CBG MEB

Public Assessment Report

Scientific discussion

Atorvastatine Aurobindo 10 mg,20 mg, 40 mg, and 80 mg, film-coated tablets

(Atorvastatin calcium trihydrate)

NL/H/2982/001-004/DC

Date: 16 March 2015

This module reflects the scientific discussion for the approval of Atorvastatine Aurobindo film-coated tablets. The procedure was finalised on 3 July 2014. 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 10 mg, 20 mg, 40 mg, and 80 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 (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 approved 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 product Lipitor 10 mg, 20 mg, 40 mg, and 80 mg film-coated tablets (NL License RVG 21081-21083 and 27148). The 10 mg, 20 mg, and 40 mg strengths have been registered in the Netherlands by Pfizer B.V. since 21 April 1997 through MRP DE/H/0109/001-003. The 80 mg strength has been registered in the Netherlands by Pfizer B.V. since 4 June 2002 through MRP DE/H/0109/004. In addition, reference is made to Lipitor authorisations in the individual member states (reference product).

The concerned member states (CMS) involved in this procedure were Bulgaria (only 10 mg, 20 mg, and 40 mg), Cyprus, Denmark, France, Germany, Malta, Poland, Portugal, Romania, Spain, Sweden, and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Atorvastatine Aurobindo 10 mg is a white, elliptical [9.8 mm x 5.2 mm] film-coated tablet, debossed with “Y” on one side and “77” on other side.
Atorvastatine Aurobindo 20 mg is a white, elliptical [12.3 mm x 6.5 mm] film-coated tablet, debossed with “Y” on one side and “78” on other side.
Atorvastatine Aurobindo 40 mg is a white, elliptical [15.5 mm x 8.1 mm] film-coated tablet, debossed with “Y” on one side and “79” on other side.
Atorvastatine Aurobindo 80 mg is a white, elliptical [19.4 mm x 10.4 mm] film-coated tablet, debossed with “Y” on one side and “72” on other side.

The tablets are packed in in polyamide/ Aluminium foil/ PVC - Aluminium foil blisters packs and HDPE bottle packs with polypropylene closure. The bottle pack contains silica gel as desiccant.

The excipients are:

Tablet core – mannitol, copovidone, sodium carbonate anhydrous, croscarmellose sodium, silicified microcrystalline cellulose (contains silica, colloidal anhydrous and microcrystalline cellulose), lactose monohydrate, sodium lauryl sulfate, silica colloidal anhydrous, and magnesium stearate
Tablet coat - poly vinyl alcohol – part hydrolyzed, titanium dioxide (E171), talc, lecithin (soya), and xanthan gum.

The four 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 very slightly soluble in water, slightly soluble in ethanol and practically insoluble in methylene chloride Polymorphic form I is used. Atorvastatin calcium exhibits isomerism having chiral carbon at 3 and 5 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 European Pharmacopoeia.

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 3 full-scale batches.

Stability of drug substance
For the substance of the first manufacturer, the MAH claims a shelf-life of 24 months without any special storage conditions. Three batches have been put on stability (18 months at 25°C/60% RH, 6 months at 40°C/75% RH). Storage under long-term and accelerated conditions did not show any up- or downward trends indicating that the batches remain stable during the storage period of 18 months.
For the substance of the other manufacturer, the MAH claims a shelf-life of 36 months when stored below 30°C.Three batches have been put on stability (24 months at 30°C/65% RH, 6 months at 40°C/75% RH). Storage under long-term and accelerated conditions did not show any up- or downward trends indicating that the batches remain stable during the storage period of 24 months. The proposed re-test periods and storage conditions are considered acceptable for both manufacturers.

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 characterized and the development was based on these results. Relevant optimization studies on the excipients and manufacturing process were performed. Dissolution results are provided for the biobatches of the 80 mg test and reference product, as well as all strengths of the test product. Similarity has been sufficiently demonstrated. The biowaiver of strength for the 10, 20, and 40 mg film-coated tablets is considered acceptable from a chemical-pharmaceutical point of view.

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, HPLC assay, related substance by HPLC, 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
Stability data have been provided on three batches of each strength, stored for 24 months at 25°C/60% RH and for 6 months at 40°C/75% RH, packed in Alu/Alu-blister or HDPE bottles. All stability results met the set requirements and the proposed shelf-life of 24 months is acceptable. Photostability studies have been performed as per ICH guidance. No degradation is noted under these conditions; the product is considered photostable.The in-use stability studies are performed simulating withdrawal of 1 tablet per day for a period of 270 days (9 months). The product remains stable over time, only slight variation is noted in water content. An in-use storage time is not included in the SmPC, this is acceptable.
The proposed storage condition (none) is considered acceptable.

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.

The following post-approval commitments were made:
- The MAH committed to conduct validation on the first three batches of common blend each with four different batch sizes.
- The process validation activity on the first three batches for each strength will be conducted, if manufactured.
- The MAH committed to conduct dissolution profile studies for the first three production batches with the proposed higher batch. This will be done in the release media and the results will be compared against the bio-batch of the test product.
- The MAH committed to perform validation of batches manufactured with the active substance from one of the manufacturers for the first three batches of the larger batch size of the common blend, and for the additional batches of all strengths of the minimum batch size.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Atorvastatine Aurobindo 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 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 generic application, the MAH has submitted a 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 Aurobindo 80 mg (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
A biowaiver has been granted for the 10 mg, 20 mg, and 40 mg strengths, based on the following:

- 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 2 atorvastatin formulations under fasted conditions. There were 3 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 2 periods as described is acceptable. Subjects who completed 2 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 2 periods with 2 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 analyzed. One because the subject was not able to swallow the tablet, the other due to fever. For the following 11 subjects blood samples were analyzed, 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 2nd 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 Cmax is reached

**ln-transformed values*

Table 2 Geometric means and 90% Confidence interval for o-hydroxy 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 p-hydroxy 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 3 adverse events were recorded in the study out of which 1 event was recorded in the subjects dosed with test product and 2 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 tablets.

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 – Sleep disturbances (incl. insomnia and nightmares)

	– Diabetes mellitus
Important potential risks	– Interstitial lung disease – Sexual dysfunction – Interstitial lung disease
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 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

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, 20, 40, 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 Aurobindo10 mg, 20 mg, 40 mg, and 80 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Lipitor 10, 20, 40 mg, and 80 mg 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 essential similarity has been demonstrated for Atorvastatine Aurobindo 10 mg, 20 mg, 40 mg, and 80 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 July 2014.

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