IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Lercanidipine Hydrochloride Pinewood 20 mg film-coated tablets
Lercanidipine hydrochloride
PA0281/269/002

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.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Lercanidipine Hydrochloride Pinewood 10 mg & 20 mg film coated tablets, from Pinewood Laboratories Ltd, on <date of authorisation> for the treatment of mild to moderate essential hypertension in adults.
This application for a national marketing authorisation was submitted in accordance with Article 10(1) of Directive 2001/83/EC and is referred to as a "generic" application.
Lercanidipine Hydrochloride Pinewood 10mg & 20mg Film Coated Tablets, are 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	Lercanidipine Hydrochloride Pinewood 10 mg & 20 mg film coated tablets
Name(s) of the active substance(s) (INN)	Lercanidipine hydrochloride
Pharmacotherapeutic classification (ATC code)	C08CA13
Pharmaceutical form and strength(s)	10mg & 20mg Tablets
Marketing Authorisation Number(s) in Ireland (PA)	PA0281/269/001-002
Marketing Authorisation Holder	Pinewood Laboratories Ltd
MRP/DCP No.	IE/H/1274/001-002/DC
Reference Member State	IE
Concerned Member State	

II. QUALITY ASPECTS

II.1. Introduction
This application is for Lercanidipine Hydrochloride Pinewood 10 mg & 20 mg film coated tablets.

II.2 Drug substance

The active substance is lercanidipine hydochloride, an established active substance, 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

Lercanidipine Hydrochloride Pinewood 10 mg Film coated Tablets:Each Film coated tablet contains 10 mg lercanidipine hydrochloride equivalent to 9.4 mg lercanidipine
Lercanidipine Hydrochloride Pinewood 20 mg Film coated Tablets:Each Film coated tablet contains 20 mg lercanidipine hydrochloride equivalent to 18.8 mg lercanidipine

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 European/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 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 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 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 Lercanidipine Hydrochloride Pinewood 10 mg & 20 mg Film Coated Tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Zanidip 10mg and 20 mg film-coated tablets on the European market. No new preclinical data have been submitted. This is acceptable for this type of application.

III.2 Pharmacology

N/A

III.3 Pharmacokinetics

N/A

III.4 Toxicology

N/A

III.5 Ecotoxicity/environmental risk assessment

Since Lercanidipine Hydrochloride Pinewood 10 mg & 20 mg film coated tablets are intended for generic substitution, it will not lead to an increased exposure to the environment. Further environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of lercanidipine are well known. As lercanidipine is widely used and a well-known active substance the applicant has not provided additional studies, and further studies are not required. Overview based on literature review was provided and is acceptable for this type of generic application.

IV. CLINICAL ASPECTS

IV.1 Introduction

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

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Zanidip 10 mg & 20 mg film-coated tablets marketed by Recordati Industria Chimica e Farmaceutica SpA.

For this generic application, the applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Lercanidipine Hydrochloride Pinewood 10 mg & 20 mg film coated tablets were compared with the pharmacokinetic profile of the reference product Carmen® 10 mg & 20 mg film-coated tablets. Carmen® is the licensed reference product in Germany and is part of the same global marketing authorisation as Zanidip.

A single-dose, randomised, three-period, two-treatment, three-sequence, crossover bioequivalence study was carried out. Lercanidipine Hydrochloride Pinewood 10 mg film-coated tablets was compared to the reference product Carmen® 10 mg film-coated tablets. Based on the pharmacokinetic parameters of active substance, the reference tablet Carmen® 10mg marketed by Recordati Industria Chimica e Farmaceutica SpA and test tablet Lercanidipine Hydrochloride Pinewood 10 mg 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 single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out. Lercanidipine Hydrochloride Pinewood 20 mg film-coated tablets was compared to the reference product Carmen® 20 mg film-coated tablets. Based on the pharmacokinetic parameters of active substance, the reference tablet Carmen® 20mg marketed by Recordati Industria Chimica e Farmaceutica SpA and test tablet Lercanidipine Hydrochloride Pinewood 20 mg are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Lercanidipine hydrochloride is a well known active substance with established efficacy and tolerability. This medicinal product is the same as the originator product on the European market.

The content of the SmPC approved during the decentralised procedure is in accordance with that accepted for the reference product Zanidip 10 mg & 20 mg film-coated tablets marketed by Recordati Industria Chimica e Farmaceutica SpA.

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

IV.2 Pharmacokinetics

Lercanidipine Hydrochloride Pinewood is completely absorbed after 10-20 mg oral administration and peak plasma levels, 3.30 ng/ml ± 2.09 s.d. and 7.66 ng/ml ± 5.90 s.d. respectively, occur about 1.5-3 hours after dosing. Due to the high first pass metabolism, the absolute bioavailability of Lercanidipine Hydrochloride Pinewood orally administered to patients under fed conditions is around 10%, although it is reduced to 1/3 when administered to healthy volunteers under fasting conditions. Distribution from plasma to tissues and organs is rapid and extensive.
The degree of serum protein binding of lercanidipine exceeds 98%. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction of the drug may be increased.

Lercanidipine Hydrochloride Pinewood is extensively metabolised by CYP3A4; no parent drug is found in the urine or the faeces. It is predominantly converted to inactive metabolites and about 50% of the dose is excreted in the urine. Elimination occurs essentially by biotransformation. A mean terminal elimination half life of 8-10 hours was calculated and the therapeutical activity lasts for 24 hours because of its high binding to lipid membrane. No accumulation was seen upon repeated administration.

IV.3 Pharmacodynamics

Lercanidipine is a calcium antagonist of the dihydropyridine group and inhibits the transmembrane influx of calcium into cardiac and smooth muscle. The mechanism of its antihypertensive action is due to a direct relaxant effect on vascular smooth muscle thus lowering total peripheral resistance.
Despite its short pharmacokinetic plasma half-life, lercanidipine is endowed with a prolonged antihypertensive activity because of its high membrane partition coefficient, and is devoid of negative inotropic effects due to its high vascular selectivity.
Since the vasodilatation induced by Lercanidipine Hydrochloride Pinewood is gradual in onset, acute hypotension with reflex tachycardia has rarely been observed in hypertensive patients.

IV.4 Clinical Efficacy

The efficacy of lercanidipine hydrochloride in the proposed indications is established in clinical use. No additional efficacy clinical studies to demonstrate efficacy have been included in the application and none are required for a generic application.

IV.5 Clinical Safety

The overall safety profile of lercanidipine is established and generally known. No new safety studies are provided and none are required.
The reported adverse events in the bioequivalence study were mild to moderate in severity and resolved and no serious adverse events were observed.
The safety information in the SmPC and Package Leaflet are in line with those of the reference product and other similar products.

Risk Management Plan

A Risk Management Plan, version 0.1, dated 31 March 2023 has been 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 Lercanidipine Hydrochloride Pinewood 10 mg & 20 mg film coated tablets. It is concluded that routine pharmacovigilance and risk minimisation measures are sufficient.

Summary table of safety concerns as approved in RMP:

Summary of safety concerns	
Important identified risks	None
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

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required. The applicant has submitted the results of a suitable bioequivalence study with the 10 mg and 20 mg strengths which both demonstrated bioequivalence of the test products against the reference products, in accordance with the relevant guidance. No additional tests are required for this application.
The applicant has also submitted a clinical overview and summary of the evidence demonstrating the efficacy and safety of this product in clinical practice.

V. OVERALL CONCLUSIONS

Lercanidipine Hydrochloride Pinewood 10 mg & 20 mg film coated tablets are a generic form of Zanidip 10 mg & 20 mg film-coated tablets. Zanidip film-coated tablets are a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown for both the 10 and 20 mg strengths and is 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 Lercanidipine Hydrochloride Pinewood 10 mg & 20 mg film coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

The HPRA, on the basis of the data submitted considered that Lercanidipine Hydrochloride Pinewood 10 mg & 20 mg film coated tablets, from Pinewood Laboratories Ltd demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

30.04.2030