IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Atorvastatin Bluefish 20 mg Film-coated tablets
Atorvastatin Calcium Trihydrate
PA1436/027/002

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 Bluefish 10mg, 20mg, 30mg, 40mg, 60mg & 80mg Film-coated tablets, from Bluefish Pharmaceuticals AB on 30/11/2018 for:

Hypercholesterolaemia
Atorvastatin Bluefish 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 Bluefish 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 original decentralised procedure application was NL/H/3796/001-006 with Netherlands (NL) as reference member state (RMS) and concerned member state (CMS) Poland (PL) which completed on 15th June 2017. During the mutual recognition procedure NL/H/3796/001-006/E/001 which ended on 26th September 2018, CMS' Ireland (IE) and Austria (AT) were added. Ireland (IE) took over as RMS on 11/12/2019. During repeat use procedure IE/H/1099/001-006/E/002 which completed on 9/6/2021, CMS Spain (ES) was added.

The legal bases are:
10mg, 20mg, 40mg, 80mg: 10(1) of Directive 2001/83/EC
30mg, 60mg: 10(3) of Directive 2001/83/EC

These products are subject to prescription.

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 Bluefish 10mg, 20mg, 30mg, 40mg, 60mg & 80mg Film-coated tablets
Name(s) of the active substance(s) (INN)	PREGABALIN
Pharmacotherapeutic classification (ATC code)	C10AA05
Pharmaceutical form and strength(s)	10mg, 20mg, 30mg, 40mg, 60mg & 80mg Film-coated tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA1436/027/001-006
Marketing Authorisation Holder	Bluefish Pharmaceuticals AB
MRP/DCP No.	IE/H/1099/001-006/E02
Reference Member State	IE
Concerned Member State	ES

II. QUALITY ASPECTS

This application is for Atorvastatin Bluefish 10 mg, 20 mg, 40 mg, 60 mg and 80 mg film-coated tablets.

II.2 Drug substance

The active substance is Atorvastatin calcium trihydrate, an established active substance described in the European Pharmacopoeia, monograph number 2191, and is manufactured in accordance with the principles of Good Manufacturing

Practice (GMP). EDQM Certificate of suitability (CEP) procedure is used. The manufacturer of the drug substance Atorvastatin calcium trihydrate dihydrate has obtained a certificate of suitability and the CEP is presented in the documentation.

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
Atorvastatin Bluefish tablets 10 mg film-coated tablets: white oblong, film-coated tablets, embossed 10 on one side and 'ATV' on the other side and length: 8.3 mm; width: 4.2 mm.
Atorvastatin Bluefish 20 mg film-coated tablets: white oblong film-coated tablets, embossed 20 on one side and 'ATV' on the other side and 10.6 mm; width: 5.3 mm
Atorvastatin Bluefish 30 mg film-coated tablets: white oblong film-coated tablets, embossed 30 on one side and 'ATV' on the other side and 12.2 mm; width 6.1 mm
Atorvastatin Bluefish 40 mg film-coated tablets: white oblong film-coated tablets, embossed 40 on one side and 'ATV' on the other side and 13.3 mm; width: 6.7 mm
Atorvastatin Bluefish 60 mg film-coated tablets: white oblong film-coated tablets, embossed 60 on one side and 'ATV' on the other side and 15.3 mm width: 7.6 mm
Atorvastatin Bluefish 80 mg film-coated tablets: white oblong film-coated tablets, embossed 80 on one side and 'ATV' on the other side and length: 16.8 mm; width: 8.3 mm).

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. Use of the excipients is justified.

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 and 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 Tablets, and the tests and control limits are considered appropriate for this type of product.
Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory description and validation data for analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

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 Bluefish 10 mg, 20 mg, 40 mg, 60 mg and 80 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Lipitor film-coated tablets, MAH Pfizer B.V., authorised since April 21st 1997 on the European market. No new preclinical data have been submitted. As such, no pre-clinical assessment has been made on the application. This is acceptable for this type of application.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the MR procedure is in accordance with that accepted for the reference product Lipitor film-coated tablets marketed by Pfizer B.V.

Lipitor is known in several other EU member states under the product names Sortis and they are both from the same Global Marketing Authorisation.

A single-dose, randomised, two-treatment, two-sequence, four-period, replicate crossover study was carried out. Pfizer compared Atorvastatin 80mg DSM film-coated tablet, to the reference product Sortis 80 mg from the German market. Based on the pharmacokinetic parameters of active substance atorvastatin, the reference tablet Sortis 80mg marketed by Pfizer and test tablet Atorvastatin 80mg DSM film-coated tablet 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 for the 10, 20, 30, 40 and 60 mg strengths was accepted. The results of the bioequivalence study performed with the Atorvastatin 80mg DSM film-coated tablet therefore apply to the other strengths.

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 (C_{max}) occur within 1 to 2 hours.

Distribution

Mean volume of distribution of atorvastatin is approximately 381 l. Atorvastatin is [3] 98% bound to plasma proteins.

Biotransformation

Atorvastatin is metabolized by cytochrome P450 3A4 to ortho- and parahydroxylated derivatives and various beta-oxidation products.

Elimination

Atorvastatin is eliminated primarily in bile following hepatic and/or extrahepatic metabolism. However, atorvastatin does not appear to undergo significant enterohepatic recirculation. Mean plasma elimination half-life of atorvastatin in humans is approximately 14 hours. The half-life of inhibitory activity for HMG-CoA reductase is approximately 20 to 30 hours due to the contribution of active metabolites.

IV.3 Pharmacodynamics

Atorvastatin belongs to the pharmacotherapeutic group: Lipid modifying agents, HMG-CoA-reductase inhibitors, ATC code: C10AA05.

Atorvastatin is a selective, competitive inhibitor of HMG CoA reductase, the rate-limiting enzyme responsible for the conversion of 3-hydroxy-3-methyl-glutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Triglycerides and cholesterol in the liver are incorporated into very low-density lipoproteins (VLDL) and released into the plasma for delivery to peripheral tissues. Low-density lipoprotein (LDL) is formed from VLDL and is catabolized primarily through the receptor with high affinity to LDL (LDL receptor).

Atorvastatin lowers plasma cholesterol and lipoprotein serum concentrations by inhibiting HMG-CoA reductase and subsequently cholesterol biosynthesis in the liver and increases the number of hepatic LDL receptors on the cell surface for enhanced uptake and catabolism of LDL.

IV.4 Clinical Efficacy

Atorvastatin is a well-known active substance with established efficacy for the proposed indications as per the reference product Lipitor film-coated tablets from Pfizer B.V.

IV.5 Clinical Safety

The safety profile of atorvastatin is well-known as per the reference product Lipitor film-coated tablets from Pfizer B.V.

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 Bluefish 10mg, 20mg, 30mg, 40mg, 60mg & 80mg Film-coated tablets.

The revised RMP (version 2.0, dated 09/06/2020) is acceptable. Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of Safety Concerns	
Important identified risks	Toxic liver injury
	Rhabdomyolysis (including cases due to increased plasma levels of atorvastatin in concomitant use of CYP3A4 inhibitor)
	Bleeding due to concomitant use of coumarin anti-coagulant agents.
Important potential risks	None
Missing Information	None

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.

IV.6 Discussion on the clinical aspects

The legal bases for these applications for marketing authorisations for Atorvastatin Bluefish 10mg, 20mg, 30mg, 40mg, 60mg & 80mg Film-coated tablets are:

10mg, 20mg, 40mg, 80mg: 10(1) of Directive 2001/83/EC
30mg, 60mg: 10(3) of Directive 2001/83/EC
The reference product is Lipitor film-coated tablets authorised in the Netherlands.
A bioequivalence study was performed for the highest strength (80mg) and bioequivalence to the reference product was shown. A biowaiver was accepted for the other strengths.

The proposed product information (SmPC and PL) is in accordance with the reference product information.

V. OVERALL CONCLUSIONS

Atorvastatin Bluefish 10mg, 20mg, 30mg, 40mg, 60mg & 80mg Film-coated tablets are generic/hybrid forms of Lipitor film-coated tablets. Lipitor film-coated tablets are well-known medicinal products 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 Bluefish 10mg, 20mg, 30mg, 40mg, 60mg & 80mg Film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

29/11/2023