL receptor activity coupled with a beneficial change in the quality of circulating LDL particles. Atorvastatin is effective in reducing LDL-C in a limited number of patients with homozygous familial - hypercholesterolaemia, a population that has not usually responded to lipid-lowering medication.

Atorvastatin has been shown to reduce total-C, LDL-C, apolipoprotein B, and triglycerides in a dose related manner. Atorvastatin produced a variable but small increase in apolipoprotein A1. However, there was no clear dose response effect.

Review of the current clinical database of 24 complete studies shows that atorvastatin increases HDL-cholesterol and reduces the LDL/HDL and total cholesterol/HDL ratios.

These results are consistent in patients with heterozygous familial hypercholesterolaemia, nonfamilial forms of hypercholesterolaemia, and mixed hyperlipidaemia, including patients with noninsulin-dependent diabetes mellitus.

Reductions in total-C, LDL-C and apolipoprotein B have been proved to reduce risk for cardiovascular events and cardiovascular mortality.

IV.4 Clinical Efficacy

The clinical efficacy of atorvastatin is well established.

IV.5 Clinical Safety

The clinical efficacy of atorvastatin is well established. A Risk Management Plan is not required in line with the known safety profile of the active substance..

The Marketing Authorisation Holder submitted a set of documents describing the Pharmacovigilance system, including information on the availability of an EU Qualified Person for Pharmacovigilance (EU QPPV) and the means for notification of adverse reaction reports in the EU or from a Third Country.

The schedule for Periodic Safety Update Reports (PSUR) submission has been addressed in line with this being a generic product. As atorvastatin is a well-established product with a known safety-profile, a 3-year-cycle for PSUR submission has been agreed.

V OVERALL CONCLUSIONS

Atorvastatin 10mg, 20mg, 40mg & 80mg film-coated tablets are a generic form of Lipitor Tablets. Atorvastatin is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The IMB, on the basis of the data submitted considered that Atorvastatin 10mg, 20mg, 40mg & 80mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.