CBG MEB

Public Assessment Report

Scientific discussion

Atorvastatine Aurobindo 30 mg and 60 mg, film-coated tablets

(atorvastatin calcium trihydrate)

NL/H/2982/005-006/DC

Date: 16 November 2017

This module reflects the scientific discussion for the approval of Atorvastatine Aurobindo 30 mg and 60 mg, film-coated tablets. The procedure was finalised on 10 April 2017. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Atorvastatine Aurobindo 30 mg and 60 mg, film-coated tablets from Aurobindo Pharma B.V.

The product is indicated for:

Hypercholesterolaemia
Atorvastatin 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.

Atorvastatin is also indicated to reduce total-C and LDL-C in adults with homozygous familial hypercholesterolaemia as an adjunct to other lipid-lowering treatments (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 SmPC 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 decentralised procedure concerns a line extension to the existing marketing authorisations of Atorvastatine Aurobindo 10 mg, 20 mg, 40 mg and 80 mg, film-coated tablets (NL/H/2982/001-004/DC), which were approved for marketing in the Netherlands on 6 March 2015. The current application adds two new strengths, 30 mg and 60 mg, to the marketing authorisation of Atorvastatine Aurobindo. The new strengths fall within the dosing scheme for Atorvastatin Aurobindo, which remains identical as for the previously registered strengths.

The 30 mg and 60 mg strengths of Atorvastatine Aurobindo are not available for the innovator product, Lipitor film-coated tablets (NL License RVG 21081-21083 and 27148). Lipitor 10 mg, 20 mg, and 40 mg have been registered in the Netherlands by Pfizer B.V. since 21 April 1997 through mutual recognition procedure DE/H/0109/001-003. The 80 mg strength has been registered in the Netherlands by Pfizer B.V. since 4 June 2002 through mutual recognition procedure DE/H/0109/004.

The concerned member states (CMS) involved in this procedure were Denmark, Spain, Poland and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC as a hybrid application. For the clinical data of atorvastatin, reference is made to the existing marketing authorisations of Atorvastatine Aurobindo 10 mg, 20 mg, 40 mg and 80 mg, film-coated tablets.

II. QUALITY ASPECTS

II.1 Introduction

Atorvastatine Aurobindo 30 mg is a white, round film-coated tablet, debossed with “N” on one side and “30” on other side.
Atorvastatine Aurobindo 60 mg is a white, oval film-coated tablet, debossed with “N” on one side and “60” on other side.

The tablets are packed in in polyamide/aluminium foil/PVC-Aluminium foil blisters packs.

The excipients are:
Tablet core – mannitol, copovidone, sodium carbonate anhydrous (E500), croscarmellose sodium (E468), silicified microcrystalline cellulose (E460) (contains silica, colloidal anhydrous and microcrystalline cellulose), lactose monohydrate, sodium lauryl sulfate, silica colloidal anhydrous, and magnesium stearate (E572).
Tablet coat - poly vinyl alcohol – part hydrolysed, titanium dioxide (E171), talc, lecithin (soya) (E322), and xanthan gum.

The two strengths have dose-proportional compositions.

II.2 Drug Substance

The active substance is atorvastatin calcium (as trihydrate), an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white powder, which is practically insoluble in water, slightly soluble in ethanol and practically insoluble in methylene chloride. Polymorphic form I is used. Atorvastatin calcium exhibits isomerism having a chiral carbon at the three and five position of its structure (R-isomer).

Two different manufacturers are used for the production of the active substance. For both manufacturers, the CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

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

Quality control of drug substance
The specification is set in line with the Ph.Eur. monograph, with additional requirements for residual solvent benzene, particle size and microbial contamination. The specification is considered acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches.

Stability of drug substance
The active substance is stable for 48 months (manufacturer-I) or 60 months (manufacturer-II) 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 development of the product has been described, the choice of excipients is justified and their functions are explained. The innovator product was characterised and the development was based on these results. Relevant optimisation studies on the excipients and manufacturing process were performed. Pharmaceutical development has been adequately performed.

One bioequivalence study has been submitted comparing Atorvastatine Aurobindo 80 mg, film-coated tablets with the reference product, Lipitor 80 mg film-coated tablets. The biowaiver for the additional strengths 30 mg and 60 mg is considered acceptable. The MAH provided comparative dissolution data. At pH 1.2 and pH 4.5 the f_2 similarity factor for 30 mg versus 80 mg was below 50. The f_2 factor for the 60 mg versus 80 mg tablet was in all three pH media above 50. The lack of similarity between different strengths of the 30 mg and 80 mg tablets is attributed to lack of sink conditions in different media owing to low solubility of drug substance and is not formulation related. In view of this the MAH has carried out dissolution profile using “three tablets of 30 mg strength” comparing it against the dissolution profile obtained using “one tablet of 80 mg strength” in different media. The dissolution profiles so obtained were evaluated and were found similar when compared at the same dose.

Manufacturing process
The manufacturing process includes milling, sifting, blending, and lubrication steps, followed by compression and film coating. Validation data on the process is considered adequate. The MAH will conduct process validation on the first three commercial batches post approval.

Control of excipients
The excipients comply with Ph.Eur. except for coating and cellulose, for which an acceptable in house specification is applied.

Quality control of drug product
The product specification includes tests for description, identification, (also for colorant), average mass, uniformity of dosage units (content uniformity), water content, dissolution, assay, related substance, thickness, and microbiological quality. The release and shelf-life specifications are the same with the exception of limits for water content and related substances. The specification is considered acceptable. The analytical methods have been adequately described and validated. Batch analysis results for several batches (using both drug substance manufactures) of all strengths showed compliance to the specification.

Stability of drug product
The submission and validation batches are also the stability batches. The 10 mg, 20 mg, 40 mg and 80 mg strength batches have been stored up to 36 months at 25°C/60% RH and 6 months at 40°C/75% RH. The new 30 mg and 60 mg strengths have been stored up to 12 months in long-term conditions and 6 months in accelerated conditions. All stability results met the set requirements and a shelf-life of 24 months is considered acceptable. The storage condition (no specific storage condition required) is also considered acceptable. Special precaution with respect to protection from light is not necessary for atorvastatin tablets.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate is the only excipient of animal origin. It is prepared without the use of other ruminant materials than milk and calf rennet. The supplier of lactose monohydrate has provided the required TSE/BSE certificate.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Atorvastatine Aurobindo 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)

The 30 mg and 60 mg strengths for atorvastatin have not yet been registered in the Netherlands. However, the strengths are already included in the dosing schedule as titration steps. Therefore it is argued that Atorvastatin Aurobindo 30 mg and 60 mg film-coated tablets 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

This product is a hybrid formulation of Lipitor tablets, which is available on the European market. Reference is made tot the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Atorvastatin is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this line extension, the bioequivalence study with the higher 80 mg strength that was used for the initial procedure (NL/H/2982/001-004/DC) has been submitted and a biowaiver has been requested for the additional strengths (30 mg and 60 mg). The bioequivalence study and the biowaiver will be discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Atorvastatine Aurobindo 80 mg, film-coated tablets (Aurobindo Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Lipitor 80 mg film-coated tablets (Pfizer Ireland Pharmaceuticals).

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

Biowaiver
Results of the bioequivalence study with the 80 mg tablets can be extrapolated to the dose-proportional 30 mg and 60 mg tablet strengths, respectively, since all conditions mentioned in the current Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled:

- The pharmaceutical products are manufactured by the same manufacturer and process.
- The drug kinetics are linear in the therapeutic dose range.
- The qualitative compositions of the different strengths are the same.
- The ratio between the active ingredient and the excipients is the same.
- The dissolution profiles are similar under identical conditions for the additional strengths and the strength that is used in the bioequivalence study.

Bioequivalence study
Design
A single-dose, randomised, open label, two-treatment, three sequence, three period, partial replicate crossover bioequivalence study was carried out under fasted conditions in 48 healthy subjects, aged 18-43 years. Each subject received a single dose (80 mg) of one of the two atorvastatin formulations under fasted conditions. There were three dosing periods, separated by a washout period of 13 days. The subjects received the test product once and the reference product twice.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 9, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The intra-subject variability of the reference product was investigated using the partial replicate design which is acceptable. The sampling scheme and wash-out between periods is acceptable in the light of the expected pharmacokinetic parameters of both the parent and the metabolites. However, the assessment of bioequivalence is based on the parent compound atorvastatin alone and not on the metabolites. Furthermore, the inclusion of subjects only completing two periods as described is acceptable. Subjects who completed two periods with at least one test and one reference treatment were included in pharmacokinetic and statistical analysis and were considered for bioequivalence, subjects who completed a minimum of two periods with two references in the study were to be analysed for intra-subject variability.

Overall, the design of the study is acceptable. According to the SmPC, atorvastatin may be taken at any time of the day, with or without food. Therefore, a study under fasted conditions is appropriate.

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. In particular the calculation of the widening of the acceptance criteria has been performed in accordance with the guideline.

Results
Two subjects were withdrawn in period 1 and blood samples were not analysed. One because the subject was not able to swallow the tablet, the other due to fever. For the following 11 subjects blood samples were analysed, but were not included in statistical analysis. Two subject were not included due to vomiting in period 1; seven subjects were absent for period 2, one subject was excluded because of vomiting in period 2 and one subject was voluntarily withdrawn in the second period. Two subjects completed two periods of the study, but received the reference product in both of them so bioequivalence evaluation in these subjects was not possible.
The remaining 33 subjects completed either two or all three periods of the study, including one period in which they received the test product, and were eligible for pharmacokinetic analysis. Blood samples were analysed for atorvastatin, ortho-hydroxylated atorvastatin, and para-hydroxylated atorvastatin.

Table 1. Geometric means and 90% confidence interval for atorvastatin (n, test=33; n, reference = 64)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	405 ± 203	411 ± 204	114 ± 70	1.25 (0.33 - 4.0)
Reference	369 ± 199	376 ± 199	100 ± 79	0.75 (0.33 - 6.0)
***Ratio (90% CI)**	1.04 (0.94 - 1.16)	1.04 (0.94 - 1.15)	1.11 (0.96 - 1.29)	--
CV (%)	29.9	29.0	42.4	--
CV of reference (%)	31.9	30.7	44.3	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until C_{max} is reached

**ln-transformed values*

Table 2. Geometric means and 90% confidence interval for ortho-hydroxylated atorvastatin (n, test=33; n, reference = 64)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	499 ± 271	508 ± 273	84 ± 52	1.75 (0.75 - 4.0)
Reference	477 ± 242	485 ± 243	81 ± 53	1.25 (0.5 - 6.0)
***Ratio (90% CI)**	1.02 (0.93 - 1.11)	1.01 (0.93 - 1.10)	1.05 (0.92 - 1.19)	--
CV (%)	23.4	22.9	35.8	--
CV of reference (%)	26.4	25.7	38.6	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

ln-transformed values

Table 3. Geometric means and 90% Confidence interval for para-hydroxylated atorvastatin (n, test=33; n, reference = 64)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	123 ± 77	131 ± 82	9.8 ± 7.1	4.0 (0.5 - 16)
Reference	109 ± 63	117 ± 69	7.7 ± 6.8	4.0 (0.5 - 16)
***Ratio (90% CI)**	1.06 (0.96 - 1.16)	1.05 (0.96 - 1.15)	1.23 (1.08 - 1.42)	--
CV (%)	25.5	24.7	38.7	--
CV of reference (%)	30.0	29.1	52.3	--

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

ln-transformed values

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and $AUC_{0-\infty}$ of atorvastatine, supported by the data of the metabolites, are within the bioequivalence acceptance range of 0.80 - 1.25. Based on the intra-subject CV of the reference product (44.3%) the 90% confidence interval for ln-transformed data of C_{max} was widened to the range 72.48 - 137.97%. The 90% CI for ln-transformed data of atorvastatin C_{max} was within this range. Based on the submitted bioequivalence study Atorvastatine Aurobindo 80 mg is considered bioequivalent with Lipitor 80 mg film-coated tablets.

A total of three adverse events were recorded in the study out of which one event was recorded in the subjects dosed with test product and two events were recorded in the subjects dosed with reference product. All three subjects experienced vomiting. The events were mild or moderate in severity, and were possibly or unlikely associated with study drug administration, and resolved without sequel.

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 Aurobindo.

Summary table of safety concerns as approved in RMP

Important identified risks	• Hepatotoxicity (increased transaminases, hepatitis, jaundice) • Haemorrhagic stroke • Rhabdomyolysis, de myopathy, myositis, myalgia, CK increases, myoglobinuria and myoglobinaemia • Interaction with CYP3A4 inhibitors • Diabetes mellitus
Important potential risks	• Interstitial lung disease • Sexual dysfunction
Important missing information	• Use in pregnancy or lactation • Paediatric use

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 and a biowaiver that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

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. The contents of the PL are identical to the agreed wording of the innovator product Lipitor 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets (DE/H/0109/001-004), except for the product specific information. Therefore user testing of the contents is not considered necessary. Further, regarding layout reference is made to the approved PL for Metoprolol Aurobindo (SE/H/1201/001-002/DC). The bridging report has been found acceptable. Separate user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Atorvastatine Aurobindo 30 mg and 60 mg film-coated tablets have a proven chemical-pharmaceutical quality and are hybrid forms of Lipitor 10 mg, 20 mg, 40 mg, and 80 mg film-coated tablets. Lipitor is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 the hybrid application for Atorvastatine Aurobindo 30 mg and 60 mg film-coated tablets is approvable and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 April 2017.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached