IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Phenylephrine Hydrochloride 10 mg/ml solution for injection/infusion
Phenylephrine Hydrochloride
PA1418/011/001

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 Phenylephrine Hydrochloride 10 mg/ml Solution for Injection or Infusion, from Athlone Laboratories Limited on 4th November 2022 for the treatment of hypotensive states during spinal anaesthesia or drug-induced hypotension.

This national application for a marketing authorisation was submitted to HPRA in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a 'generic' application. The European reference product is HIDROCLORURO DE FENILEFRINA ALTAN 10 mg/ml, Solución inyectable (70.638) authorised in Spain since 5th March 2009.

Phenylephrine Hydrochloride 10 mg/ml Solution for Injection or Infusion is prescription only, for supply through pharmacy and for promotion 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	Phenylephrine Hydrochloride
Name(s) of the active substance(s) (INN)	Phenylephrine Hydrochloride
Pharmacotherapeutic classification (ATC code)	C01CA06 phenylephrine
Pharmaceutical form and strength(s)	10 mg/ml solution for injection/infusion
Marketing Authorisation Number(s) in Ireland (PA)	PA1418/011/001
Marketing Authorisation Holder	Athlone Pharmaceuticals Limited

II. QUALITY ASPECTS

II.1. Introduction
This application is for Phenylephrine Hydrochloride 10 mg/ml Solution for Injection or Infusion.

II.2 Drug substance
The active substance is phenylephrine hydrochloride 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
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)
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 relevant pharmacopoeial monographs 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 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 Phenylephrine Hydrochloride 10 mg/ml Solution for Injection or Infusion.

III. NON-CLINICAL ASPECTS

III.1 Introduction
This active substance is a generic formulation of HIDROCLORURO DE FENILEFRINA ALTAN 10 mg/mL Solucion inyectable 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.

III.2 Pharmacology
Pharmacodynamic properties of phenylephrine are well known. As phenylephrine is a widely used, well-known active substance, the applicant has not provided additional non-clinical studies and further studies are not required. A non-clinical overview based on literature review is, thus, appropriate.

III.3 Pharmacokinetics
Pharmacokinetic properties of phenylephrine are well known. As phenylephrine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. A non-clinical overview based on literature review is, thus, appropriate.

III.4 Toxicology
Toxicological properties of phenylephrine are well known. As phenylephrine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. A non-clinical overview based on literature review is, thus, appropriate.

III.5 Ecotoxicity/environmental risk assessment
A rationale for the absence of ERA studies has been provided. Since Phenylephrine Hydrochloride 10 mg/ml Solution for Injection or Infusion is a generic product, it will not lead to an increased exposure to the environment.

III.6 Discussion on the non-clinical aspects
A non-clinical overview based on literature review of the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. There are no objections to approval of Phenylephrine Hydrochloride 10 mg/ml Solution for Injection or Infusion from a non-clinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

This national application for a marketing authorisation was submitted to HPRA in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a 'generic' application. The European reference product is HIDROCLORURO DE FENILEFRINA ALTAN 10 mg/ml, Solución inyectable (70.638) authorised in Spain since 5th March 2009.

A bioequivalence study was not submitted and is not required as the medicinal product is presented as an aqueous solution for parenteral administration containing the same amount of the same active substance as the reference product.

The content of the SmPC approved during the national procedure is generally in accordance with that accepted for the reference product.

IV.2 Pharmacokinetics

Distribution

When injected subcutaneously or intramuscularly, phenylephrine takes 10 to 15 minutes to act. Subcutaneous and intramuscular injections are effective for up to about one and up to two hours respectively. Intravenous injections are effective for up to about 20 minutes.

Biotransformation

Phenylephrine is metabolised in the liver by monoamine oxidase.

Elimination

The metabolites, their route and rate of excretion have not been identified.

IV.3 Pharmacodynamics

Pharmacotherapeutic group: Adrenergic and dopaminergic agents, ATC code: C01C A06.

Phenylephrine hydrochloride is a sympathomimetic agent with mainly direct effects on adrenergic receptors. It has predominantly alpha-adrenergic activity and is without significant stimulating effects on the central nervous system at usual doses. After injection it produces peripheral vasoconstriction and increased arterial pressure. It also causes reflex bradycardia.

IV.4 Clinical Efficacy

The clinical efficacy of phenylephrine hydrochloride is well established. No additional efficacy clinical studies to demonstrate efficacy have been included in the application. This is appropriate for this type of application. The indications and posology are the same as those of the reference product.

IV.5 Clinical Safety

The clinical safety of phenylephrine hydrochloride is well established. No additional safety clinical studies have been submitted and none are required for this type of application. The safety information in the summary of product characteristics is in line with the reference product and other similar authorised products.

Risk Management Plan

A risk management plan was submitted, 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 Phenylephrine Hydrochloride.

Summary of safety concerns:

Important identified risks	Hypersensitivity Arrhythmia
Important potential risks	Extravasation
Missing information	Intravenous use in paediatric population

Routine pharmacovigilance activities and routine risk minimisation activities are suggested, which is endorsed.

PSURs
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.
• For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects
The clinical aspects of phenylephrine hydrochloride are well-established.

V. OVERALL CONCLUSIONS

Phenylephrine Hydrochloride 10 mg/ml Solution for Injection or Infusion is a generic form of HIDROCLORURO DE FENILEFRINA ALTAN 10 mg/ml, Solución inyectable which is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

As the product is formulated as an aqueous solution for parenteral administration containing the same active substance in the same amounts as the reference product, it is exempt from the requirement to demonstrate bioequivalence with the reference product. This is in compliance with CHMP guidance documents.

The SmPC and PIL are 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 Phenylephrine Hydrochloride 10 mg/ml Solution for Injection or Infusion demonstrated adequate evidence of efficacy for the approved indications as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

Following MRP/DCP procedure:
Discussion in CMD(h), specific obligations, follow-up measures, if applicable.

VI. REVISION DATE

November 2023

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
MA transfer	CRN00D893	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Athlone Pharmaceuticals Limited New PA number: PA1418/011/001	N/A	24/11/2023