IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Atorvastatin OPKO 40 mg film coated tablets
Atorvastatin calcium trihydrate
PA23271/001/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Atorvastatin OPKO 40mg film-coated tablets, from Opko Health Spain S.L.U. on 9th June 2023 for the treatment of hypercholesterolaemia and prevention of cardiovascular disease.

With Ireland as the Reference Member State, marketing authorisations are applied for in IE and ES under procedure IE/H/1205/001/DC. This decentralised application is submitted as a generic application according to Article 10(1) of Directive 2001/83/EC. The active substance, atorvastatin (as calcium trihydrate), is not considered a new active substance. The reference product is Lipitor 40 mg Film-coated tablet (MAH: Pfizer) authorised in Ireland since 14 November 1997.

This product is subject to medical prescription which may be renewed. Supply is through pharmacies only and advertising allowed to healthcare professionals only.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Atorvastatin OPKO 40 mg film coated tablets
Name(s) of the active substance(s) (INN)	Atorvastatin calcium trihydrate
Pharmacotherapeutic classification (ATC code)	C10AA05
Pharmaceutical form and strength(s)	40 mg film coated tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA 23271/001/001
Marketing Authorisation Holder	Opko Health Spain S.L.U
MRP/DCP No.	IE/H/1205/001/DC
Reference Member State	IE
Concerned Member State	ES

II. QUALITY ASPECTS

II.1. Introduction

This application is for Atorvastatin OPKO 40 mg film coated tablets.

II.2 Drug substance

The active substance is Atorvastatin Calcium Trihydrate, an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each film-coated tablet contains atorvastatin calcium trihydrate, corresponding to 40 mg of atorvastatin.
The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients/*Ancillary Substances*)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Atorvastatin OPKO 40 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance, atorvastatin, is a generic formulation of Lipitor 40 mg Film-coated tablet (Pfizer). No new preclinical data have been submitted.

The pharmacodynamic, pharmacokinetic and toxicological properties of atorvastatin are well known. As atorvastatin is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The overview provided based on literature review is thus appropriate.
or

III.2 Ecotoxicity/environmental risk assessment

Since Atorvastatin OPKO 40 mg film-coated tablets 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.3 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of atorvastatin are well known. As atorvastatin is a widely used, well-known active substance, and this is a generic application, the applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology provided is adequate.

IV. CLINICAL ASPECTS

Atorvastatin is a well known active substance with established efficacy and tolerability.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product, Lipitor, marketed by Pfizer Ireland Pharmaceuticals.

For this generic application, the applicant has submitted 1 bioequivalence study in which the pharmacokinetic profile of the test product Atorvastatin 80 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Lipitor 80 mg film-coated tablets. It is noted that bioequivalence is conducted on the 80mg strength and a biowaiver of strength is applied for the 40 mg strength for which the applicant is applying. Given that full data on the 80 mg strength is available in the dossier and the biowaiver of strength criteria are met in line with the *Guideline on the Investigation of Bioequivalence*, this is accepted from a scientific perspective.

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover, full replicate. oral bioequivalence study was carried out. Atorvastatin 80mg film-coated tablets of Medreich Limited., India, was compared to the reference product Lipitor (Atorvastatin 80 mg film-coated tablets of Pfizer Ireland Pharmaceuticals, Operations Support Group, Ringaskiddy, Co Cork, Ireland. Based on the pharmacokinetic parameters of active substance, the reference tablet Lipitor 80 mg marketed by Pfizer and test tablet Atorvastatin 80 mg film-coated tablets are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance. A biowaiver has been accepted for the applied for product, Atorvastatin OPKO 40mg film-coated tablets.

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

IV.2 Pharmacokinetics

Absorption
Atorvastatin is rapidly absorbed after oral administration, maximum plasma concentrations (Cmax) occur within 1 to 2 hours. The low absolute bioavailability of atorvastatin parent drug of approximately 12% -14% is due to presystemic clearance in the gastrointestinal mucosa and/or firstpass metabolism in the liver, its primary site of action. The systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. Although food decreases rate and extent (Cmax, AUC) of drug absorption by approximately 25.2% and 8.6% respectively, LDL-C reduction is similar whether atorvastatin is given with or without food. Following evening drug administration atorvastatin plasma concentrations are 30% lower for Cmax and AUC when compared with morning drug administration. However, LDL-C reduction is the same regardless of the time of day of administration. Extent of absorption increases in proportion to atorvastatin dose. Dose dependent reductions in LDL cholesterol levels ranging from 41% to 61% have been reported for the dose range of 10 to 80 mg/dl. Grapefruit juice in large amounts has been shown to interfere with the metabolism of atorvastatin, causing increases in Cmax and AUC.

Distribution
Mean volume of distribution of atorvastatin is approximately 381 L, determined following administration of 5 mg as an intravenous infusion. Plasma protein binding is up to 98%.

Metabolism
Atorvastatin undergoes extensive hepatic and/or extra-hepatic metabolism. Atorvastatin is metabolized by cytochrome P450 3A4 to ortho (= 2-OH)- and para-(= 4-OH)hydroxylated derivates and various beta-oxidation products. Atorvastatin and its 2-OH- and 4-OH- metabolites were found to have equal inhibitory effects on HMG-CoA reductase in vitro. The active metabolites are responsible for approximately 70% of the inhibition of HMG-CoA reductase. Atorvastatin is extensively metabolized in the gut wall and liver, at least in part by the CYP3A4 enzymes. The 2-OH- and 4-OH-atorvastatin metabolites have HMG-CoA reductase inhibitory activity equal to that of Atorvastatin. Approximately 70% of atorvastatin's pharmacological activity is attributed to active metabolites. However, the 4-OH-metabolite has much lower concentrations and may not contribute significantly to the drug activity. Therefore, additional to the plasma concentrations of atorvastatin, concentrations of the active metabolite ortho-hydroxyatorvastatin (2-OH-Atorvastatin) were measured.

Elimination
T 1/2β is approximately 14 hours however due to the contribution of active metabolites the inhibitory activity for HMG-CoA reductase is approximately 20 – 30 hours.

Drug-Drug interactions and drugs whose pharmacokinetics are influenced by atorvastatin
Theoretically, all drugs that are inhibitors of CYP3A4 isoenzyme have the potential to increase atorvastatin plasma concentrations during their concomitant use.
SmPC Section 4.5, Table 1 and Table 2 adequately cover potential interactions and provides clinical recommendations to mitigate/minimize toxicity.

The clinical overview on the clinical pharmacology is adequate.

IV.3 Pharmacodynamics

Atorvastatin is a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase which is used for the treatment of hypercholesterolemia. HMG-CoA reductase is the rate-limiting enzyme in de novo cholesterol synthesis.
HMG-CoA reductase inhibitors appear to reduce the production of mevalonic acid from HMG-CoA, resulting in a reduction in hepatic cholesterol synthesis. This in turn results in a compensatory increase in the expression of high affinity low-density lipoprotein (LDL) receptors on hepatocyte membranes and stimulation of LDL catabolism. It is in this manner that atorvastatin produces the lowering of plasma total and LDL cholesterol levels observed in patients with hypercholesterolemia. Reductions in the hepatic pool of cholesterol have also been associated with a decrease in the rate of production of very-low-density lipoprotein (VLDL) and/or LDL by the liver.
Atorvastatin reduces total-C, LDL-C, VLDL-C, Apo B, and TG, and increases HDL-C in patients with hypercholesterolemia and mixed dyslipidemia. Therapeutic response is seen within 2 weeks, and maximum response is usually achieved within 4 weeks and maintained during chronic therapy

IV.4 Clinical Efficacy

No new clinical trials were submitted as part of this application. The clinical overview on the clinical efficacy is adequate.

IV.5 Clinical Safety

No new clinical trials were submitted as part of this application. The clinical overview on the clinical safety is adequate.

Risk Management Plan

The applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Atorvastatin OPKO 40 mg film-coated tablets.

Summary of safety concerns	
Important identified risks	- Skeletal muscle effects (including Immune-mediated necrotizing myopathy), rhabdomyolysis and rhabdomyolysis-related events - Hepatic failure
Important potential risks	None
Missing information	None

Pharmacovigilance Plan
Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

The submitted Risk Management Plan, version 1.0, signed 06/03/2023 is considered acceptable.

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

IV.6 Discussion on the clinical aspects

This application contains a review of published clinical data and bioequivalence has been shown between the test product Atorvastatin 80mg film coated-tablet and the reference product Lipitor 80mg film-coated tablet. A biowaiver has been accepted for the applied for product, Atorvastatin OPKO 40mg film-coated tablets.

V. OVERALL CONCLUSIONS

In general, it is widely accepted that the benefit risk of Atorvastatin OPKO 40 mg film-coated tablets is positive. From a clinical and quality perspective the overall assessment outcome of Atorvastatin OPKO 40 mg film-coated tablets is positive.

Safety issues arise mostly due to drug-drug interactions and these risks are detailed in the SmPC.

Atorvastatin OPKO 40 mg film-coated tablets is a generic form of Lipitor. Lipitor is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Atorvastatin OPKO demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile, has granted a marketing authorisation.

VI. REVISION DATE

02.05.2028