COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

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

(NL/H/5399/001-004/MR)

11 May 2022

This module reflects the scientific discussion for the approval of Atorvastatine Liconsa. The procedure was finalised at 18 February. 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 Liconsa 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets, from Laboratorios Liconsa S.A.

Hypercholesterolaemia
Atorvastatine Liconsa 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 Liconsa 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
Atorvastatine Liconsa is also indicated for the 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.

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

This mutual recognition procedure concerns a generic application claiming essential similarity with 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). A National Marketing Authorisation for this product was granted on December 2017 (RVG 122032-035). The dossier of this product is identical to Atorvastatine Xiromed (DK/H/2592), with exception of the MAH.

The concerned member states (CMS) involved in this procedure were Germany, Poland and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Atorvastatine Liconsa 10 mg film-coated tablets
Round, biconvex film-coated tablets with bisection line on one side and debossed 10 on other side.

Atorvastatine Liconsa 20 mg film-coated tablets
Round, biconvex film coated tablets with bisection line on one side and debossed 20 on other side.

Atorvastatine Liconsa 40 mg film-coated tablets
Round, biconvex film-coated tablets with bisection line on one side and debossed 40 on other side.

Atorvastatine Liconsa 80 mg film-coated tablets
Oblong, biconvex film-coated tablets with bisection line on one side and debossed 80 on other side.

And contains as active substance 10 mg, 20 mg, 40 mg or 80 mg of atorvastatin, as atorvastatin calcium trihydrate.

The film-coated tablets are packed in PVC-PE-PVDC/Aluminium and Oriented polyamide-aluminium- polyvinylchloride (PVC) / aluminium foil blisters.

The excipients are:

Tablet core – calcium carbonate (E170), cellulose – microcrystalline (E460), lactose monohydrate, croscarmellose sodium, copovidone, crospovidone, mangnesium stearate (E470b), sodium laurilsulfate, silica – colloidal anhydrous and talc.

Film-coat – Hypromellose (E464), macrogol 400 and titanium dioxide (E171).

The four 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.). Atorvastatin calcium trihydrate is a white to almost white powder and is very slightly soluble in water, slightly soluble In ethanol and practically insoluble in methylene chloride. Atorvastatin calcium trihydrate exhibits both isomerism and polymorphism, the manufacturer of the active substance consistently produces the polymorphic form I.

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
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 and meets the requirements of the monograph in the Ph.Eur. and the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The active substance is stable for five years when stored in polyethylene bags and containers. 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. Dissolution profiles comparing the drug product to the reference products and were adequately performed. The development of the product has been described, the choice of excipients is justified and their functions explained.

Manufacturing process
The manufacturing process has been validated according to relevant European/ICH guidelines. The manufacturing process consists of two parts: the production of a common blend and the compression of the common blend into tablets. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The choice of excipients is justified and their functions explained. 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, uniformity of mass, hardness, friability, disintegration, diameter and thickness. 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 batches for each strength from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for seven batches for each strength stored at long term (25°C ± 2°C/60% ± 5% RH) (36 months) intermediate (30°C ± 2°C/65% ± 5% RH) (12 months) and accelerated (40°C ± 2°C/75% ± 5% RH) (six months) in accordance with applicable European guidelines demonstrating the stability of the product for 36 months. On basis of the data submitted, a shelf life was granted of 36 months when stored in the original packaging.

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 for lactose monohydrate 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 Liconsa 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 Liconsa 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 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 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atorvastatine Liconsa 80 mg film-coated tablets (Laboratorios Liconsa S.A., Spain) is compared with the pharmacokinetic profile of the reference product Sortis (also known as Lipitor) 80 mg film-coated tablets (Pfizer Pharma GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The application concerns the strengths 10, 20, 40 and 80 mg. The bioequivalence study was carried out with the 80 mg strength and biowaiver is applied for the remaining 10, 20 and 40 mg strengths. The following criteria according to the guideline was taken into account in support of the biowaiver:

- Atorvastatin 10 mg, 20 mg, 40 mg film-coated tablets are manufactured by the same manufacturer and using the same manufacturing process.
- The qualitative composition of atorvastatin 10 mg, 20 mg, 40 mg film-coated tablets is the same as that of atorvastatin 80 mg film-coated tablets.
- Atorvastatin 10 mg, 20 mg, 40 mg film-coated tablets are dose proportional with atorvastatin 80 mg film-coated tablets. Thus, the ratio of amount of active substance and the excipients is the same for all the strengths.
- The dissolution profile of Atorvastatin 10 mg, 20 mg, 40 mg film-coated tablets is similar to atorvastatin 80 mg film-coated tablets.

- The pharmacokinetics of atorvastatin is linear regarding AUC, whereas Cmax increases more than proportionally with increasing dose.

As all the requirements for a biowaiver were fulfilled, it was concluded that the biowaiver for the 10 mg, 20 mg and 40 mg strengths is accepted.

Bioequivalence studies

Design

A open-label, randomized, two-treatment, two-sequence, three-period crossover, reference-replicate, single-dose bioavailability study was carried out under fasted conditions in 45 healthy male subjects, aged 19-49 years. Each subject received a single dose (80 mg) of one of the two atorvastatin calcium trihydrate formulations each period. The tablet was orally administered with 240 ml water after an overnight fast. There were three dosing periods, separated by a washout period of 14 days.

Blood samples were collected at pre-dose and at 0.167, 0.333, 0.500, 0.667, 0.833, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.0, 12.0, 24.0, 36.0, and 48.0 hours after administration of the products.

The design of the study is acceptable.

Atorvastatin calcium trihydrate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of atorvastatin calcium trihydrate. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

Out of a total of 45, 44 subjects were eligible for pharmacokinetic analysis. One subject withdrew due to personal reasons.

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=44	AUC_{0-t} (pg.h/ml)	$AUC_{0-\infty}$ (pg.h/ml)	C_{max} (pg/ml)	Residual area	t_{max} (h)	K_{el} (h^{-1})	$t_{1/2}$ (h)
Parameters: mean (SD, CV%)							

Test	186343.54 (85903.74, 46.10)	190600.14 (86941.22, 45.61)	45044.57 (28458.05, 63.18)	2.41 (2.33, 96.81)	1.30 (0.92, 70.84)	0.0738 (0.0128, 17.37)	9.75 (2.22, 22.77)
Reference (1st dose)	192476.44 (90406.55, 46.97)	196911.71 (91799.05, 46.62)	49334.61 (31603.85, 64.06)	2.44 (1.86, 76.14)	0.962 (0.593, 61.68)	0.0717 (0.0107, 14.95)	9.93 (1.93, 19.40)
Reference (2nd dose)	182585.52 (76768.26, 42.05)	187453.46 (79177.19, 42.24)	47713.06 (22042.75, 46.20)	2.51 (1.61, 63.91)	0.974 (0.802, 82.39)	0.0718 (0.0121. 16.81)	9.97 (1.97, 19.81)

$AUC_{0-\infty}$ 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
CV coefficient of variation

**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 80 – 125%. Based on the submitted bioequivalence study Atorvastatine Liconsa is considered bioequivalent with Sortis (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 Liconsa.

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

Important identified risks	- Hepatotoxicity (increased transaminases, hepatitis and jaundice) - Haemorrhagic stroke - Rhabdomyolysis, myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia - Interaction with CYP3A4 inhibitors/OATP1B1 inhibitors - Diabetes mellitus - Severe skin reactions - Interstitial lung disease

Important potential risks	- Use during pregnancy and breastfeeding
Missing information	- Use in paediatric patients <10 years of age

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 testing the PL was English. The test consisted of a pilot test with four participants, followed by two rounds with ten 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 Liconsa 10 mg, 20 mg, 40 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.

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 concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Atorvastatine Liconsa with the

reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 18 February 2022.

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