

## **Public Assessment Report**

### **Scientific discussion**

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

**NL/H/4925/001-004/DC**

**Updated on: 12 February 2026**

This module reflects the scientific discussion for the approval of Atorvastatine AmaroX 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets. The procedure was finalised on 28 October 2021. 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
CRO	Contract Research Organisation
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 AmaroX 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets, from AmaroX Pharma B.V.

The products are indicated for:

### ***Hypercholesterolaemia***

Atorvastatine AmaroX are 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 AmaroX are 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 (see section 5.1 of the SmPC), 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 products Lipitor 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets which have been registered in Germany by Pfizer in 1996 (DE/H/0109/001) (original product). In the Netherlands, Lipitor have been registered since 21 April 1997 for the 10, 20, and 40 mg dose strengths (RVG 21081-3) and since 4 June 2002 for the 80 mg dose strength (RVG 27148) via mutual recognition procedure DE/H/109/01-04.

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

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

### **General comments on the application**

The initial marketing authorisation for Atorvastatin AmaroX was granted by the Medicines Evaluation Board (MEB) on 28 October 2021. To demonstrate essential similarity with the innovator, bioequivalence data of one study conducted at the CRO Synchron Research Services, Ahmedabad, India were submitted.

On 19 July 2022 a CMDh referral was raised (Article 31 Referral EMEA/H/A-31/1515, CRO Synchron-referral) and the CHMP recommended the suspension of the marketing authorisation of a number of generic medicines tested at Synchron Research Services, Ahmedabad, India. This, because after multiple inspections conducted in Europe (EMA) and the USA (Food and Drug Administration (FDA)), serious concerns were raised related to the suitability of the quality management system and the overall reliability of data generated at Synchron and submitted to support marketing authorisation in EU Member States. Following this recommendation, the MEB temporarily suspended the marketing authorisation of Atorvastatin AmaroX on 14 December 2022.

With the submission of data (through variation NL/H/4925/001-004/II/003) of a new bioequivalence study conducted at CRO Clantha Research Limited, the Marketing Authorisation Holder (MAH) adequately demonstrated the bioequivalence of the product with the innovator Lipitor 80 mg tablet under fasting conditions. The results also support the biowaiver for the additional strengths 10 mg, 20 mg and 40 mg. Therefore, the MEB and concerned member states consider that all issues and uncertainties regarding the clinical aspects of the product have been resolved and the variation is considered acceptable. The MEB subsequently lifted the temporary suspension and re-granted the marketing authorisation for this product on 22 May 2025. Please refer to Annex 1. Type II of Variation Final Variation Assessment Report, at the end of this PAR.

## II. QUALITY ASPECTS

### II.1 Introduction

Atorvastatine AmaroX 10, 20, 40 and 80 mg are white coloured, oval shaped, biconvex film coated tablets with one side embossed "10", "20", "40" or "80", respectively, and other side plain.

The 10, 20, 40 and 80 mg film-coated tablets contain as active substance atorvastatin calcium trihydrate equivalent to 10, 20, 40 and 80 mg atorvastatin, respectively.

The film-coated tablets are packed in available in Alu-Alu blister packs.

The excipients are:

*Tablet core* – mannitol, sodium laurilsulfate, colloidal anhydrous silica, sodium carbonate (E500), butylhydroxyanisole, microcrystalline cellulose, croscarmellose sodium (E468) and magnesium stearate (E572).

*Film-coat* – hypromellose, microcrystalline cellulose and stearic acid.

The different strengths are fully dose proportional. The excipients and packaging are usual for this type of dosage form.

## 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, is very slightly soluble in water, slightly soluble in ethanol and practically soluble in methylene chloride. The active substance is manufactured as polymorphic form I. For the drug substance, two CEPs have been provided

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

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

### Quality control of drug substance

The active substance specification by the finished product manufacturer is considered adequate to control the quality is in line with the Ph. Eur. monograph and an additional requirement for control of residual solvents of the CEP. Further, the specification includes additional tests for polymorphic form, aniline content, benzene and particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines.

Batch analytical data demonstrating compliance with the drug substance specification have been provided for three commercial scale batches for the drug substance according to both CEPs.

### Stability of drug substance

#### *Manufacturer I*

Stability data on several production scale batches of drug substance have been provided stored at 25°C/60% RH (up to 48 months) and 40°C/75% RH (six months). The batches were packed in double LDPE bags (inner transparent, outer black) in HDPE containers. The batches were tested for description, identity, polymorphism, water, assay, related substances, enantiomeric purity, aniline content and residual solvents. No clear trends or changes were seen in any of the tested parameters and all parameters were within the specification limits at both storage conditions. The provided stability data justify the claimed retest period of 48 months without any special storage requirements.

*Manufacturer II*

Stability data on 23 batches of drug substance manufactured in the period from February 2016 to September 2020 have been provided that were stored at 25°C/60% (up to 48 months for several batches) and RH 40°C/75% RH (up to six months for most batches). The batches were packed in double LDPE bags (inner transparent, outer black) placed in a HDPE container and evaluated for description, identity, polymorphic form, water, sodium, assay, related substances, enantiomeric purity and aniline content. No clear trends or changes were seen in any of the tested parameters at both storage conditions. Results of photostability testing as part of the forced degradation studies showed no degradation of the samples after exposure to ICH Q1B light conditions. The provided stability data justify the claimed retest period of 48 months without any special storage requirements.

### **II.3 Medicinal Products**

Pharmaceutical development

The products are established pharmaceutical forms and their development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the reference products, dissolution method development, formulation and manufacturing process optimisation studies and the performance of comparative *in vitro* dissolution studies at 3 pH's. The dissolution method development has been adequately described and the choice for the finalised dissolution method for routine control has been adequately justified. The discriminatory power of the method has been demonstrated.

A bioequivalence study was performed with a batch of the 80 mg test product versus a batch of the corresponding reference product strength. A biowaiver was requested for the additional product strengths. Both will be discussed in section IV.

Manufacturing process

The manufacturing process consists of the manufacturing of granules, followed by manufacturing of the core tablets. The core tablets are then film-coated and packed in blisters. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for four to five pilot scale batches of each strength and three full scale batches per strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients

The excipients comply with Ph.Eur. requirements. Functionality related characteristics are controlled where relevant. The film-coating material is controlled with in-house requirements. The specifications are acceptable.

Quality control of drug products

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identity of atorvastatin calcium

and butylhydroxyanisole, average mass, hardness, loss on drying, dissolution, uniformity of dosage units, butylhydroxyanisole content, assay, related substances, residual ethanol and microbiological quality. Except for related substances, the release and shelf life requirements are identical. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate risk evaluation concerning the presence of nitrosamine impurities in the drug product has been provided.

Satisfactory validation data for the analytical methods have been provided.

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

#### Stability of drug products

Stability data on the products have been provided on four full production scaled batches of the 20 mg and 40 mg strength and on five full production scaled batches of the 10 mg and 80 mg strength. The batches were stored at 25°C/60% RH (36 months) and 40°C/75% RH (six months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al-Al blisters. Except for an increase in total impurities at both storage conditions, no clear trends or changes were observed in any of the tested parameters at both storage conditions in any of the batches. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light.

Based on the data submitted, a shelf life could be granted of 36 months without any special storage requirements.

#### Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

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

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

### III. NON-CLINICAL ASPECTS

#### III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Atorvastatine AmaroX are 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

These products are generic formulations of Lipitor which are available on the European market. Reference is made to the preclinical data obtained with the innovator products. 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. However, after the referral and temporary suspension of this product, new bioequivalence data has been submitted, to replace the study described in this section. Please refer to Annex 1. Type II of Variation Final Variation Assessment Report, at the end of this PAR for the new data and conclusion on the clinical aspects.

#### IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atorvastatine AmaroX 80 mg film-coated tablets (Indswift Ltd., India) is compared with the pharmacokinetic profile of the reference product Lipitor 80 mg film-coated tablets (Pfizer Ireland Pharmaceuticals, Ireland).

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

#### Biowaiver

The MAH has requested a biowaiver for the 10 mg, 20 mg and 40 mg product strengths. The following criteria of the *Guideline on the Investigation of Bioequivalence* are met:

- The different drug product strengths are manufactured by the same manufacturing process.
- The strengths have the same qualitative composition.
- The composition of the strengths are quantitatively proportional.
- Similarity in dissolution is adequately demonstrated between the 80 mg biobatch versus the additional strengths in pH 1.2, pH 4.5 and pH 6.8 dissolution medium.

Therefore, the results of the bioequivalence study with the 80 mg product strength can be extrapolated to the 10, 20 and 40 mg product strengths.

#### Bioequivalence study

##### *Design*

A open label, randomised, two-treatment, three-period, three-sequence, reference replicated single dose, crossover bioequivalence study was carried out under fasted conditions in 57 healthy male subjects, aged 18 – 44 years. Each subject received a single dose (80 mg) of one of the two atorvastatin formulations. The reference formulation was administered twice, i.e. in two periods. The tablet was orally administered with 250 ml water after an overnight fast. There were three dosing periods, separated by a washout period of ten days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36 and 48 hours after administration of the products.

The design of the study is acceptable.

Atorvastatin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of atorvastatin. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with the *Guideline on the investigation of bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr \*\*).

##### *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*

One subject withdrew from the study due to personal reasons. 56 subjects were eligible for pharmacokinetic analysis. The pharmacokinetic variables of atorvastatin, ortho-hydroxy-atorvastatin and para-hydroxy-atorvastatin of the test and reference products are shown in Table 1, 2 and 3.

**Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of total atorvastatin under fasted conditions.**

Treatment N=56	AUC <sub>0-t</sub> (ng.h/ml)	AUC <sub>0-∞</sub> *** (ng.h/ml)	C <sub>max</sub> (ng/ml)	t <sub>max</sub> (h)
Test	199 $\pm$ 94	207 $\pm$ 96	44 $\pm$ 23	1.0 (0.25 – 4.0)
**Reference	182 $\pm$ 86	189 $\pm$ 87	42 $\pm$ 21	0.5 (0.5 – 5.0)
*Ratio (90% CI)	1.11 (1.06 – 1.16)	-	1.05 (0.97 – 1.15)	-
CV (%)	23.2	-	28.0	-

AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity  
AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours  
C<sub>max</sub> maximum plasma concentration  
t<sub>max</sub> time for maximum concentration  
CV coefficient of variation

*\*In-transformed values*

*\*\* Average of both periods*

*\*\*\* n=54 for Test, as the elimination phase could not be reliable estimated*

**Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of ortho-hydroxy-atorvastatin under fasted conditions.**

Treatment N=56	AUC <sub>0-t</sub> (ng.h/ml)	AUC <sub>0-∞</sub> ** (ng.h/ml)	C <sub>max</sub> (ng/ml)	t <sub>max</sub> (h)
Test	432 $\pm$ 156	437 $\pm$ 158	52 $\pm$ 27	1.5 (0.5 – 6.0)
*Reference	375 $\pm$ 121	387 $\pm$ 123	43 $\pm$ 20	1.5 (0.5 – 8.0)

AUC<sub>0-∞</sub> area under the plasma concentration-time curve from time zero to infinity  
AUC<sub>0-t</sub> area under the plasma concentration-time curve from time zero to t hours  
C<sub>max</sub> maximum plasma concentration  
t<sub>max</sub> time for maximum concentration

*\* Average of both periods*

*\*\* n=55 for Test, as the elimination phase could not be reliable estimated*

**Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean  $\pm$  SD,  $t_{max}$  (median, range)) of para-hydroxy-atorvastatin under fasted conditions.**

Treatment N=56	AUC <sub>0-t</sub> (ng.h/ml)	AUC <sub>0-∞</sub> ** (ng.h/ml)	C <sub>max</sub> (ng/ml)	t <sub>max</sub> (h)
Test	67 $\pm$ 32	82 $\pm$ 36	4.2 $\pm$ 2.6	4.0 (0.7 – 36.0)
*Reference	60 $\pm$ 28	77 $\pm$ 31	3.3 $\pm$ 2.1	5.0 (0.5 – 12.0)
<b>AUC<sub>0-∞</sub></b> area under the plasma concentration-time curve from time zero to infinity <b>AUC<sub>0-t</sub></b> area under the plasma concentration-time curve from time zero to t hours <b>C<sub>max</sub></b> maximum plasma concentration <b>t<sub>max</sub></b> time for maximum concentration				

\* Average of both periods

\*\* n=50 for Test, and n=55 for Reference, as the elimination phase could not be reliably estimated

#### Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC<sub>0-t</sub> and C<sub>max</sub> of total atorvastatin are within the bioequivalence acceptance range of 0.80 – 1.25. For ortho-hydroxy-atorvastatin and para-hydroxy-atorvastatin only the ratios were calculated for supportive reasons. Considering that the metabolites have the same activity, analysis of the stereoisomers is deemed not necessary.

Based on the submitted bioequivalence study the 80 mg product strength of Atorvastatine Amarox is considered bioequivalent with the 80 mg product strength of 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 Amarox.

**Table 4. Summary table of safety concerns as approved in RMP**

Important identified risks	<ul style="list-style-type: none"> <li>• Hepatic failure</li> <li>• Skeletal muscle effects, rhabdomyolysis and rhabdomyolysis-related events</li> <li>• Concomitant use of coumarin anticoagulants/warfarin</li> </ul>
Important potential risks	<ul style="list-style-type: none"> <li>• None</li> </ul>
Missing information	<ul style="list-style-type: none"> <li>• None</li> </ul>

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 80 mg product strength is similar to the pharmacokinetic profile of the 80 mg reference product strength. A biowaiver has been granted for the 10 mg, 20 mg and 40 mg product strengths. Risk management is adequately addressed. These generic medicinal products can be used instead of the reference products.

### **V. USER CONSULTATION**

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Atorvastatine Mylan 10, 20, 40 and 80 mg Film-Coated Tablets (BE/H/157/01-04/DC) for content and to Levettiracetam Hetero (PT/H/515/01-04/DC) for design/layout. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

### **VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION**

Atorvastatine AmaroX 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Lipitor 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets. Lipitor are well-known medicinal products with established favourable efficacy and safety profiles. 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 AmaroX with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 28 October 2021.

Please refer to Annex 1 at the end of this PAR for the updated overall conclusion and benefit/Risk assessment.

## 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/4925/001-4/IA/001	Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products: - Other variation.	Yes	4-1-2024	Approved	N.A.
NL/H/4925/001-4/IA/002	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 wording agreed by the competent authority. Update of product information as per PSUSA wordings PSUSA/00010347/202310	Yes	9-10-2024	Approved	N.A.
*NL/H/4925/001-4/II/003	Other variations not specifically covered elsewhere in the variation Annex which involve the submission of studies to the competent authority. See Annex 1.	No	22-5-2025	Approved	N.A.
NL/H/4925/001-4/IA/004	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.	No	16-8-2025	Approved	N.A.

	<ul style="list-style-type: none"> <li>• European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.</li> <li>○ Updated certificate from an already approved manufacturer.</li> </ul>				
NL/H/4925/001-4/IA/005	Change in the batch size (including batch size ranges) of the finished product: <ul style="list-style-type: none"> <li>- Up to 10-fold compared to the originally approved batch size.</li> </ul>	No	30-7-2025	Approved	N.A.
NL/H/4925/003/IA/006	Change in the batch size (including batch size ranges) of the finished product: <ul style="list-style-type: none"> <li>- Up to 10-fold compared to the originally approved batch size.</li> </ul>	No	8-9-2025	Approved	N.A.
NL/H/4925/001-4/IA/007	Change in the name and/or address of a manufacturer/importer of the finished product ( including batch release or quality control testing sites): <ul style="list-style-type: none"> <li>- All other.</li> </ul>	No	15-10-2025	Approved	N.A.

\* See at the end of this PAR: Annex 1. Type II of Variation Final Variation Assessment Report.

## Annex I – Type II Variation NL/H/4925/1-4/II/003 Final Variation Assessment Report

### I. RECOMMENDATION

Based on the review of the data on efficacy, the RMS considers that the variation for Atorvastatin AmaroX 10, 20, 40 and 80 mg tablets, indicated for:

#### ***Hypercholesterolaemia***

Atorvastatine AmaroX are 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 AmaroX are 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 (see section 5.1 of the SmPC), as an adjunct to correction of other risk factors.

C.I.13 - HUMAN AND VETERINARY MEDICINAL PRODUCTS - Submission of additional clinical and non-clinical studies, including BE-studies. (CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008) Submission of a new bioequivalence study, following Article 31 Referral EMEA/H/A-31/1515 (CRO, Synchron Research Services- referral).

**is approvable.**

## II. EXECUTIVE SUMMARY

### II.1 Scope of the variation

C.I.13 - HUMAN AND VETERINARY MEDICINAL PRODUCTS - Submission of additional clinical and non-clinical studies, including BE-studies. (CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) no 1234/2008).

Submission of a new bioequivalence study, following Article 31 Referral EMEA/H/A-31/1515 (CRO, Synchron Research Services- referral).

Atorvastatin AmaroX 10, 20, 40 and 80 mg tablets were initially proven bioequivalent to the EU innovator Lipitor 80 mg tablets by performing a bioequivalence study in 2011 at the Clinical Research Organisation (CRO) Synchron Research Services, Ahmedabad, India (study no. ATO/2010/632, 80 mg strength, biowaiver of additional strengths for the 10, 20 and 40 mg tablet). However, as an outcome of an Article 31 Referral, (EMEA/H/A-31/1515) on the benefit-risk balance of the bioequivalent studies performed at Synchron Research Services, Ahmedabad, India, EMA's human medicines committee (CHMP) has recommended the suspension of the marketing authorisations of a number of generic medicines tested by Synchron Research Services, Ahmedabad, India.

Consequently, the bioequivalence study for Atorvastatin AmaroX tablets—was repeated at CRO Cliantha Research Limited, Ahmedabad, India (study no. C1B02154, 80 mg strength, reference product Sortis 80 mg tablet (year 2022)). Bioequivalence could not be shown for  $C_{max}$ . The study was repeated at Synchron Research Services, Ahmedabad, India (study no. 22-106, 80 mg strength, reference product Sortis 80 mg tablet (year 2022)). Bioequivalence could not be shown for  $C_{max}$ . The study was repeated at Synchron Research Services, Ahmedabad, India (study no. 23-029, 80 mg strength, reference product Lipitor 80 mg (year 2023)).

However, as an outcome of an Article 31 Referral, triggered by the Spanish Agency of Medicines and Medical Devices (AEMPS) on the benefit-risk balance of the bioequivalent studies performed at Synchron Research Services, Ahmedabad, India, EMA's human medicines committee (CHMP) has recommended the suspension of the marketing authorisations of a number of generic medicines tested by Synchron Research Services, Ahmedabad, India.

The recommendation followed a good clinical practice (GCP) inspection which showed irregularities in study data and inadequacies in study documentation and in the computer systems and procedures to appropriately manage study data. This raised serious concerns about the validity and reliability of data from bioequivalence studies conducted at the CRO.

Consequently, the bioequivalence study was repeated at Cliantha Research Limited, Ahmedabad, India (study no. C1B04195). The result show that Atorvastatin AmaroX 80 mg tablets is bioequivalent to the reference product Lipitor 80 mg tablet under fasting conditions. A biowaiver for the additional strengths 10 mg, 20 mg and 40 mg has been adequately supported. Consequently, the MEB has regranted the marketing authorisation for this product. An overview of the assessment of the study is described below.

### III. SCIENTIFIC DISCUSSION

#### III.1 Introduction

In this application, a generic status is claimed for Atorvastatin AmaroX tablets versus the European innovator Lipitor tablets. To compare the rate and extent of absorption between Atorvastatine 80 mg tablets and Lipitor 80 mg tablets, a bioequivalence study was conducted with the 80 mg strength using as a reference product the European innovator sourced from the Irish market (with Upjohn EESV as MAH). For the additional strengths 10 mg, 20 mg and 40 mg a biowaiver has been granted.

##### GCP aspects

The MAH has submitted as report the single dose pivotal bioequivalence study carried out at Clantha Research Limited, Ahmedabad, India. Quality assurance documents were provided. The study centre has been inspected by different EU regulatory agencies. No triggers for inspection have been identified in the current study.

#### III.2 Clinical study reports

The MAH has submitted one pivotal bioequivalence study carried out at Clantha Research Limited, Ahmedabad, India (study no. C1B04195). The design of the conducted study is considered sufficient and meets the recommendations of the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr.

#### III.3 Biowaiver

This application concerns Atorvastatine AmaroX tablets in the strengths 10 mg, 20 mg, 40 mg and 80 mg. The different strengths are fully dose proportional. The bioequivalence study is carried out with the 80 mg strength, which is acceptable for a drug with linear pharmacokinetics.

The different drug product strengths are manufactured by the same manufacturing process, have the same qualitative composition and are quantitatively proportional, so the general requirements a), b) and c) for a waiver of additional strengths of the Guideline on the investigation of bioequivalence are met.

No new dissolution data has been submitted for this application, as the MAH leans on the bridging in vitro dissolution data as submitted in the initial application. This is acceptable, as the 80 mg used in the new bioequivalence study is identical to the 80 mg study used in the initial application.

### III.4 PHARMACOKINETIC STUDIES

#### III.4.1 STUDY C1B04195: SINGLE DOSE FASTING STUDY, 80 MG TABLET

- Description

Single dose oral bioequivalence study of Atorvastatin 80 mg film-coated tablets and Lipitor (atorvastatin) 80 mg film-coated tablets in healthy adult human subjects under fasting conditions.

- Study design

This was a single-dose, fully replicate design, randomised, crossover comparative bioequivalence study under fasted conditions. Eighty healthy male subjects, aged 23 - 54 years, were dosed. The subjects received a single dose (80 mg; 1 x 80 mg tablet) of the test and reference atorvastatin formulation after an overnight fast. The tablets were administered in solid form with 240 mL water. The washout period was 7 days between periods 1, 2 and 3 and 10 days between period 3 and 4.

Blood samples were collected pre-dose and at 0.25, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 7, 9, 12, 16, 24, 36 and 48 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate. Fasting conditions have been applied, which is appropriate, as the tablet can be taken with or without food.

- Population studied

Eighty healthy male subjects, aged 23 - 54 years, were dosed in period 1 of this study; 76, 74 and 75 subjects completed period 2, 3 and 4, respectively. A total 78 subjects completed the study (at least two periods of the study of which at least one period with the reference formulation), in accordance with protocol. 74 subjects were included in the calculation of the within-subject variability of reference. An overview of the reasons for dropout/withdrawn of the subjects is shown in table 1.

**Table 1. Overview reasons for dropout/withdrawn of subjects.**

Period	Number of subjects	Reason for dropout/withdrawn
1	1	personal reasons
2	1	personal reasons
2	1	positive test for drugs of abuse
3	1	vomiting
3	2	positive test for alcohol
	3	personal reasons
4	2	personal reasons
	1	positive test for alcohol

- 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

The pharmacokinetic variables of atorvastatin of the test and the reference are shown in table 2.

**Table 2. The pharmacokinetic variables of atorvastatin of the Test and Reference (as mean  $\pm$  s.d.; t<sub>max</sub> as median (range)).**

Treatment N=*	Atorvastatin 80 mg tablet dose 80 mg Test	Lipitor 80 mg tablet dose 80 mg Reference
AUC <sub>(0-t)</sub> (ng.h/ml)	320 $\pm$ 182	343 $\pm$ 198
AUC <sub>(0-inf)</sub> (ng.h/ml)	327 $\pm$ 183	349 $\pm$ 199
C <sub>max</sub> (ng/ml)	73 $\pm$ 59	79 $\pm$ 61
t <sub>max</sub> (h)	1.00 (0.50 – 9.00)	1.25 (0.50 – 9.00)
t <sub>1/2</sub> (h)	8.8 $\pm$ 4.1	8.7 $\pm$ 4.6

\* n=150 for test and 152 for reference

The results of the statistical analysis are listed in table 3.

**Table 3. Statistical evaluation on atorvastatin pharmacokinetic variables**

	AUC <sub>(0-t)</sub>	C <sub>max</sub>
Ratio's (test/ref)	0.93	0.89
90% confidence intervals:	0.89 – 0.98	0.82 – 0.97
Res. coeff. of variation*	24.2%	40.8%

\* within-subject variability based upon reference/reference comparison

Safety:

There was no serious adverse events (SAEs) reported in the study. A total of nine adverse events (AEs) were reported by eight subjects during the entire study. AEs were mild in severity. There were four AEs (blood glucose increased, nausea, white blood cell count increased and platelet count decreased) which were considered possibly related to the test formulation. There were five AEs (nausea, vomiting, blood bilirubin increased and blood glucose increased) which were considered possibly related to the reference formulation.

- Pharmacokinetic conclusion

Based on the pharmacokinetic parameters of atorvastatin, the reference and test are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence interval calculated for  $AUC_{0-t}$  and  $C_{max}$  were within the normal range of acceptability (0.80 – 1.25).

#### IV. UPDATED OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Based on the submitted bioequivalence study, through Type II Variation NL/H/4925/001-4/II/003, Atorvastatine AmaroX 80 mg tablet is considered bioequivalent with the Lipitor 80 mg tablet, under fasted conditions.

The biowaiver for the additional 10 mg, 20 mg and 40 mg strengths has been adequately supported. The variation is considered acceptable.