IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Clonidine hydrochloride 100 micrograms/ 5 ml Oral Solution
Clonidine hydrochloride
PA22697/020/001

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

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Clonidine hydrochloride 100mcg/5ml Oral solution, from Syri Pharma Limited t/a Thame Laboratories, on 1st August 2025 for the treatment of hypertension that has failed to respond adequately to other anti-hypertensives.

This application for a marketing authorisation was submitted in accordance with Article 10(3) of Directive 2001/83/EC and is referred to as a hybrid application, a form of generic application. The reference product is Catapres Tablets 100 micrograms by Glenwood GmbH, Germany (PA2256/003/001), registered in the Reference Member State since 01.04.1979.

With Ireland as the Reference Member State in this decentralised procedure, Syri Pharma Limited t/a Thame Laboratories, applied for the Marketing Authorisation for Clonidine hydrochloride 100 micrograms/5ml Oral Solution in Ireland and Malta.

The medicinal product has been authorised for supply in Ireland as a prescription only medicine.

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	Clonidine hydrochloride 100mcg/5ml Oral solution
Name(s) of the active substance(s) (INN)	Clonidine hydrochloride
Pharmacotherapeutic classification (ATC code)	C02AC01
Pharmaceutical form and strength(s)	100mcg/5ml Oral solution
Marketing Authorisation Number(s) in Ireland (PA)	PA22697/020/001
Marketing Authorisation Holder	Syri Pharma Limited t/a Thame Laboratories
MRP/DCP No.	IE/H/1328/001/DC
Reference Member State	IE
Concerned Member State	MT

II. QUALITY ASPECTS

II.1. Introduction

This application is for Clonidine hydrochloride 100mcg/5ml Oral solution.

II.2 Drug substance

The active substance is Clonidine 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 drug product is a clear, colourless solution for oral use containing 0.10 mg (100 micrograms) of the active substance clonidine hydrochloride per 5 mL.

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 the BP and 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 liquid preparations for oral use, 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 the Ph. Eur. and EU legislative requirements for use with foodstuffs.

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 Clonidine hydrochloride 100mcg/5ml Oral solution.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of clonidine hydrochloride 100mcg/5ml oral solution on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

The pharmacodynamic, pharmacokinetic and toxicological properties of clonidine hydrochloride are well known.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since clonidine hydrochloride 100mcg/5ml oral solution is intended for generic substitution, this will not lead to an increased exposure to the environment. Additional studies on environmental risk assessment are therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of clonidine hydrochloride are well known. As clonidine hydrochloride is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. A nonclinical overview based on literature review was provided and is acceptable. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the decentralised procedure is generally in accordance with that accepted for the reference product Catapres Tablets 100 micrograms by Glenwood GmbH, Germany.

For this generic application, the applicant has submitted one bioequivalence study in which the pharmacokinetic profile of the test product Clonidine hydrochloride 100mcg/5ml Oral solution, Syri Pharma Limited t/a Thame Laboratories, is compared with the pharmacokinetic profile of the reference product Catapres Tablets 100 micrograms, Glenwood GmbH. Based on the pharmacokinetic parameters of the active substance, the reference tablet and test oral solution are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

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

IV.2 Pharmacokinetics

The applicant submitted data from one bioequivalence study, BE/22/183, conducted between the test (Clonidine Hydrochloride 100micrograms/ 5ml Oral Solution of Syri Limited, UK) and reference (Catapres 100micrograms Tablet of Glenwood GmbH, Germany) immediate release oral formulations. This was an open label, randomised, two treatment, two period, two sequence, balanced, single oral dose, two way crossover bioequivalence study conducted under fasting conditions. The study was conducted in accordance with regulatory guidance.

The mean pharmacokinetic (PK) parameters for the test and reference products for clonidine are presented below:

Pharmacokinetic parameter (unit)	Mean ± SD (CV %)	
	Test Product (A)	Reference Product (B)
C_{max} (pg/mL)	422.36±88.44(20.94)	402.74±72.34(17.96)
AUC_{0-t} (hr.pg/mL)	6302.72±1117.73(17.73)	6079.44±982.39(16.16)
AUC_{0-inf} (hr.pg/mL)	6725.64±1157.75(17.21)	6549.27±1041.08(15.90)
T_{max} (hr)*	1.375(1.000-4.017)	1.500(0.667-6.000)
$t_{1/2}$ (hr)	13.517±2.616(19.352)	12.834±1.756(13.686)
K_{el} (hr^{-1})	0.054±0.013(24.660)	0.055±0.008(13.792)
AUC Ratio (%)	93.72±2.89(3.08)	92.87±2.44(2.63)
Residual area (%)	6.28±2.89(45.95)	7.13±2.44(34.25)

N- Number of evaluated subjects; *Median (Range) is provided

Table 1. Mean pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) (N=18)

The Ln-transformed primary PK parameters for clonidine were evaluated for bioequivalence and the results are presented below:

Table 2. Bioequivalence assessment of clonidine (N=18)

Parameter (unit)	Geometric Least-Squares Means[1]		Test-to-Reference Ratio[2]	ISCV%[3]	90% Confidence Interval Limits[4]		Power (%)
	Test	Reference			Lower	Upper	
LnC_{max} (pg/mL)	413.87	396.63	104.35	16.22	95.00	114.61	97.05
$LnAUC_{0-t}$ (hr.pg/mL)	6207.72	6009.29	103.30	8.19	98.50	108.33	100.00

1. For log_e-transformed results (Ln), value is the least-squares geometric mean.
2. Ratio% of geometric least-squares means for log_e-transformed results.
3. ISCV%= %Intra-subject coefficient of variation calculated from the mean square term of the ANOVA.
4. Confidence interval on ratio.

The 90% confidence intervals for the ratio (test/reference) of geometric least square means based on Ln-transformed primary PK parameters Cmax and AUC0-t were found within the acceptable bioequivalence limits of 80.00% to 125.00% for Clonidine. The results of the study demonstrated that the test and reference products were bioequivalent.

IV.3 Pharmacodynamics

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

IV.4 Clinical Efficacy

No new efficacy data were submitted and none were required for this type of application.

IV.5 Clinical Safety

Other than safety data from the submitted bioequivalence study, no new safety data were submitted and none were required for this type of application. The test and reference products were equally well tolerated. No new or unexpected safety findings emerged from this study.

Risk Management Plan

The MAA 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 the medicinal product(s) applied for authorisation.

The approved summary of safety concerns is outlined in the table below:

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

Routine risk minimisation measures and routine pharmacovigilance activities are proposed to address the safety concerns outlined above and this is considered acceptable.

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.
• 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

Data submitted from the pivotal clinical study demonstrated bioequivalence between the test, Clonidine hydrochloride 100mcg/5ml Oral solution, Syri Pharma Limited t/a Thame Laboratories, and reference, Catapres Tablets 100 micrograms, Glenwood GmbH medicinal products. Catapres Tablets 100 micrograms is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

V. OVERALL CONCLUSIONS

OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Clonidine hydrochloride 100mcg/5ml Oral solution is a generic form of Catapres Tablets 100 micrograms. Catapres Tablets 100 micrograms 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 Clonidine hydrochloride 100mcg/5ml Oral solution demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a Marketing Authorisation.

VI. REVISION DATE

19.06.2030