COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

# Public Assessment Report

# Scientific discussion

# Atorvastatine STADA 30 mg and 60 mg film-coated tablets

## (atorvastatin calcium trihydrate)

## NL/H/3346/005-006/DC

## Date: 25 September 2019

**This module reflects the scientific discussion for the approval of Atorvastatine STADA 30 mg and 60 mg film-coated tablets. The procedure was finalised on 9 July 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.**

# List of abbreviations

| | |
|---|---|
| ASMF | Active Substance Master File |
| CEP | Certificate of Suitability to the monographs of the European Pharmacopoeia |
| CHMP | Committee for Medicinal Products for Human Use |
| CMD(h) | Coordination group for Mutual recognition and Decentralised procedure for human medicinal products |
| CMS | Concerned Member State |
| EDMF | European Drug Master File |
| EDQM | European Directorate for the Quality of Medicines |
| EEA | European Economic Area |
| 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 30 mg and 60 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 hybrid application. The application was submitted as a line extension to the initial dossier for Atorvastatine STADA 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets (NL/H/3346/001-004/DC). Reference is made to the innovator product Lipitor 10 mg, 20 mg, 40 mg, and 80 mg film-coated tablets (NL Licence 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(3) 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 tablets have a score line on one side, which is not intended for breaking the 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.
*Film-coat* – hypromellose, macrogol, titanium dioxide (E171) and talc.

The tablet strengths are dose proportional.

## II.2 Drug Substance

The active substance is atorvastatin calcium 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 substance 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 Atorvastatine STADA 80 mg and the corresponding Lipitor reference product. Comparative dissolution profiles were provided in three different media. Bioequivalence was shown in vivo.

For the 30 mg and 60 mg strengths a biowaiver of strength was proposed. Comparative dissolution studies in support of the biowaiver have been performed at the same dose level versus the BE study test batch (i.e. 8 x 30 mg and 4 x 60 mg vs. 3 x 80 mg in phosphate buffer pH 6.8, 0.1 N HCl and acetate buffer pH 4.5. The biowaiver for the 30 mg and 60 mg strengths is considered justified.

Manufacturing process

The manufacturing process consists of direct compression followed by film-coating. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 2 batches of both strengths.
The product is manufactured using conventional manufacturing techniques.

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 2 batches of each strength 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 2 batches per strength stored at 25°C/60% RH (up to 48 months) 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 36 months without special storage conditions when packed in oPA-Alu-PVC/Al blister has been granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate is manufactured using materials exclusively of vegetable origin. Lactose monohydrate is manufactured from milk sourced from healthy animals in the same condition as milk collected for human consumption without the use of other ruminant materials than calf rennet.

## II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Atorvastatine STADA 30 mg and 60 mg has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

# 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 hybrid 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.

## IV.2 Pharmacokinetics

To support the application, the MAH has submitted in the initial submission (NL/H/3346/001-004/DC) 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 study was conducted as a monocentric, open, randomized, single-dose, four-period, replicate, crossover trial, under fasting conditions in 48 healthy volunteers. Bioequivalence was demonstrated. The 90% confidence intervals calculated for $AUC_{0-t}$ and $C_{max}$ were within the bioequivalence acceptance range of 0.80 – 1.25.

<u>Biowaiver</u>
A biowaiver has been granted for the 30 mg and 60 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 was used in the bioequivalence study.

### 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.

**Table 2. Summary table of safety concerns as approved in RMP**

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|---|---|
| Important identified risks | • Skeletal muscle effects<br>• Hyperglycaemia, which may require diabetes care in patients with diabetes risk factors<br>• Stevens-Johnson syndrome and toxic epidermal necrolysis<br>• Concomitant use of coumarin anticoagulants/ warfarin<br>• Hepatic failure<br>• Interstitial lung disease |
| Important potential risks | • Haemorrhagic stroke<br>• Other autoimmune events |
| Missing information | • Use in paediatric patients < 10 years old |

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. Based on a bioequivalence study with Atorvastatine STADA 80 mg versus the reference product, bioequivalence has been demonstrated. Risk management is adequately addressed. This hybrid 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 30 mg and 60 mg film-coated tablets have a proven chemical-pharmaceutical quality and is a hybrid form of Lipitor 10 mg, 20 mg, 40 mg, and 80 mg film-coated tablets. 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, based on a bioequivalence study with Atorvastatine STADA 80 mg vs. Lipitor 80 mg film-coated tablets. A biowaiver was granted for the 30 mg and 60 mg strengths.

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 9 July 2019.

## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

| Procedure number | Scope | Product Information affected | Date of end of procedure | Approval/ non approval | Summary/ Justification for refuse |
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