IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Atorvastatin Genericon 10 mg film-coated tablets
Atorvastatin calcium trihydrate
PA23172/001/001

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 Genericon 10, 20, 40, 80 mg film-coated tablets, from Genericon Pharma Gesellschaft m.b.H., on 28th October 2022 for

Hypercholesterolaemia
Atorvastatin Genericon 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 Genericon 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), as an adjunct to correction of other risk factors.

The legal basis for this submission in IE is article 10.1 of directive 2001/83/EC as amended.
The originator product is Sortis film-coated tablet by PFIZER PHARMA PFE GmbH, registered since 1997-01-09.

This product is subject to prescription which may be renewed (B), supply is through pharmacies only with advertising allowed to HCPs.

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 Genericon 10mg Film-coated tablet
Name(s) of the active substance(s) (INN)	Atorvastatin (as calcium trihydrate)
Pharmacotherapeutic classification (ATC code)	C10AA05
Pharmaceutical form and strength(s)	10mg Film-coated tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA23172/001/001
Marketing Authorisation Holder	Genericon Pharma Gesellschaft m.b.H.,
MRP/DCP No.	IE/H/1170/001/DC
Reference Member State	IE
Concerned Member State	AT HR

II. QUALITY ASPECTS

II.1. Introduction

This application is for Atorvastatin Genericon 10mg, 20 mg, 40 mg, 80 mg film-coated tablets.

II.2 Drug substance

The active substance is atorvastatin, present as atorvastatin calcium trihydrate. It is 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 10 mg, 20 mg, 40 mg, or 80 mg of atorvastatin depending on the strength indicated.
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 GMP at suitably qualified manufacturing sites.

The manufacturing process has been validated for certain aspects according to relevant European/ICH guidelines. Any outstanding validation will be appropriately conducted in line with these guidelines.

P.4 Control of Other Substances (Excipients)

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 general 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 sites 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 Genericon 10 mg, 20mg, 40 mg and 80 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Sortis (Pfizer) Tablets. 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.

III.2 Ecotoxicity/environmental risk assessment

Since Atorvastatin Genericon 10 mg, 20 mg, 40 mg, and 80 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

IV.1 Introduction
ATC Code: C10AA05
Pharmacortherapeutic group: HMG-CoA reductase inhibitors (statins)

Atorvastatin is a synthetic HMG-CoA reductase inhibitor (Statin**).**

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols including cholesterol. It also has a secondary effect of reducing triglyceride levels.
Atorvastatin reduces levels of cholesterol and lipoproteins in plasma by inhibiting of HMG-CoA reductase and by inhibiting the synthesis of cholesterol in the liver, and it increases a number of hepatic LDL receptors on the cellular surface, accelerating the absorption and catabolism of LDL. Atorvastatin reduces the production of LDL and a number of LDL particles. It also decreases LDL-cholesterol levels in patients with homozygous familial hypercholesterolemia.
It has been demonstrated that reduction of total cholesterol, LDL-cholesterol and triglycerides decreases the risk of cardiovascular morbidity and cardiovascular mortality.
Atorvastatin is currently approved as an adjunct to diet for reduction of elevated total cholesterol, LDL cholesterol, apolipoprotein B and triglycerides in patients with primary hypercholesterolemia (including heterozygous, familial hypercholesterolemia) or mixed hyperlipidaemia, when response to diet and other non-pharmacological measures are inadequate. Atorvastatin is also indicated to reduce total- or LDL-cholesterol in patients suffering from homozygous familial hypercholesterolemia, either combined with procedures such as aphaeresis and in the absence of the availability of such trreatments. Furthermore, Atorvastatin is indicated as primary prevention of cardiovascular events. Approved doses include 10, 20, 40 and 80mg once daily, independent of meals. The patient should be placed on a standard cholesterol-lowering diet before receiving a statin and should continue on this diet during treatment. The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response.
The usual starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more. The maximum dose is 80 mg once a day.

Therapeutic indications
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), as an adjunct to correction of other risk factors.

Posology and method of administration

Posology

The patient should be placed on a standard cholesterol-lowering diet before receiving Atorvastatin and should continue on this diet during treatment with Atorvastatin.

The dose should be individualised according to baseline LDL-C levels, the goal of therapy, and patient response.

Starting dose is 10 mg once a day. Adjustment of dose should be made at intervals of 4 weeks or more.

The maximum dose is 80 mg once a day.

Co-administration with other medicines

In patients taking hepatitis C antiviral agents elbasvir/grazoprevir concomitantly with atorvastatin, the dose of atorvastatin should not exceed 20 mg/day (see sections 4.4 and 4.5).

Primary hypercholesterolaemia and combined (mixed) hyperlipidaemia

The majority of patients are controlled with Atorvastatin 10 mg once a day. A therapeutic response is evident within 2 weeks, and the maximum therapeutic response is usually achieved within 4 weeks. The response is maintained during chronic therapy.

Heterozygous familial hypercholesterolaemia

Patients should be started with Atorvastatin 10 mg daily. Doses should be individualised and adjusted every 4 weeks to 40 mg daily. Thereafter, either the dose may be increased to a maximum of 80 mg daily or a bile acid sequestrant may be combined with 40 mg atorvastatin once daily.

Homozygous familial hypercholesterolaemia

Only limited data are available (see section 5.1).
The dose of atorvastatin in patients with homozygous familial hypercholesterolemia is 10 to 80 mg daily (see section 5.1). Atorvastatin should be used as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) in these patients or if such treatments are unavailable.

Prevention of cardiovascular disease

In the primary prevention trials the dose was 10 mg/day. Higher doses may be necessary in order to attain (LDL-) cholesterol levels according to current guidelines.

Renal impairment

No adjustment of dose is required (see section 4.4).

Hepatic impairment

Atorvastatin should be used with caution in patients with hepatic impairment (see sections 4.4 and 5.2). Atorvastatin is contraindicated in patients with active liver disease (see section 4.3).

Elderly

Efficacy and safety in patients older than 70 using recommended doses are similar to those seen in the general population.

Paediatric population

Hypercholesterolaemia

Paediatric use should only be carried out by physicians experienced in the treatment of paediatric hyperlipidaemia and patients should be re-evaluated on a regular basis to assess progress.

For patients with Heterozygous Familial Hypercholesterolemia aged 10 years and above, the recommended starting dose of atorvastatin is 10 mg per day (see section 5.1). The dose may be increased to 80 mg daily, according to the response and tolerability. Doses should be individualized according to the recommended goal of therapy. Adjustments should be made at intervals of 4 weeks or more. The dose titration to 80 mg, daily is supported by study data in adults and by limited clinical data from studies in children with Heterozygous Familial Hypercholesterolemia (see sections 4.8 and 5.1).

There are limited safety and efficacy data available in children with Heterozygous Familial Hypercholesterolemia between 6 to 10 years of age derived from open-label studies. Atorvastatin is not indicated in the treatment of patients below the age of 10 years. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Other pharmaceutical forms/strengths may be more appropriate for this population.

Method of administration
Atorvastatin is for oral administration. Each daily dose of atorvastatin is given all at once and may be given at any time of day with or without food.

The applicant has conducted one bioequivalence study, at 80mg, to support this application. A biowaiver has been submitted for the 10mg, 20mg and 40mg doses.

The 'ten-year rule' applies and, in accordance with these provisions the Applicant has not conducted clinical studies in support of this application. However, a bioequivalence study has been performed to determine therapeutic equivalence and to complete the demonstration of essential similarity within the terms of article 10(2)(b) Directive 2004/27/EC.
To support the application, the applicant has submitted as one bioequivalence study. This is a comparative single-dose bioavailability study of two 80 mg atorvastatin tablet
formulations in healthy volunteers under fasting conditions. The study code is OTA-2413-10.

This was a single centre, randomized, single-dose, 3-period crossover reference-replicate BA study to compare the bioavailability of the test ATORVASTATIN versus and the reference SORTIS®, under fasting conditions.
A total of 45 healthy, male subjects were enrolled in this study. 44 subjects completed the study. In accordance with the study protocol, data from all subjects who completed the three study periods and for whom the pharmacokinetic profile was adequately characterized were used for pharmacokinetic and statistical analyses (N=44). Subject No. 25 was not included in the pharmacokinetic and statistical analyses since there was no
available concentration in Period 3.
Blood samples for PK analysis were taken at designated times.
Bioequivalence with the reference product was demonstrated.

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, efficacy and safety 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.

IV.5 Clinical Safety

No new clinical trials were submitted as part of this application.

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 Atorvastatin.

The submitted Risk Management Plan, version 1.0 signed 26.01.2021 is considered acceptable. Summary of safety concerns as approved in RMP:

Summary of safety concerns	
Important identified risks	None
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.

Periodic Safety Update Report (PSUR)

- With regard to PSUR submission, the MAH should take the following into account:
- 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.

Common renewal date
The common renewal date shall be 5 years following authorisation.

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 Atorvastatin (SORTIS) 80mg film coated tablet.

V. OVERALL CONCLUSIONS

In general, it is widely accepted that the benefit risk of Atorvastatin is positive.
Safety issues arise mostly due to drug-drug interactions and these risks are detailed in the SmPC.
From a clinical and quality perspective the overall assessment outcome of Atorvastatin Genericon 10, 20, 40, 80 mg film-coated tablets is positive.

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.

VI. REVISION DATE

Common renewal date
The common renewal date shall be 5 years following authorisation.