Public Assessment Report

Decentralised Procedure

ATORVASTATIN 10 MG FILM-COATED TABLETS
ATORVASTATIN 20 MG FILM-COATED TABLETS
ATORVASTATIN 40 MG FILM-COATED TABLETS
ATORVASTATIN 80 MG FILM-COATED TABLETS

(Atorvastatin calcium trihydrate)

Procedure No: UK/H/3637/001-4/DC

UK Licence No: PL 34088/0008-11

ALKALOID-INT D.O.O.
LAY SUMMARY

On 30 August 2012, Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovenia, Slovakia and the UK agreed to grant Marketing Authorisations to Alkaloid –INT.d.o.o for the medicinal products Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets (PL 34088/0008-11; UK/H/3637/001-4/DC). The licences were granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After a subsequent national phase, Marketing Authorisations were granted in the UK on 25 October 2012. These are Prescription-Only Medicines (POM).

Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets contain atorvastatin as the active ingredient. Atorvastatin belongs to a group of medicines known as statins, which are lipid (fat) regulating medicines.

Atorvastatin is used to lower lipids known as cholesterol and triglycerides in the blood when a low fat diet and life style changes on their own have failed. If you are at an increased risk of heart disease, atorvastatin can also be used to reduce such risk even if your cholesterol levels are normal. You should maintain a standard cholesterol lowering diet during treatment.

No new or unexpected safety concerns arose from these applications and it was judged that the benefits of taking Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets outweigh the risks and therefore Marketing Authorisations were granted.
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# Module 1

| **Product Name** | Atorvastatin 10 mg film-coated tablets  
|                 | Atorvastatin 20 mg film-coated tablets  
|                 | Atorvastatin 40 mg film-coated tablets  
|                 | Atorvastatin 80 mg film-coated tablets. |
| **Type of Application** | Generic, Article 10.1 |
| **Active Substances** | Atorvastatin calcium trihydrate |
| **Form** | Film-coated tablets |
| **Strength** | 10 mg, 20 mg, 40 mg and 80 mg. |
| **MA Holder** | ALKALOID-INT d.o.o.  
|               | Šlandrova ulica 4  
|               | 1231 Ljubljana - Črnuče  
|               | Slovenia |
| **Reference Member State (RMS)** | UK |
| **Concerned Member States (CMS)** | Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovenia and Slovakia |
| **Procedure Number** | UK/H/3637/001-4/DC |
| **Timetable** | Day 210–30 August 2012. |
Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4
Labelling

Carton:

For oral use.
Read the package leaflet before use.

MA Holder: ALKALOID-INT d.o.o.
SDLovnica ulica 4, 1221 Ljubljana-Crnuče, Slovenia
FI 35088/0068

Each tablet contains 10 mg atorvastatin as atorvastatin calcium trihydrate. Also contains lactose. See leaflet for further information.

Keep out of the reach and sight of children.

Store below 25°C.

30 tablets
ATORVASTATIN 10 mg
film-coated tablets
atorvastatin
POM

braille reads
atorvastatin
10 mg
tables
Blister:
PAR Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets

**Carton:**

For oral use. Read the package leaflet before use.

MA Holder: ALKALOID-INT d.o.o., Šentrtove ulica 4,1231 Ljubljana-Crmoč, Slovenia
PL 3408860009

Each tablet contains 20 mg atorvastatin as atorvastatin calcium trihydrate. Also contains lactose. See leaflet for further information.

Keep out of the reach and sight of children.

Store below 25°C.

**Blisters:**
Blister:
PAR Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets

Carton:

For oral use.
Read the package leaflet before use.
MA Holder: ALKALOID-INT d.o.o.
Sandmanova ulica 4, 1221 Ljubljana-Crmoče, Slovenia
PL 34998/0011

Each tablet contains 80 mg atorvastatin as atorvastatin calcium trihydrate.
Also contains lactose. See leaflet for further information.
Keep out of the reach and sight of children.
Store below 25°C.

braille reads
atorvastatin
80 mg
tablets
Blister:
Module 5
Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets (PL 34088/0008-11; UK/H/3637/001-4/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovenia and Slovakia as Concerned Member States (CMS). These products are prescription-only medicines (POM).

Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets are indicated for:

- **Hypercholesterolaemia**
  Atorvastatin is indicated as an adjunct to diet for reduction of elevated total cholesterol (total-C), low-density lipoprotein (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 non-pharmacological measures is inadequate.

- **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 SmPC), as an adjunct to correction of other risk factors.

These are abridged applications submitted under Article 10(1) of Directive 2001/83/EC as amended, cross-referring to Lipitor 10mg, 20mg, 40mg and 80mg Tablets (Pfizer Ireland Pharmaceuticals, UK), which were first authorised on 07 November 1996 (10 mg, 20 mg and 40 mg strength) and 15 August 2000 (80 mg strength). The reference products have been registered in the EEA for more than 10 years, hence the period of data exclusivity has expired. The reference product used in the bioequivalence study was Sortis 80 mg film-coated tablets (Parke-Davis GmbH/Pfizer Pharma GmbH) taken from the German market. It has been confirmed that this product is identical to the equivalent product in the UK (Lipitor 80mg Tablets).

Atorvastatin is a selective, competitive HMG-CoA reductase inhibitor. Atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver, and by increasing the number of hepatic low-density lipoprotein (LDL) receptors on the cell-surface to enhance uptake and catabolism of LDL. Atorvastatin also reduces LDL production and the number of LDL particles.
No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic versions of the originator products that have been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support these applications, comparing the test product Atorvastatin 80 mg film-coated tablets (Alkaloid –INT.d.o.o) with the reference product Sortis 80 mg film-coated tablets (Parke-Davis GmbH/Pfizer Pharma GmbH).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic versions of the originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 210) on 30 August 2012. After the subsequent national phase, the licences were granted in the UK on 25 October 2012.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Atorvastatin 10 mg film-coated tablets  
Atorvastatin 20 mg film-coated tablets  
Atorvastatin 40 mg film-coated tablets  
Atorvastatin 80 mg film-coated tablets |
| Name(s) of the active substance(s) (INN) | Atorvastatin calcium trihydrate |
| Pharmacotherapeutic classification (ATC code) | Lipid modifying agents, HMG-CoA-reductase inhibitors, (C10AA05). |
| Pharmaceutical form and strength(s) | 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets |
| Reference numbers for the Mutual Recognition Procedure | UK/H/3637/001-4/DC |
| Reference Member State | United Kingdom |
| Concerned Member State | Bulgaria, Czech Republic, Hungary, Poland, Romania, Slovenia and Slovakia |
| Marketing Authorisation Number(s) | PL 34088/0008-11 |
| Name and address of the authorisation holder | ALKAloid-INT d.o.o.  
Šlandrova ulica 4  
1231 Ljubljana - Črnuče  
Slovenia |
III  SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Active substance

INN: Atorvastatin calcium trihydrate
Chemical names: Calcium(3R,5R)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenyl carbamoyl)-5-(propan-2-yl)-1H-pyrrol-1-yl]-3,5dihydroxyheptanoate calcium trihydrate

\[ \beta R, \delta R)-2-(4-\text{fluorophenyl})-\beta,\delta-\text{dihydroxy-5-(1-methyl ethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1Hpyrrole-1-heptanoic acid, calcium trihydrate} \]

Structure:

![Structure of Atorvastatin Calcium Trihydrate](image)

Molecular formula: \((C_{33}H_{34}FN_{2}O_{5})_2 \text{Ca. } 3H_2O\)
Molecular mass: 1209.42
Appearance: Atorvastatin calcium trihydrate is a white or almost white powder.
Solubility: Atorvastatin calcium trihydrate is very slightly soluble in water, slightly soluble in ethanol (96%) and practically insoluble in methylene chloride

Atorvastatin calcium trihydrate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

**P. Medicinal Product**

**Other Ingredients**

Other ingredients consist of the pharmaceutical excipients lactose monohydrate / microcrystalline cellulose, calcium carbonate, copovidone VA 64, crospovidone type B croscarmellose sodium, sodium laurilsulfate, colloidal anhydrous silica, talc, magnesium stearate and opadry white Y-1-7000 (comprising of hypromellose, titanium dioxide E 171 and macrogol 400).

All excipients comply with their respective European Pharmacopoeia monographs with the exception of opadry white Y-1-7000 which is controlled to suitable in-house specifications. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

**Pharmaceutical Development**

The objective of the development programme was to formulate stable, robust, film-coated tablets containing 10 mg, 20 mg, 40 mg or 80 mg atorvastatin, which could be considered generic medicinal products of Lipitor 10mg, 20mg, 40mg and 80mg Tablets (Pfizer Ireland Pharmaceuticals, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

**Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial scale and has shown satisfactory results.

**Finished Product Specification**

The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.
Container-Closure System
All strengths of the finished product are packaged in polyvinylchloride (PVC)/polyvinylidene chloride (PVdC)/hard aluminium foil blister strips in pack sizes of 30 film-coated tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years with the storage conditions ‘Store below 25°C.’

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA forms are satisfactory.

Quality Overall Summary
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical view-point.

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of atorvastatin are well-known, no new non-clinical studies are required and none have been provided.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Since Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets are intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment (ERA) is therefore not deemed necessary.

There are no objections to the approval of these products from a non-clinical view-point.
III.3 CLINICAL ASPECTS

Pharmacokinetics

In support of these applications, the marketing authorization holder has submitted the following bioequivalence study:

A randomised, single-dose, three-period, crossover reference-replicate bioavailability study to compare the pharmacokinetics of the test product Atorvastatin 80 mg film-coated tablets (Alkaloid –INT.d.o.o) versus the reference product Sortis 80 mg film-coated tablets (Parke-Davis GmbH/Pfizer Pharma GmbH) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 80 mg tablet administered after an overnight fast of at least 10 hours. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 14 days.

The pharmacokinetic results for atorvastatin are presented below [mean, standard deviation (SD) and % confidence intervals):

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Test (ATORVASTATIN (A))</th>
<th>Fast Administration</th>
<th>Reference (SORTIS® (B))</th>
<th>Second Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>CV (%)</td>
<td>Mean</td>
</tr>
<tr>
<td>AUC0-0</td>
<td>184343.54</td>
<td>85903.74</td>
<td>46.50</td>
<td>192474.44</td>
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<tr>
<td>AUC0-t</td>
<td>190690.14</td>
<td>89541.22</td>
<td>45.81</td>
<td>196911.71</td>
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<tr>
<td>Cmax</td>
<td>49544.57</td>
<td>28458.05</td>
<td>63.18</td>
<td>49334.56</td>
</tr>
<tr>
<td>Residual area (%)</td>
<td>2.41</td>
<td>2.33</td>
<td>96.51</td>
<td>2.44</td>
</tr>
<tr>
<td>Tmax</td>
<td>1.39</td>
<td>0.92</td>
<td>70.84</td>
<td>0.962</td>
</tr>
<tr>
<td>T1/2</td>
<td>1.09</td>
<td>1.12</td>
<td>-</td>
<td>0.667</td>
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<tr>
<td>K12</td>
<td>0.0738</td>
<td>0.0128</td>
<td>17.37</td>
<td>0.0717</td>
</tr>
<tr>
<td>T1/2</td>
<td>9.75</td>
<td>2.22</td>
<td>22.77</td>
<td>9.93</td>
</tr>
</tbody>
</table>

* Median and interquartile ranges are presented.

AUC0-0 area under the plasma concentration-time curve from time zero to infinity
AUC0-t area under the plasma concentration-time curve from time zero to t hours
Cmax maximum plasma concentration
Tmax time at which peak concentration is achieved
K12 % of the total amount of drug in body eliminated per unit of time
T1/2 elimination half life

The treatment comparisons for atorvastatin are presented below: (ratio of least-squares means, 90% Confidence Interval):

| Statistical Analysis | Ratio of LS Means 1 | 90% Geometric C.I. 2 | CV 1
<table>
<thead>
<tr>
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<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td>Lower</td>
</tr>
<tr>
<td>AUC0-0</td>
<td>98.89%</td>
<td>93.80%</td>
<td>104.26%</td>
</tr>
<tr>
<td>AUC0-t</td>
<td>98.83%</td>
<td>93.87%</td>
<td>104.06%</td>
</tr>
<tr>
<td>Cmax</td>
<td>92.70%</td>
<td>82.42%</td>
<td>104.25%</td>
</tr>
</tbody>
</table>

1 Calculated using least-squares means (In-transformed data)
2 90% Geometric Confidence Interval using In-transformed data

AUC0-0 area under the plasma concentration-time curve from time zero to infinity
AUC0-t area under the plasma concentration-time curve from time zero to t hours
Cmax maximum plasma concentration
CVWR within-subject variability
The 90% confidence intervals for AUC and $C_{\text{max}}$ for test versus reference product for atorvastatin are within predefined acceptance criteria specified in "Guideline on the Investigation of Bioequivalence" (CPMP/EWP/QWP/1401/98 Rev 1/, Corr). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 10 mg, 20 mg and 40 mg and 80 mg strengths of the product meet the criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 80 mg strength can be extrapolated to the 10 mg, 20 mg and 40 mg strengths.

**Pharmacodynamics**
No new pharmacodynamic data were submitted and none were required for these applications.

**Efficacy**
No new efficacy data were submitted and none were required for these applications.

**Safety**
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

**MAA Forms**
The MAA forms are satisfactory.

**Clinical Overview**
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Pharmacovigilance System and Risk Management Plan**
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

**Conclusion**
There are no objections to the approval of these products from a clinical view-point.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The quality characteristics of Atorvastatin 10 mg, 20 mg, 40 mg and 80 mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of atorvastatin are well-known.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant’s Atorvastatin 80 mg film-coated tablets and its respective reference product Sortis 80 mg film-coated tablets (Parke-Davis GmbH/Pfizer Pharma GmbH). As the 10 mg, 20 mg, 40 mg and 80 mg strengths of the product meet the biowaiver criteria specified in “Guideline on the Investigation of Bioequivalence” (CPMP/EWP/QWP/1401/98 Rev 1/, Corr), the results and conclusions of the bioequivalence study on the 80 mg strength can be extrapolated to the 10 mg, 20 mg and 40 mg strengths.

SAFETY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of atorvastatin is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE
The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, and in line with current guidelines.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with atorvastatin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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