COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atorvastatine Centrient 10 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg film-coated tablets (atorvastatin calcium trihydrate)

NL/H/3795/001-006/DC

Date: 23 March 2023

This module reflects the scientific discussion for the approval of Atorvastatine Centrient 10 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg film-coated tablets. The procedure was finalised on 14 June 2017. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Centrient 10 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg film-coated tablets, from Centrient Pharmaceuticals Netherlands B.V.

The product is indicated for:

Hypercholesterolaemia
Atorvastatine Centrient 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.

Atorvastatine Centrient 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 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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC for the 10 mg, 20 mg, 40 mg and 80 mg strengths and article 10 (3) of Directive 2001/83/EC for the 30 mg and 60 mg strength.

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Lipitor (RVG 21081-21083, 27148) which has been registered in the Netherlands by Pfizer B.V. since April 1997 and June 2002 (for the 80 mg strength) (original product).

The concerned member states (CMS) involved in this procedure was Italy.

II. QUALITY ASPECTS

II.1 Introduction

Atorvastatine Centrient is a white, oblong film-coated tablet, embossed with 10, 20, 30, 40, 60, 80 on one side and 'ATV' on the other side.

These tablets contain as active substance 10 mg, 20 mg, 30 mg, 40 mg, 60 mg or 80 mg of atorvastatin (as calcium trihydrate), respectively.

The excipients are:
Tablet core –microcrystalline cellulose (E460), lactose monohydrate, calcium carbonate (E170), hydroxypropyl cellulose (E463), croscarmellose sodium type A (E468), silica hydrophobic colloidal (E551), magnesium stearate (E572);
Film-coating – hypromellose (E464), macrogol, titanium dioxide (E171), talc (E553b).

The different tablet strengths are fully dose proportional.

The tablets are packed in blisters composed of PA/Alu/PVC - Alu or PVC/PVDC - Alu.

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 or almost white powder and is very slightly soluble in water, slightly soluble in ethanol (96 per cent) and practically insoluble in methylene chloride.

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. Certain information in a CEP is considered confidential and therefore not described in this report.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality, meets the requirements of the monograph in the Ph.Eur. and additional requirements for residual solvents as stated on the CEP. Batch analytical data demonstrating compliance with this specification have been provided for six full-scale batches.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

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 formulation was optimised by a quality by design approach and the final formulation was used to prepare a batch of the 80 mg strength, which was used in a bioequivalence study with the reference product. In support of the bioequivalence study, and to obtain a biowaiver of strengths for the lower strengths, comparative dissolution studies were performed. Comparative dissolution was shown at all pH's and thereby the proposed biowaiver of strengths can be accepted. The packaging and manufacturing process have been justified. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The manufacturing process consists of blending and sieving, followed by tabletting, film-coating and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for five batches, of which sub-batches were made to make tablets of all strengths, in accordance with the relevant European guidelines

Control of excipients

The excipients comply with Ph. Eur. requirements. 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, disintegration, water content, identity, assay, content uniformity, dissolution, related substances, and microbiological quality. 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 two to four batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

For the 10 mg, 20 mg, 40 mg and 80 mg strengths, stability data on the product have been provided for thirteen batches stored at 25°C/ 60% RH (24 months) and 40°C/75% RH (6 months). For the 30 mg and 60 mg strength stability data were provided on two batches of each strength stored at stored at 25°C/ 60% RH (6 months) and 40°C/75% RH (6 months). This is in accordance with the ICH stability guideline. The batches were stored in PA/Alu/PVC - Alu blisters or PVC/PVDC - Alu blisters. Although upward trends are observed for total impurities the results are within specification under long term and accelerated conditions in both packaging materials.

Photostability studies were performed and showed that some degradation was observed for the unpackaged product, however, all results remained within specification and no special storage conditions are required. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions need to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and 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

Based on the submitted dossier, the member states consider that Atorvastatine Centrient 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 Centrient is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was 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 was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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 calcium trihydrate is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The member states agreed that no further clinical studies are required, besides the bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atorvastatine Centrient 80 mg film-coated tablets (Centrient Pharmaceuticals Netherlands B.V., The Netherlands) was compared with the pharmacokinetic profile of the reference product Lipitor 80 mg from Pfizer Pharma GmbH, Germany. The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Biowaiver

A biowaiver of strength was requested for the lower strengths. The following conditions were fulfilled:

- The products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- Appropriate *in vitro* dissolution data are available for all strengths at three pH values.
- The strengths are dose proportional.

This is in line with the requirements of the EMA Guideline on Bioequivalence.

Bioequivalence studies

Design

A single-dose, randomised, four-period, two-treatment, two-sequence, crossover bioequivalence study was conducted under fasted conditions in 36 healthy (17 male and 19 female subjects, aged 18-54 years. Each subject received a single dose (80 mg) of one of the two atorvastatin calcium trihydrate formulations. The tablet was orally administered with 200 mL water after an overnight fast. There were four dosing periods, separated by a washout period of twelve days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.50, 0.75, 1.00, 1.33, 1.67, 2.0, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours after administration of the products.

The design of the study is acceptable.

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

For personal reasons one subject withdrew consent during period four. All subjects were included in the pharmacokinetic and statistical analyses. Only period 4 of the subject who withdrew consent was excluded from the statistical evaluation of bioequivalence.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of atorvastatin calcium trihydrate, 80 mg, under fasted conditions.

Treatment N=36, excluding period 4 of one subject	AUC_{0-t} (µg.h/mL)	$AUC_{0-\infty}$ (µg.h/mL)	C_{max} (µg/mL)	t_{max} (h)
Test	155 ± 88	158 ± 89	44 ± 28	1.2 (0.5 – 4.0)
Reference	134 ± 75	137 ± 76	37 ± 22	0.75 (0.3 – 2.5)
***Ratio (90% CI)**	1.16 (1.09 – 1.23)	-	1.10 (0.99 – 1.23)	-

$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t}	Area under the plasma concentration curve extrapolated to infinite time. AUC0-∞ does not need to be reported when AUC0-72h is reported instead of AUC0-t
C_{max}	Maximum plasma concentration
t_{max}	Time after administration when maximum plasma concentration occurs
CI	Confidence interval

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Atorvastatine Centrient 80 mg is considered bioequivalent with Lipitor 80 mg.

The results of the bioequivalence study with the 80 mg formulation can be extrapolated to other strengths 10 mg, 20 mg, 30 mg, 40 mg and 60 mg according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6. 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 Centrient.

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

Important identified risks	Skeletal muscle effects (including Immune-mediated necrotizing myopathy) Rhabdomyolysis and rhabdomyolysis-related events Hepatic failure.
Important potential risks	Haemorrhagic stroke in patients with prior haemorrhagic stroke or lacunar infarct.
Missing information	None.

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 language used for the purpose of user evaluating the PL was English.
The test consisted of: a pilot test with two participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL 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, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Atorvastatine Centrient 10 mg, 20 mg, 30 mg, 40 mg, 60 mg and 80 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms 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.

In the Board meeting of 14 June 2017 it was discussed that there were some questions regarding the batch-to-batch consistency and the granting of the biowaiver. Subsequently the results of the process validation were provided and demonstrated that the manufacturing process of all strengths of Atorvastatine Centrient is capable of rendering reproducible products with the desired dissolution properties. The manufacturing process of the drug product was therefore regarded as validated. No additional information was required.

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 Centrient with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 June 2017.

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
NL/H/3795/IB/001/G	Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location Change in the (invented) name of the medicinal product - for Nationally Authorised Products. Name change in Italy.	No	19-04-2018	Approved	N/A
NL/H/3795/IB/002/G	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar - Implementation of change(s) for which no new additional data are submitted by the MAH Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006SmPCSmPC - Implementation of change(s) for which no new additional data are submitted by the MAH	Yes	19-04-2019	Approved	N/A
NL/H/3795/IB/003/G	Change in the name and/or address of the marketing authorisation holder Change in the (invented) name of the medicinal product - for Nationally Authorised Products.	Yes	09-07-2019	Approved	N/A
NL/H/3795/IB/004/G	Change(s) in the SMPC, Labelling or Package Leaflet of human medicinal products intended to implement the PSUFU outcome for lupus-like syndrome and for muscle rupture in SmPC and PL.	Yes	12-08-2021	Approved	N/A
NL/H/3795/IB/005/G	Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the	No	15-11-2021	Approved	N/A

	Pharmacovigilance System Master File (PSMF) location Change in the (invented) name of the medicinal product - for Nationally Authorised Products. Name change in Italy.				
NL/H/3795/001-006/R/001	Renewal	No	15-03-2022	Approved	N/A