COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Atorvastatine Liconsa 30 mg and 60 mg film-coated tablets (atorvastatin calcium trihydrate)

NL/H/5512/001-002/DC

Date: 25 June 2024

This module reflects the scientific discussion for the approval of Atorvastatine Liconsa 30 mg and 60 mg film-coated tablets. The procedure was finalised on 3 May 2023. 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
FT-IR	Fourier-transform Infrared Spectroscopy
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
XRD	X-Ray Diffraction
XRPD	X-Ray Powder Diffraction

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Atorvastatine Liconsa 30 mg and 60 mg film-coated tablets, from Laboratorios Liconsa S.A.

The product is indicated for: hypercholesterolaemia and prevention of cardiovascular disease.

Hypercholesterolaemia
The product 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.
The product 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 up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application.

In this decentralised procedure, essential similarity is proven between the new product and the innovator (reference) product Sortis 80 mg film-coated tablets, which has been registered in Germany by Pfizer Pharma PFE GmbH (original product). In the Netherlands, Lipitor 80, filmomhulde tabletten 80 mg has been registered since 2002 by the procedure DE/H/0109/004.

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

II. QUALITY ASPECTS

II.1 Introduction

Atorvastatine Liconsa is a film-coated tablet. The two strengths can be distinguished by the different size, shape, colour and debossing of the tablets.

Atorvastatine Liconsa 30 mg is a round, biconvex film-coated tablet with a bisection line on one side and debossed with 30 on other side, with a diameter 10.0 mm ± 0.3 mm. Each film-

coated tablet contains as active substance 30 mg atorvastatin (as atorvastatin calcium trihydrate).

Atorvastatine Liconsa 60 mg is a round, biconvex film-coated tablet with a bisection line on one side and debossed with 60 on other side, with a diameter 13.0 mm ± 0.3 mm. Each film-coated tablet contains as active substance 60 mg atorvastatin (as atorvastatin calcium trihydrate).

The excipients are:
Core: calcium carbonate (E170), microcrystalline cellulose (E460), lactose monohydrate, croscarmellose sodium, copovidone, crospovidone, magnesium stearate (E470b), sodium laurilsulfate, silica (colloidal anhydrous) and talc.
Film coat: hypromellose (E464), macrogol 400 and titanium dioxide (E171).

The two tablet strengths are dose proportional.

The film-coated tablets are packed in Transparent Triplex polyvinyl chloride/polyethylene/polyvinylidene chloride (PVC/PE/PVdC) aluminium blisters.

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 very slightly soluble in water. The drug substance shows polymorphism and is consistently manufactured as polymorphic form I. This was demonstrated by comparative Fourier-transform infrared spectroscopy (FT-IR spectra) and X-Ray Powder Diffraction (XRPD) patterns. Four different CEP's have been provided for the drug substance.

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 considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and additional requirements of the respective CEP's, with an additional in-house requirement for XRD (X-Ray Diffraction) and particle size distribution. The specification is acceptable in view of the route of synthesis and

the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches from each supplier.

Stability of drug substance

The active substance is stable for 60 months (manufacturer I) and 48 months (manufacturer II) when stored under the stated conditions. Assessment thereof was part of granting the CEPs (and has been granted by the EDQM).

Manufacturer III provided stability data on the active substance for several production scaled batches stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (6 months). The stability data show no clear trends or changes in any of the tested parameters at both storage conditions. All results were in compliance with the specification limits. The claimed retest period of 48 and 60 months without any special storage requirements is justified based on the presented stability data.

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. The pharmaceutical development is mainly described for the already authorised 10 mg, 20 mg, 40 mg and 80 mg tablets from the same manufacturer. The main development studies described are the characterisation of the reference product, formulation optimisation studies and manufacturing process development. Although the score line on the tablets is only to facilitate breaking for ease of swallowing and not to divide into equal doses, it has been demonstrated that the tablets can be divided into equal halves. The choices of the packaging and manufacturing process are justified. A bioequivalence study has been performed with the 80 mg product. The claimed biowaiver for the additional 30 mg and 60 mg strengths is justified. The general biowaiver criteria have been justified and satisfactory comparative in-vitro dissolution data at three pH's have been submitted. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are blending and lubrication, dry compression, film-coating and packaging. The two strengths are manufactured from the same common blend. The manufacturing has been described in sufficient detail. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three pilot scaled batches and three full scaled batches of the common blend and on three pilot scaled batches of each product strength in accordance with the relevant European guidelines. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. or in-house (film-coating) requirements with additional control of functionality-related characteristics where relevant. 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, diameter, colour, identity, dissolution, assay, uniformity of dosage units, related substances and microbiological quality. The release and shelf-life requirements are identical except for assay and related substances. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three pilot scaled batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided from three production scaled batches per strength stored at 25°C/ 60% RH (12 months), 30°C/65% RH (12 months) and 40°C/75% RH (6 months) in accordance with applicable ICH guidelines. At all three storage conditions an increase in impurities is observed. Results for assay and dissolution were variable at all three storage conditions, but without any clear trends. No clear trends or changes were seen in any of the other tested parameters and all results were in compliance with the shelf-life specification. A photostability study in accordance with ICH Q1B showed that the drug products are not sensitive to light. On basis of the data submitted, a shelf life was granted of 24 months. No specific storage conditions needed 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 for lactose monohydrate 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 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 hybrid 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 Sortis 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 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) was compared with the pharmacokinetic profile of the reference product Sortis 80 mg film-coated tablets (Pfizer Pharma PFE GmbH, Germany).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution study results and composition. Dissolution profiles were performed in pH 2.2, 4.5 and pH 6.8 buffer media. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing. Biowaivers are requested for the 30 mg and 60 mg strengths based on comparative dissolution studies.

Biowaiver

The following general requirements must be met where a waiver for additional strength is claimed, according to the EMA Bioequivalence guideline:

a. the pharmaceutical products are manufactured by the same manufacturing process,
b. the qualitative composition of the different strengths is the same,
c. the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths (for immediate release products coating components, capsule shell, colour agents and flavours are not required to follow this rule),
d. appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing.

Bioequivalence studies

Design

A single-dose, randomised, three-period, two-treatment, three-sequence, crossover bioequivalence study was carried out under fasted conditions in 44 healthy male subjects, aged 19-49 years. Each subject received a single dose (80 mg) of one of the two atorvastatin formulations. The tablet was orally administered with 240 mL water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, 36, and 48 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

45 subjects enrolled in the study. One subject withdrew for personal reasons in period III. 44 subjects were eligible for pharmacokinetic analysis.

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

Treatment N = 44	**AUC_{0-t} (pg.h/mL)**	**$AUC_{0-\infty}$ (pg.h/mL)**	**C_{max} (pg/mL)**	**t_{max} (h)**
Test	186344 ± 85904	190600 ± 86941	45045 ± 28458	1.0 (0.3 – 4.0)
Reference, 1st administration	192476 ± 90407	196912 ± 91799	49335 ± 31604	0.7 (0.3 – 2.5)
Reference, 2nd administration	182586 ± 76768	187453 ± 79177	47713 ± 22043	0.7 (0.3 – 5.0)
***Ratio (90% CI)**	0.99 (0.94 – 1.04)	0.99 (0.94 – 1.04)	0.93 (0.82 – 1.04)	-

$AUC_{0-\infty}$	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 the last measurable plasma concentration / to t = 72 hours
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 Atorvastatin Liconsa 80 mg is considered bioequivalent with Sortis 80 mg.

The results of the study with 80 mg formulation can be extrapolated to other strengths 30 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 Atorvastatin Liconsa.

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 Sortis. 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 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 Liconsa 30 mg and 60 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Sortis 80 mg film-coated tablets. Sortis 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 Liconsa with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 May 2023.

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/5512 /IA/001/G	**Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product** • *Primary packaging site* • *Secondary packaging site*	No	05-07-2023	Approved	N/A
NL/H/5512 /IA/001-2/G	**Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance, For a starting material/reagent/intermediate used in the manufacturing process of the active substance, For an excipient** • *Updated certificate from an already approved manufacturer*	No	07-03-2024	Approved	N/A
NL/H/5512 /IB/003/G	**Change in the (invented) name of the medicinal product** • *for Nationally Authorised Products* **Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use** • *Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location*	Yes No	18-04-2024	Approved	N/A