*CMDh/223/2005*
*February 2014*

# Public Assessment Report

# Scientific discussion

# Lercanidipine Pensa 10 mg film-coated tablet
# Lecarnidipine Pensa 20 mg film-coated tablet
# (Lercanidipine hydrochloride)

## ES/H/0922/001-002/DC

## Date: 07 Abril 2025

**This module reflects the scientific discussion for the approval of Lercanidipine Pensa 10 and 20 mg film-coated tablets EFG. The procedure was finalised at 25/10/2024. For information on changes after this date please refer to the module 'Update'.**

# I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lercanidipine Pensa 10 mg, 20 mg film-coated tablets, from Towa Pharmaceutical, S.A.

The product is indicated for the treatment of mild to moderate essential hypertension in adults. A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10.1 of Directive 2001/83/EC.

# II. QUALITY ASPECTS

## II.1 Introduction

Lercanidipine Hydrochloride 10 mg is presented as film-coated tablet containing 10 mg of lercanidipine hydrochloride, equivalent to 9.4 mg of lercanidipine, as active substance.

Lercanidipine Hydrochloride 20 mg is presented as film-coated tablet containing 20 mg of lercanidipine hydrochloride, equivalent to 18.8 mg of lercanidipine, as active substance.

The maximum daily dose is 20 mg of lercanidipine hydrochloride.

The product is available in PVC/PVDC/Aluminium blister, as described in section 6.5 of the SmPC.

## II.2 2.2Drug Substance

The ASMF procedure is used to support the quality of the drug substance lercanidipine hydrochloride.

***General Information***

Nomenclature:

INN: Lercanidipine hydrochloride

Chemical name:

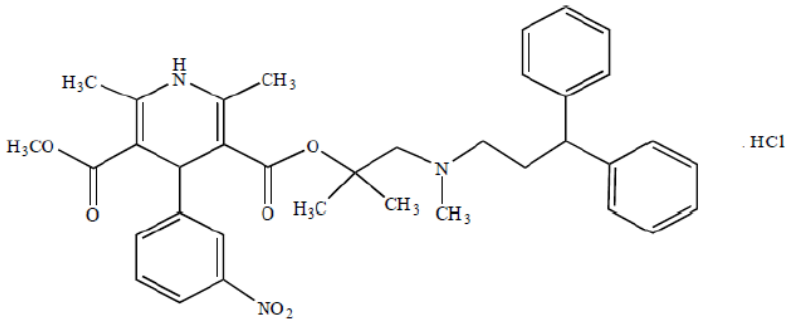
1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid-2-[(3,3-diphenylpropyl) methylamino]-1,1-dimethylethyl methyl ester hydrochloride

OR

(±)-1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl) pyridine-3,5-dicarboxylic acid-2-[N-(3,3-diphenylpropyl)-N-methylamino]-1,1-dimethylethyl methyl diester hydrochloride

CAS-No: [132866-11-6]

Structure:



Molecular formule: $C_{36}H_{41}N_3O_6.HCl$
Molecular mass: 648.2

General Properties:

- Appearance: yellow coloured microcrystalline, odourless, citrine powder.

- Solubility: readily soluble in chloroform and methanol, practically insoluble in water.

- It shows polymorphism.

- Lercanidipine has a chiral centre and exhibits stereoisomerism.

- Lercanidipine Hydrochloride belongs to BCS class II.

***Manufacture, process controls and characterisation***

The description of the manufacturing process is properly detailed. The specifications of the materials used in the synthesis are sufficient and adequate. The profile of impurities, including residual solvents, of these materials which can influence the quality of the active substance are well defined and controlled. The acceptance criteria for the critical stages and the information on the quality and control of intermediates are adequate.

***Specification, analytical procedures, batch analysis***

Active substance specifications are considered appropriate and limits justified. Analytical methods are correctly described and validation carried out according to ICH. Batch results support consistent production.

***Container closure system***

The choice of the container closure system is properly justified. Compliance with the relevant requirements and/or regulations is confirmed.

***Stability***

Stability studies have been performed in accordance with current guidelines. Protocol, controlled parameters and test methods are considered adequate. The packaging material is similar to that proposed for storage. Proposed re-test period and storage conditions are justified.

## II.3 Medicinal Product

***Description of the product***

Lercanidipine Hydrochloride 10 mg is presented as a yellow colored, round shaped biconvex film-coated tablet with break-line on one side and plain on the other side, with a diameter of approximately 6.5 mm.
Lercanidipine Hydrochloride 20 mg is presented as a pink colored, round shaped biconvex film-coated tablet with break-line on one side and plain on the other side, with a diameter of approximately 8.5 mm.

The qualitative composition of the finished product is as follows:

*Lercanidipine Hydrochloride 10 mg*
Tablet core:
Lercanidipine hydrochloride
Maize starch
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous
Cellulose, microcrystalline
Poloxamer
Sodium stearyl fumarate
Macrogol

Film coating
Hypromellose
Macrogol
Iron oxide yellow (E172)
Titanium dioxide (E 171)

*Lercanidipine Hydrochloride 20 mg*
Tablet core:
Lercanidipine hydrochloride
Cellulose, microcrystalline
Maize starch
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous
Povidone
Sodium stearyl fumarate

Film coating
Hypromellose
Macrogol
Iron oxide red (E172)
Titanium dioxide (E 171)

The packaging material intended for the commercial use consists in PVC/PVDC/Aluminium blister.

***Pharmaceutical Development***

The development of the product has been described, the choice of excipients is justified and their functions explained.

The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.

The choice of dissolution method is considered appropriate. The information presented supports the proposed quality control dissolution method.

***Manufacture of the product***

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

Sufficient validation data are provided.

***Excipients***

Excipients used are well known and of appropriate quality.

None of the excipients is of animal origin.

Scientific data and/or certificates are presented to guarantee compliance with the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents* for these excipients.

***Product specification, analytical procedures, batch analysis***

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

***Container closure system***

The finished product is packaged in PVC/PVDC/Aluminium blister.The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed .

***Stability***

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

**Shelf-life:** 3 years.

**Storage conditions:**

Lercanidipine hydrochloride 10 mg film-coated tablets: Store in the original package in order to protect from light.
Lercanidipine hydrochloride 20 mg film-coated tables: Do not store above 30 ºC.

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### II.4 Discussion on chemical, pharmaceutical and biological aspects

# III. NON-CLINICAL ASPECTS

### III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of lercanidipine hydrochloride are well known. As lercanidipine hydrochloride is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

### III.2 Environmental Risk Assessment (ERA)

Since Lercanidipine Pensa 10 mg and 20 mg film-coated tablets is a generic product, it will not lead to an increased exposure to the environment. Therefore, additional ERA studies are not deemed necessary.

## IV. CLINICAL ASPECTS

### IV.1 Introduction

Lercadinipine is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an immediate release formulation, the MAH has submitted two bioequivalence studies with the 10 and 20 mg strengths according to the Guideline on the investigation of bioequivalence, which is discussed below.

### IV.2 Pharmacokinetics

Biowaiver
NA

Bioequivalence studies

1. *Study code*

**PK-09-110**

*GCP compliance*
The study was conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

*Clinical and analytical facilities*
Bio-Evaluation Centre. Torrent Pharmaceuticals Ltd Village: Bhat Dist-Gandhinagar Gujarat-382428.

*Design.*
A randomised, single-dose, two-treatment, three-period, three sequence, crossover replicate bioequivalence study was carried out under fasted conditions in 54 healthy male subjects, aged 18-44 years. Each subject received a single dose (10 mg tablet) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight

fast of at least ten hours. There were two dosing periods, separated by a washout period of 7 days.

*Analytical and statistical methods*
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

*Results*
54 subjects, were included in the study. 54 subjects were treated, 51 subjects completed the study and were used in the statistical analysis according to the protocol.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

*Summary of assessment bioequivalence studies.*

**Table 1. Pharmacokinetic parameters for S-lercanidipine (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range). ANOVA Mixed Procedure. Without subject #39.**

| **Treatment** | **$AUC_{0-t}$** pg/ml/h | **$AUC_{0-\infty}$** pg/ml/h | **$C_{max}$** pg/ml | **$t_{max}$** h |
|---|---|---|---|---|
| **Test [N=51]** | 8885.359 ±4623.83 | 9410.523 ±4632.66 | 2420.633 ±1153.42 | 1.33 (0.75-3.00) |
| **Reference [N=102]** | 8789.363 ±5703.99 | 9313.095 ±5741.63 | 2235.066 ±1512.66 | 1.67 (0.75-6.00) |
| ***Ratio (90% CI)** | 104.97 (**93.50-117.85**) | 104.58 (94.27-116.01) | 114.47 (**100.66-130.19**) [$] | - |

**$AUC_{0-t}$** Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-72h}$ can be reported instead of $AUC_{0-t}$, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
**$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when $AUC_{0-72h}$ is reported instead of $AUC_{0-t}$
**$C_{max}$** Maximum plasma concentration
**$t_{max}$** Time until Cmax is reached

**ln-transformed values*

[$]As this is a replicate design and the intra-subject CV% for Cmax of the reference is 36.47%, according to section 4.1.10 from the Guideline on the investigation of bioequivalence, Cmax acceptance limits can be widened up to 75.77- 131.97%. Therefore, the 90% CI of 100.66-130.19% for Cmax is considered acceptable and it is within the new acceptance interval.

**Table 2. Pharmacokinetic parameters for R-lercanidipine (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range). ANOVA Mixed Procedure. Without subject #39.**

| Treatment | $AUC_{0-t}$ pg/ml/h | $AUC_{0-\infty}$ pg/ml/h | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test [N=51]** | 9853.741 ±6484.60 | 10441.839 ±6729.08 | 2481.537 ±1399.71 | 1.33 (0.75-3.00)) |
| **Reference [N=102]** | 9493.384 ±6071.65 | 10116.044 ±6197.85 | 2253.344 ±1544.76 | 1.67 (0.75-6.00) |
| ***Ratio (90% CI)** | 103.85 (**62.75-116.28**) | 102.80 (92.36-114.41 | 114.43 (**100.40-130.43**) $ | - |

**$AUC_{0-t}$** Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-72h}$ can be reported instead of $AUC_{0-t}$ in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
**$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when $AUC_{0-72h}$ is reported instead of $AUC_{0-t}$
**$C_{max}$** Maximum plasma concentration
**$t_{max}$** Time until Cmax is reached

**ln-transformed values*

$ As the intra-subject CV% for Cmax of the reference was 37.96%, although it is stated in the protocol that the bioequivalence was going to be assessed according to the data of S-lercanidipine, also R-lecarnidipine has a 90% CI for Cmax within the widened acceptance interval of 75.00- 133.45%.

*2. Study code*

**PK-11-035**

*GCP compliance*
The study was conducted in accordance with Good Clinical Practice (GCP) standards. Monitoring reports and certificates of audits carried out by the Quality Assurance Unit are presented. The sites have been previously inspected by EU regulatory authorities.

*Clinical and analytical facilities*
Bio-Evaluation Centre. Torrent Pharmaceuticals Ltd Village: Bhat Dist-Gandhinagar Gujarat-382428.

*Design.*
A randomised, single-dose, two-treatment, two-period, two sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 18-44 years. Each subject received a single dose (20 mg tablet) of one of the two active substance formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least ten hours. There were two dosing periods, separated by a washout period of 10 days.

*Analytical and statistical methods*
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples.
The 90% confidence interval (90% CI) of the ratio of the test formulation to the reference formulation for the log-transformed values of Cmax and AUC was calculated using an ANOVA model. This model included the covariates sequence, period, formulation and subject nested to sequence. Bioequivalence was defined when the 90% CI of the ratios (test/reference) for Cmax and AUC was in the range 80.00 -125.00%.
The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

*Results*
56 subjects, were included in the study. 56 subjects were treated, 53 subjects completed the study and were used in the statistical analysis according to the protocol.
The inclusion and exclusion criteria are considered acceptable for a bioequivalence study.

*Summary of assessment bioequivalence studies.*

**Table 1. Pharmacokinetic parameters for S-lercanidipine (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range)**

| Treatment | $AUC_{0-t}$ pg/ml/h | $AUC_{0-\infty}$ pg/ml/h | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test [N=53]** | 25651.634±15033.34 | 26773.916±15586.40 | 5850.334±3438.54 | 2.00 (1.00-4.00) |
| **Reference [N=53]** | 24873.723 ± 11315.71 | 25990.024 ± 11843.81 | 5257.965 ± 2226.99 | 1.75 (0.67-6.00) |
| ***Ratio (90% CI)** | **97.44 (84.32-112.61** | NR | **104.45 (91.05-119.83)** | - |

**$AUC_{0-t}$** Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-72h}$ can be reported instead of $AUC_{0-t}$, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
**$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when $AUC_{0-72h}$ is reported instead of $AUC_{0-t}$
**$C_{max}$** Maximum plasma concentration
**$t_{max}$** Time until Cmax is reached

**ln-transformed values*

**Table 2. Pharmacokinetic parameters for R-lercanidipine (non-transformed values; arithmetic mean ± SD, $t_{max}$ median, range)**

| Treatment | $AUC_{0-t}$ pg/ml/h | $AUC_{0-\infty}$ pg/ml/h | $C_{max}$ pg/ml | $t_{max}$ h |
|---|---|---|---|---|
| **Test [N=53]** | 28066.155±17670.27 | 29679.662 ± 18492.92 | 5902.539±3465.87 | 1.75 (1.00-4.00) |
| **Reference [N=53]** | 27016.488± 13361.08 | 28384.402 ± 14054.47 | 5232.546± 2141.92 | 1.75 (0.67-5.00) |
| ***Ratio (90% CI)** | **97.96 (84.54-113.51)** | NR | **105.70 (91.59-121.98)** | - |

**$AUC_{0-t}$** Area under the plasma concentration curve from administration to last observed concentration at time t.
$AUC_{0-72h}$ can be reported instead of $AUC_{0-t}$, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
**$AUC_{0-\infty}$** Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when $AUC_{0-72h}$ is reported instead of $AUC_{0-t}$
**$C_{max}$** Maximum plasma concentration
**$t_{max}$** Time until Cmax is reached

**ln-transformed values*

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence studies Lercanidipine Pensa 10 and 20 mg film-coated tablets are considered bioequivalent with Carmen film coated tablets.

## IV.3 Clinical efficacy/clinical safety

Clinical efficacy and clinical safety properties of lercanidipine hydrochloride are well known. As lercanidipine hydrochloride is a widely used, well-known active substance, the applicant has not provided original clinical efficacy and clinical safety studies, and further studies are not required. Overview based on literature review is, thus, appropriate in the context of a generic

application. The efficacy and safety of lercanidipine have been demonstrated in several clinical trials conducted with the reference product and during post-marketing experience. Therapeutic indication proposed for Lercanidipine Pensa 10 mg and 20 mg film-coated tablets is the same as that authorized for the reference product.

### IV.4 Risk Management Plan

The MAH 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 Lecarnidipine Pensa 10 mg and 20 mg film-coated tablets (lecarnidipine hydrochloride).

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Lecarnidipine Pensa 10 mg and 20 mg film-coated tablets (lecarnidipine hydrochloride).

### IV.5 Discussion on the clinical aspects

See section IV.2

## V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to two different parent PIL: Lercanidipine Torrent 20 mg film-coated tablets (DE/H/1797/001-002/DC) for text information, and Bisoprolol Pensa 2.5 mg tablets (ES/H/0360/001/DC) for desing and layout. The bridging report submitted by the applicant has been found acceptable.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic products Lecardinipine 10 and 20 mg are found adequate. There are no objections to the approval of Lecardinipine Pensa 10 and 20 mg film coated tablets from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.