IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Atenolol 5mg/ml Oral Solution
Atenolol
PA22697/004/001

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.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/5910/1/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 03/10/2018 under procedure number IE/H/0783/1/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA22697/004/001
Marketing Authorisation Holder: SYRI Limited, t/a Thame Laboratories

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

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the application for Atenolol 5 mg/ml Oral Solution (PL 39307/0050; UK/H/5910/001/DC) could be approved. The application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS), and Ireland as Concerned Member State (CMS).

This product is a prescription-only medicine (legal classification POM).

The application was submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The originator product is Tenormin 50 mg Tablet (AstraZeneca UK Limited), which was granted a licence in Ireland on 04 February 1976. The UK reference product is Tenormin 5mg/ml Syrup (PL 17901/0051; AstraZeneca UK Limited), which was originally licensed as Tenormin Syrup 0.5% w/v (PL 00029/0195; Imperial Chemical Industries Limited), prior to 01 October 1993.

Atenolol 5 mg/ml Oral Solution is indicated for:

- Management of hypertension
- Management of angina
- Management of cardiac arrhythmias
- Early intervention in the acute phase following myocardial infarction.

This product contains the active substance atenolol. Atenolol is a beta-blocker which is $beta_1$-selective, (i.e. acts preferentially on $beta_1$- adrenergic receptors in the heart). Selectivity decreases with increasing dose. Atenolol is without intrinsic sympathomimetic and membrane-stabilising activities and as with other beta-blockers, has negative inotropic effects (and is therefore contraindicated in uncontrolled heart failure). As with other beta-blockers, the mode of action of atenolol in the treatment of hypertension is unclear. It is probably the action of atenolol in reducing cardiac rate and contractility which makes it effective in eliminating or reducing the symptoms of patients with angina.

No new clinical or non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

As the product meets the criteria regarding oral solutions specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), bioequivalence studies were not required.

The RMS has been assured that acceptable standards of Good Manufacturing Practice are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

The RMS and CMS considered that the application could be approved at the end of procedure on 23 September 2015. After a subsequent national phase, a licence was granted in the UK on 16 October 2015.

II. QUALITY ASPECTS

II QUALITY ASPECTS

II.1 Introduction

Atenolol 5 mg/ml Oral Solution is a clear colourless oral solution with an orange flavour. Each ml of oral solution contains 5mg Atenolol as the active ingredient.

Other ingredients consist of the pharmaceutical excipients, namely methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), citric acid monohydrate (E330), sodium citrate (E331), sorbitol liquid (non-crystallising) (E420), saccharin sodium (E954), orange flavour [containing propylene glycol (E1520)] and purified water.

The finished product is packaged in amber-coloured polyethylene terephthalate (PET) bottles in pack sizes of 100 ml, 150 ml and 300 ml. The bottles are closed with a tamper evident, child resistant, polypropylene/polyethylene plastic cap with a low-density polyethylene liner. A double ended polypropylene plastic spoon, which has a smaller end measuring 2.5 ml and larger end measuring 5 ml, is provided with each bottle for use as a dosing device. Not all pack sizes may be marketed.

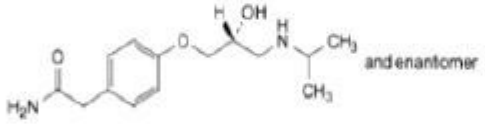
Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

II.2 Drug substance

rINN: Atenolol

Chemical name(s): 2-[4-[(2RS)-2-hydroxy-3-[(1-methylethyl)amino]propoxy]phnyl]acetamide

Structure:



Molecular formula: $C_{14}H_{22}N_2O_3$

Molecular weight: 266.3

Appearance: White or almost white powder

Solubility: Sparingly soluble in water, soluble in anhydrous ethanol, slightly soluble in methylene chloride

All aspects of the manufacture and control of the active substance atenolol from its starting materials are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

II.3 Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a globally acceptable and stable product that could be considered a generic medicinal product of the currently licensed product, Tenormin 5mg/ml Syrup (AstraZeneca UK Limited).

A satisfactory account of the pharmaceutical development has been provided.

Comparative in vitro dissolution profiles have been provided for the applicant's product versus the reference product

With the exception of the orange flavour, which is controlled according to in-house standards, all excipients comply with their respective European Pharmacopoeia monographs. None of the excipients

are sourced from animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate description of the manufacturing process. Suitable in-process controls are in place to ensure the quality of the finished product. Process validation has been carried out on three batches of finished product. The results are satisfactory.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for all working standards used.

Stability of the product
Stability studies were performed, in accordance with current guidelines, on batches of finished product in the packaging proposed for marketing.

The results from these studies support a shelf-life of 18 months with the special storage condition of "Do not store above 25°C". The100 ml and 150 ml pack size should be discarded after 30 days of first opening. The 300ml pack size should be discarded after 60 days of first opening.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that a Marketing Authorisation is granted for Atenolol 5 mg/ml Oral Solution.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPC, PIL and labels are satisfactory and, where appropriate, in line with current guidance.

III. NON-CLINICAL ASPECTS

III NON-CLINICAL ASPECTS
III.1 Introduction
The pharmacodynamic, pharmacokinetic and toxicological properties of atenolol are well known. No new non-clinical data have been submitted for this application and none are required.

The applicant has provided an overview based on published literature. The non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the product's pharmacology and toxicology.

III.2 Pharmacology
No new pharmacology data are required for this application and none have been submitted.

III.3 Pharmacokinetics
No new pharmacokinetic data are required for this application and none have been submitted.

III.4 Toxicology
No new toxicology data are required for this application and none have been submitted.

III.5 Ecotoxicity/Environmental risk Assessment (ERA)
As this product is intended for generic substitution of a product that is already marketed, no increase in environmental exposure to atenolol is anticipated. Thus the absence of an ERA is accepted.

III.6 Discussion of the non-clinical aspects
It is recommended that a Marketing Authorisation is granted for Atenolol 5 mg/ml Oral Solution.

IV. CLINICAL ASPECTS

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IV.1 Introduction

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of atenolol. The applicant's clinical overview has been written by an appropriately qualified person and is considered acceptable.

IV.2 Pharmacokinetics

A bioequivalence study was not submitted as the product meets the criteria regarding oral solutions specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The test product is an aqueous oral solution at the time of administration and contains an active substance in the same concentration as the reference product.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none are required for an application of this type.

IV.4 Clinical efficacy

No new data on efficacy have been submitted and none are required for an application of this type.

IV.5 Clinical Safety

No new data on safety have been submitted and none are required for an application of this type.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance System

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.

The MAH has submitted a RMP, 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 Atenolol 5 mg/ml Oral Solution.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Hypersensitivity	The risks (1) of hypersensitivity associated with the use of the drug product (2) associated with the use of the drug product in patients with a history of anaphylactic reactions are described in the SPC Section 4.3, 4.4, 4.5, 4.8 and PIL Section 2, 4 and appropriate advice is provided to the prescriber to minimise these risk.	None
Hypotension, particularly in patients with pre-existing hypotension	The risks of hypotension associated with the use of the drug product particularly in patients with pre-existing hypotension are described in the SPC Section 4.3, 4.8, 4.9 and PIL Section 2, 3, 4, and appropriate advice is provided to the prescriber to minimise these risk.	None

Bradycardia, particularly in patients with pre-existing low heart rate or bradycardia, first, second or third-degree heart block, or sick sinus syndrome	The risks of bradycardia (1) associated with the use of the drug product, particularly in patients with pre-existing low heart rate or bradycardia, first, second or third degree heart block, or sick sinus syndrome, and (2) associated with the concomitant use of the drug product with other medicinal products are described in the SPC Sections 4.3, 4.4, 4.5, 4.8, 4.9, and the PIL Sections 2, 3, 4, and appropriate advice is provided to the prescriber to minimise these risks.	None
Cardiac failure, worsening cardiac failure or cardiogenic shock	The risks (1) of cardiac failure and worsening of cardiac failure associated with the use of the drug product, (2) associated with the use of the drug product in patients with cardiogenic shock and cardiac failure, and (3) of cardiac failure associated with the concomitant use of the drug product with other medicinal products are described in the SPC Sections 4.3, 4.4, 4.5, 4.8, 4.9 and the PIL Sections 2, 3, 4 and appropriate advice is provided to the prescriber to minimise these risks.	None
Use in patients with metabolic acidosis	The risks associated with the use of the drug product in patients with metabolic acidosis are described in the SPC Section 4.3 and PIL Section 2 appropriate advice is provided to the prescriber to minimise these risk.	None

Peripheral arterial circulatory disturbances, particularly in those with pre-existing peripheral circulation disorders	The risks peripheral arterial circulatory disturbances associated with the use of the drug product particularly in patients with pre-existing peripheral circulation disorders are described in the SPC Section 4.3, 4.4, 4.8 and PIL Section 2, 4 and appropriate advice is provided to the prescriber to minimise these risk.	None
Unopposed alpha agonism in patients with untreated phaeochromocytoma	The risk of unopposed alpha agonism, associated with the use of the drug product in patients with untreated phaeochromocytoma is described in the SPC Sections 4.3, 4.4, and the PIL Section 2 and appropriate advice is provided to the prescriber to minimise this risk.	None
Worsening angina in patients with Prinzmetal's angina	The risk of worsening of angina associated with the use of the drug product in patients with Prinzmetal's angina is described in the SPC Section 4.4, and the PIL Sections 2 and appropriate advice is provided to the prescriber to minimise this risk.	None
Bronchospasm, particularly in patients with reversible obstructive airways disease	The risk of bronchospasm associated with the use of the drug product, particularly in patients with reversible obstructive airways disease is described in the SPC Sections 4.4, 4.8, 4.9 and the PIL Sections 2, 3, 4, and appropriate advice is provided to the prescriber to minimise this risk.	None
Masking of symptoms of thyrotoxicosis	The risks of masking of symptoms of thyrotoxicosis associated with the use of the drug product are described in the SPC Section 4.4 and the PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None

Hypoglycaemia and masking of hypoglycaemic symptoms when used with insulin and oral anti-diabetic drugs	The risks of hypoglycaemia and masking of hypoglycaemic symptoms associated with the concomitant use of the drug product with insulin and oral anti-diabetic drugs are described in the SPC Sections 4.4, 4.5 and the PIL Section 2 and appropriate advice is provided to the prescriber to minimise these risks.	None
Myocardial depression during anaesthesia	The risk of myocardial depression associated with the use of the drug product during anaesthesia is described in the SPC Sections 4.4, 4.5 and the PIL Section 2, and appropriate advice is provided to the prescriber to minimise this risk.	None
Abrupt withdrawal	The risks of abrupt withdrawal of the drug product are described in the SPC Section 4.4 and the PIL Section 3 and appropriate advice is provided to the prescriber and patient to minimise these risks.	None
Use during pregnancy and lactation	The risks associated with the use of the drug product during pregnancy and lactation are described in the SPC Section 4.6 and the PIL Section 2, appropriate advice is provided to the prescriber to minimise these risks.	None

Important Potential Risks		
Accumulation of atenolol in patients with renal impairment	The risks of accumulation of atenolol associated with the use of the drug product in patients with renal impairment are described in the SPC Sections 4.2, 4.4, 5.2 and the PIL Sections 3 and appropriate advice is provided to the prescriber to minimise these risks.	None

Missing Information		
Use in children	The SPC Section 4.2 and PIL Section 3 provides information regarding the lack of human experience of drug product in children and advises the prescriber to exercise the caution while prescribing drug product in such patients.	Not Applicable

IV.7 Discussion of the clinical aspects

It is recommended that a Marketing Authorisation is granted for Atenolol 5 mg/ml Oral Solution.

V. USER CONSULTATION

The package leaflet has been evaluated in accordance with the requirements of Articles 59(3) and 61(1) of 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 patients/users are able to act upon the information that it contains.

V. OVERALL CONCLUSIONS

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The data supplied support the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with atenolol is considered to have demonstrated the therapeutic value of the compound. The benefit-risk assessment is therefore considered to be positive.

VI. REVISION DATE

25/02/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/5910/1/DC to IE/H/0783/1/DC			