CBG MEB

Public Assessment Report

Scientific discussion

Atorvastatine STADA 10 mg, 20 mg, 40 mg and 80 mg, film-coated tablets

(atorvastatin calcium trihydrate)

NL/H/3346/001-004/DC

Date: 3 November 2016

This module reflects the scientific discussion for the approval of Atorvastatine STADA 10 mg, 20 mg, 40 mg and 80 mg, film-coated tablets. The procedure was finalised on 20 January 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Atorvastatine STADA 10 mg, 20 mg, 40 mg and 80 mg, film-coated tablets from Stada Arzneimittel AG.

The product is indicated for:

Hypercholesterolaemia
Atorvastatine STADA 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 non-pharmacological measures is inadequate.

Atorvastatine STADA 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, as an adjunct to correction of other risk factors.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Lipitor 10 mg, 20 mg, 40 mg, and 80 mg film-coated tablets (NL License RVG 21081-21083 and 27148). The 10 mg, 20 mg, and 40 mg strengths have been registered in the Netherlands by Pfizer B.V. since 21 April 1997 through MRP DE/H/0109/001-003. The 80 mg strength has been registered in the Netherlands by Pfizer B.V. since 4 June 2002 through MRP DE/H/0109/004.

The concerned member states (CMS) involved in this procedure were Germany and Italy.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Atorvastatine STADA is a white to off-white, round biconvex film-coated tablet.

The film-coated tablets are packed in OPA/Al/PVC-Al blisters.

The excipients are:
Tablet core - lactose monohydrate, powdered cellulose, calcium carbonate, pregelatinised starch, Hypromellose, croscarmellose sodium and magnesium stearate.
Tablet-coat – hypromellose, macrogol, titanium dioxide (E171) and talc.

The tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is atorvastatin calcium (as trihydrate), an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a white to off-white

crystalline powder, which is very slightly soluble in water, slightly soluble in ethanol and freely soluble in methanol. Polymorphic form I is used.

Four different manufacturers are used for the production of the active substance. For all manufacturers, the CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is set in line with the Ph.Eur. with additional tests for particle size, related substances, residual solvents and polymorphic form. The specification is considered acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for one full scaled batch per drug manufacturer.

Stability of drug substance
Stability data on the active substance have been provided for 6 batches from manufacturer-I and 4 batches from manufacturer-II. The batches from manufacturer-I were stored for 24 months at long-term conditions and 6 months at accelerated conditions. For manufacturer-II the batches were stored for 36 months at long-term and 6 months at accelerated conditions. No trends or out of specification results were observed. The retest periods of 24 months for manufacturer-I and 36 months for manufacturer-II without special storage conditions are justified.

For manufacturer-III the retest period of 24 months was included on the CEP and is acceptable.

For manufacturer-IV long term stability data up to 48 months were provided on 18 production scaled batches. No trends or out of specification results were observed. The proposed retest period of 48 months without special storage conditions is acceptable.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. A bioavailability study resulted in the development of the formulation manufactured by a direct compression process. The amount of binder was optimised and the particle size limits of the active substance were established. The pharmaceutical development of the product has been adequately performed.

One bioequivalence study was performed using the 80 mg strength and the corresponding Lipitor reference product. Comparative dissolution profiles were provided in three different media. Bioequivalence was shown *in vivo*.

For the other strengths a biowaiver of strength was proposed. Comparative data in 0,1N HCl +2% sodium dodecyl sulphate (SDS) and in acetate buffer pH 4.5 +2% SDS were provided as well as comparative dissolution data of the different strengths in 0.1N HCL and in acetate buffer pH 4.5 without surfactant. The dissolution was over 85% within 15 minutes in all media.

Manufacturing process
The manufacturing process consists of direct compression followed by film-coating. The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 24 batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass, identity, assay, uniformity of dosage units, dissolution, degradation products and microbiological quality. The release and shelf life specifications are identical with the exception of the limits for degradation products. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 18 production scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on 5 production scaled batches per strenght stored at 25°C/60% RH (9 months for 12 batches, 12 months for 11 batches and 18 months for 1 batch) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in oPA-Alu-PVC/Al blister packaging. All data remained within the specifications. It was demonstrated that the drug substance is stable under light conditions.
Based on the provided data the proposed shelf life of 24 months without special storage conditions when packed in oPA-Alu-PVC/ Al blister can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin. It is prepared without the use of other ruminant materials than milk and calf rennet. The supplier of lactose monohydrate has provided the required TSE/BSE certificate.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Atorvastatine STADA has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

One post-approval commitment was made:
- The MAH commits to perform a post-approval stability study on three batches of the highest and the lowest strength. For the other strengths one commercial batch will be included in the stability study.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Atorvastatine STADA is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Lipitor which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Atorvastatin is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atorvastatine STADA 80 mg, film-coated tablets (STADA Arzneimittel AG, Germany) is compared with the pharmacokinetic profile of the reference product Lipitor 80 mg film-coated tablets (Pfizer AB, Sweden).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver has been granted for the 10 mg, 20 mg and 40 mg strengths, based on the following:

- The pharmaceutical products are manufactured by the same manufacturer and process.
- The qualitative compositions of the different strengths are the same.
- The ratio between the active ingredient and the excipients is the same.
- The *in vitro* dissolution profiles are similar under identical conditions for the additional strengths and the strength that is used in the bioequivalence study.

Design
A monocentric, open, randomised, single-dose, four-period, replicate, crossover bioequivalence study was carried out under fasted conditions in 48 healthy subjects, aged 18-47 years. Each subject received in a random way an oral single dose of either 1 film-coated tablet (80 mg atorvastatin) of the test or the reference product with 240 ml tap water on four single occasions (two doses of the test product and two doses of the reference product for the whole study) under fasted conditions. There were 4 dosing periods, separated by a washout period of 7 days (except in 1 subject with 14 days between first and second study period only).

Blood samples were collected pre-dose, and 0.25, 0.5, 0.66, 0.87, 1, 1.33, 1.66, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, and 36 hours after administration of the products.

The design of the study is acceptable. The study was performed using a replicate design, which is common for highly variable drug products like atorvastatin film-coated tablets. The intra-subject variability was high (>30%) for the reference product. Therefore, as predefined in the protocol, the replicate design allows the bioequivalence acceptance interval for C_{max}, to be widened to 73.86-135.38%. Because of the known pharmacokinetic profile of atorvastatin, it was determined that a 7 day washout period between drug administrations would be sufficient. According to the SmPC, atorvastatin may be taken at any time of the day, with or without food. Therefore, a study under fasted conditions is appropriate.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
All subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean, t_{max} (median)) of atorvastatin under fasted conditions.

Treatment N=48	AUC_{0-t} pg.h/ml	$AUC_{0-\infty}$ pg.h/ml	C_{max} pg/ml	t_{max} h	$t_{1/2}$ h
Test	131169.19	136122.35	34506.65	0.67	7.52
Reference	136734.51	141757.42	36034.77	0.67	7.53
***Ratio (90% CI)**	1.01 (0.96 – 1.06)	--	1.00 (0.91 – 1.09)	--	--

$AUC_{0-\infty}$ 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
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Conclusion on bioequivalence study
The reference product was found to be highly variable for C_{max} with an intra-subject variability greater than 30%: the intra-individual coefficient of variation was 41.62%. Widening of the acceptance intervals for C_{max} was allowed but, based on the study results, proved not to be necessary. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Atorvastatine STADA is considered bioequivalent with Lipitor.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Atorvastatine STADA.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Hepatotoxicity (increased transaminases, hepatitis, jaundice) • Haemorrhagic stroke • Rhabdomyolysis, myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia • Interaction with CYP3A4 inhibitors • Sleep disturbances (incl. insomnia and nightmares) • Diabetes mellitus
Important potential risks	• Interstitial lung disease • Sexual dysfunction
Missing information	• Use in pregnancy and lactation • Use in children younger than 10 years

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Lipitor. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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 test consisted of: a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions allowed to analyse the comprehensibility and applicability of the PL. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

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

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Atorvastatine STADA with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 January 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product; Minor change in the manufacturing process	NL/H/3346/ 1-4/IA/001	IA	17-10-2016	7-11-2016	Approval	No