COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Lercanidipine HCl Mylan 10 mg and 20 mg, film-coated tablets (lercanidipine hydrochloride)

NL/H/5190/001-002/DC

Date: 21 February 2023

This module reflects the scientific discussion for the approval of Lercanidipine HCl Mylan 10 mg and 20 mg, film-coated tablets. The procedure was finalised on 20 May 2009 in Denmark (DK/H/1492/001-002/DC). After a transfer on 12 June 2020, the current RMS is the Netherlands. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
EMA	European Medicines Agency
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Lercanidipine HCl Mylan 10 mg and 20, film coated tablets from Mylan B.V.

For the indication and posology of the product, see the current Summary of Product Characteristics (SmPC).

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Zanidip 10 and 20 mg film-coated tablets, Recordati Pharmaceuticals Ltd. which has been registered in UK since 22 March 1996, and with the reference product Zanidip 10 mg and 20 mg film-coated tablets, MEDA which has been registered in Denmark since 27 January 1997 (10 mg) and 2 May 2003 (20 mg).

The reference member state (RMS) of the initial procedure was Denmark. The role of RMS was transferred to the Netherlands on 12 June 2020.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as film-coated tablets in the strength of 10 and 20 mg.

- The 10 mg tablet is yellow, round, biconvex 6.5 mm, film-coated, scored on one side and marked 'L' on the other side.
- The 20 mg tablet is pink, round, biconvex 8.5 mm, film-coated, scored on one side and marked 'L' on the other side.

The excipients in the tablets core are: magnesium stearate, povidone, sodium starch glycolate type A, lactose monohydrate and microcrystalline cellulose. The film-coating consists of: macrogol, polyvinyl alcohol, partly hydrolysed, talc, titanium dioxide (E 171), yellow iron oxide (E 172) and red iron oxide (E 172) (20 mg only).

The tablets are packed in blister packs (Aluminium/PVC) with push-through foil and in tablet containers (HDPE), closed with a sealed LDPE-cap.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current

manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

II.2 Drug Substance

The active substance is lercanidipine hydrochloride (amorphous form). The active substance is not described in the European Pharmacopoeia. Lercanidipine hydrochloride is a calcium antagonist of the dihydropyridine group and inhibits the transmembrane influx of calcium into cardiac and smooth muscle.

The documentation on the drug substance is presented as an EDMF for the amorphous form.

Quality control of drug substance
The chemical-pharmaceutical documentation and the quality overall summary in relation to lercanidipine hydrochloride are of sufficient quality in view of the present European regulatory requirements.

Stability of drug substance
Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

II.3 Medicinal Product

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

Quality control of drug product
The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed on 11 pilot scale batches. The batch analysis results show that the finished products meet the specifications proposed.

Stability of drug product
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. A shelf-life of 2 years when stored according to the conditions below has been accepted:

- Al/PVC blister: Do not store above 25°C. Store in the original package in order to protect from moisture.
- HDPE containers: Do not store above 25°C. Store in the original packaging. Keep the container tightly closed in order to protect from moisture.

III. NON-CLINICAL ASPECTS

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.1 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics is adequate.

IV. CLINICAL ASPECTS

IV.1 Introduction

No specific clinical studies, apart from the bioequivalence study, have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EEC as amended. The clinical overview presents a satisfactory overview of clinical pharmacology, efficacy and safety. The clinical overview is adequate.

To support the application, the applicant has submitted as report one bioequivalence study.

The application contains an adequate review of published clinical data and the bioequivalence has been shown.

IV.2 Pharmacokinetics

Absorption
Lercanidipine is completely absorbed after 10-20 mg oral administration and peak plasma levels, 3.30 ng/ml ±2.09 SD and 7.66 ng/ml ±5.90 SD respectively, occur about 1.5-3 hours after dosing. The two enantiomers of lercanidipine show a similar plasma level profile; the t_{max} is the same, C_{max} and AUC are, on average 1.2-fold higher for the (S)-enantiomer and the elimination half-lives is essentially the same for the two enantiomers. No *in vivo* interconversion of enantiomers is observed. The antihypertensive activity of lercanidipine is mainly due to its (S)-enantiomer.

Due to high first pass metabolism, the absolute bioavailability of lercanidipine 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. Oral availability increases 4-fold when lercanidipine is ingested up to 2 hours after a high fat meal. Accordingly, lercanidipine should be taken before meals.

Distribution
Distribution from plasma to tissues and organs is rapid and extensive and protein binding exceeds 98%. Since plasma protein levels are reduced in patients with severe renal or hepatic dysfunction, the free fraction may be increased.

Metabolism
Lercanidipine is extensively metabolised by CYP3A4; no parent 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
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 lercanidipine's high binding to lipid membrane. No accumulation was seen upon repeated administration. Oral administration of lercanidipine leads to plasma levels of lercanidipine not directly proportional to dosage (non-linear kinetics). After 10, 20 or 40 mg, C_{max} observed were in the ratio 1:3:8 and AUC's in the ratio 1:4:18, suggesting a progressive saturation of first pass metabolism. Accordingly, availability increases with dosage elevation.

Biowaiver
The application concerns 2 dosage strengths, 10 and 20 mg. The study was carried out with the 20 mg strength. Justification for biowaiver for the 10 strength has been provided in the module 5 report and clinical overview:

- The composition of the 10 and 20 mg strengths are qualitative the same (except for colouring agents) and directly proportional, i.e. the ratio between the amounts of active substance and excipients is the same.
- Both strengths are manufactured by the same manufacturer and process.
- Lercanidipine displays non-linear kinetics with more than dose proportional increase. Therefore 20 mg has the largest sensitivity to identify differences in the test product and reference product.
- The dissolution profiles of all strengths are similar.

Bioequivalence
To support the application, the applicant has submitted as report one bioequivalence study, in which lercanidipine 20 mg film-coated tablets are compared with Corifeo 20 mg film-coated tablets, UCB GmbH from the German market following a single dose in a replicated design under fasting conditions.

Design
The study was an open-label, randomized, two-treatment, two-sequence, four-period, replicated, crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the two administrations. 20 mg was administered in each period.

Blood samples were collected pre-dosing and at time points from 0.25 up to 48.0 hours post administration of a single-dose 20 mg film-coated tablet with 240 ml of water for the analyses of (S)- lercanidipine and (R)-lercanidipine.

Results
The blood samples were analysed for detection of (+)-S-lercanidipine and (-)-R-lercanidipine.

Table 1. Results from the study are presented below as non-transformed values for (+)-S-lercanidipine:

Treatment	AUC_{0-t} pg/ml/h (± SD)	$AUC_{0-\infty}$ pg/ml/h (± SD)	C_{max} pg/ml (± SD)
Mean Test	32681.50	34105.35	7410.64
	(12628.17)	(13143.31)	(2765.24)
Mean Reference	32662.15	33932.55	6883.88
	(9826.31)	(10152.74)	(2157.51)
***Ratio (90% CI)**	86-104	86-105	89-116

Table 2. Results from the study are presented below as non-transformed values (-)-R-lercanidipine:

Treatment	AUC_{0-t} pg/ml/h (± SD)	$AUC_{0-\infty}$ pg/ml/h (± SD)	C_{max} pg/ml (± SD)
Mean Test	35047.85	36964.40	7425.89
	(14702.06)	(15558.95)	(3095.46)
Mean Reference	33969.64	35850.95	6641.61
	(10923.09)	(11345.03)	(2058.11)
***Ratio (90% CI)**	87-108	87-107	90-118

Conclusion on bioequivalence study
The pharmacokinetic parameters have been adequately calculated, summarised and analysed. The residual areas are acceptable. The 90% CV of AUC_{0-t} and C_{max} demonstrate bioequivalence between the test product lercanidipine 20 mg film-coated tablets and the reference product, Corifeo 20 mg film- coated tablets, following a single dose replicate design under fasting conditions for (+)-S-lercanidipine and for (-)-R-lercanidipine. Thus, bioequivalence has been shown between the test and reference products in this study.

The submitted bioequivalence study is considered sufficient as support for the application. A single dose study is acceptable given that this is an immediate release product.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Lercanidipine is a well-known drug. The presented overviews are adequate. The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The benefit-risk is therefore considered acceptable.

The following commitments have been made during the procedure:

- The specification limits will be reviewed in light of 12 months stability results for commercial scale batches, available at the end of June 2010. If any change in the current limits is required, a variation application will be prepared and submitted before the end of August 2010.
- Analysis of loss on drying of tablets has been added to the stability protocol, performed annually. Next upcoming 12-months point is for batches D31534, D31535 and D31536 in May 2009. The specification limits set will be reviewed in light of the stability results obtained. Specification limits will be set as detailed above and communicated to the regulatory authorities by September 2009 at the latest.
- The first 3 production batches of each strength will be put on stability and tested according to the stability protocol as presented in section P.8.1. The first three production batches of each strength will be placed on stability before 30 June 2009. Start of the stability program will be before 30 June and up to 12 month data will be submitted to the authorities before end of August 2010.
- The finished product manufacturer confirms that a new LoA has been requested from the DMF holder and will be provided for the above mentioned procedures not later than 2 June 2009.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
NL/H/5190/ 1-2/IB/031	Safety, Efficacy, Pharmacovigilance changes - update product information regarding excipients.	Yes	19-11-2020	Approved	N/A
NL/H/5190/ 1-2/IB/032	Changes in the SmPC, labelling or package leaflet. - Update the of product information in line with the reference product.	Yes	10-11-2021	Approved	N/A
NL/H/5190/ 1-2/IB/033/G	Changes in: - manufacturing process of the intermediate or finished product. - test procedure for the finished product. - deletion of manufacturing sites for an active substance, intermediate or finished product.	Yes	27-04-2022	Approved	N/A
NL/H/5190/ 1-2/IB/035/G	Changes in: - name and/or address of manufacturer, quality control testing sites, ASMF holder or suppliers. - batch size of (intermediates used for) active substance. - specification parameters of an active substance / deletion of a non-significant specification parameter.	No	03-08-2022	Approved	N/A
NL/H/5190/ 1-2/IB/036	Change in test procedure for the finished product (including replacement or addition).	No	01-06-2022	Approved	N/A
NL/H/5190/ 1-2/IB/037	Change in the (invented) name of the medicinal product for Nationally Authorised Products.	Yes	12-01-2023	Approved	N/A