PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Lercanidipine HCl Torent 10 mg and 20 mg, film-coated tablets
Torrent Pharma GmbH, Germany

lercanidipine (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1631/001-002/DC
Registration number in the Netherlands: RVG 104340, 104342

2 August 2010

Pharmacotherapeutic group: selective calcium channel blockers with mainly vascular effects, dihydropyridine derivatives
ATC code: C08CA13
Route of administration: oral
Therapeutic indication: mild to moderate essential hypertension
Prescription status: prescription only
Date of authorisation in NL: 20 May 2010
Concerned Member States: Decentralised procedure with IT, RO, UK
Application type/legal basis: Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Lercanidipine HCl Torent 10 mg and 20 mg, film-coated tablets from Torent Pharma GmbH. The date of authorisation was on 20 May 2010 in the Netherlands. The product is indicated for mild to moderate essential hypertension.

A comprehensive description of the indications and posology is given in the SPC.

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.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Zanidip 10 and 20 mg tablets, which have been registered in the UK by Recordati Industria Chimica e Farmaceutica S.p.A since 1996. In the Netherlands, the innovator products Lerdip 10 and 20 mg tablets (RVG 20813, 28644) have been registered by Zambon Nederland BV since 11 April 1997 through mutual recognition procedure UK/H/132/001-002. In addition, reference is made to innovator authorisations in the individual member states (reference product). The product is marketed under different brand names, including Lercadip, Lerdip, Lerzam, Carmen, Zanedip and Zanidip.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product: one study with the 10 mg test product versus the reference product Carmen 10 mg, and one with the 20 mg tablets versus Carmen 20 mg, both registered in Germany. Additionally a replicate design study with the 10 mg tablets of the reference product used in the bioequivalence study was submitted. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. These generic products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products, and no paediatric development programme has been submitted.
II  SCIENTIFIC OVERVIEW AND DISCUSSION

II.1  Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is lercanidipine, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.*) or any other pharmacopoeia. Lercanidipin is a yellow powder, which is soluble in methanol. The drug substance is a racemate. As for other asymmetric 1,4-dihydropyridines, the antihypertensive activity of lercanidipine is mainly due to its (S)-enantiomer. There are 4 crystalline forms (I, II, III and IV) and one amorphous form, the latter form is applicable for the drug substance at issue.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of several reactions steps, by which only the amorphous form is formed. The substance is additionally micronized to the desired particle size. Specifications of the various used agents have been provided including the limitation of potential impurities.

Quality control of drug substance
Drug substance specifications are applied including those for identification, assay and related substances, optical rotation, water content, residual solvents and particle size. The MAH demonstrated that the water content is of no influence on the amorphous form of Lercanidipine. Furthermore it was demonstrated that no interconversion of the polymorphic form occurs during manufacturing and stability testing. Batch analysis results for 3 batches were provided with results meeting the set drug substance specification.

Stability of drug substance
Three batches have been put on stability at 25°C/60% RH (24-18-12 months) and at 40°C/75% RH (6 months). No significant trends were observed among the stability results. The stability data sufficiently support the claimed re-test period of 2 years with the storage condition: 'Store below 25°C in the original package'.

The MAH made two commitments with regard to the active substance; these can be found on page 11.

* Ph.Eur. * is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Medicinal Product

Composition
Lercanidipine HCl Torent 10 mg contains as active substance 10 mg lercanidipine hydrochloride, which is equivalent to 9.4 mg lercanidipine. The product is a yellow, round shaped biconvex, film-coated tablet with break-line on one side and plain on the other side.
Lercanidipine HCl Torent 20 mg contains as active substance 20 mg lercanidipine hydrochloride, which is equivalent to 18.8 mg lercanidipine. The product is a pink, round shaped biconvex, film-coated tablet with break-line on one side and plain on the other side.

The score lines are only to facilitate breaking for ease of swallowing and not to divide into equal doses.

The film-coated tablets are packed in PVC-Al or PVC/PVdC-Al blisters.

The excipients are:

10 mg – maize starch, sodium starch glycolate (type A), colloidal anhydrous silica, microcrystalline cellulose, poloxamer 188, sodium stearyl fumarate, macrogol 6000, hypromellose, iron oxide yellow (E172), titanium dioxide (E171).

20 mg – microcrystalline cellulose, maize starch, sodium starch glycolate (type A), colloidal anhydrous silica, povidone K 30, sodium stearyl fumarate, hypromellose, macrogol 6000, iron oxide red (E172), titanium dioxide (E171).

The compositions of both strengths of the proposed product are qualitatively different and not dose-proportional.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The MAH explained the development resulting in two different formulations for the two strengths. The tablets differ in the usage of methanol + binder Polyvidon K-30 for the 20 mg strength, while for the 10 mg strength instead Poloxamer 188 in water is used.

Bioequivalence studies have been performed for both strengths using the German reference product Carmen 10 mg and 20 mg. The particle size of the 10 mg tablets were in line with the drug substance. The 20 mg tablets are manufactured using wet granulation; therefore the particle size of the drug substance is of no consequence to the dissolution profile.

Comparative dissolution profiles between the proposed product and corresponding originator product being present on the markets of the involved RMS and CMSs have been provided for both strengths. The pharmaceutical development has been sufficiently described.

Manufacturing process
The manufacturing processes have been adequately described and consist of granulation, compression and filmcoating. In the 10 mg tablets sodium stearyl sulphate and macrogol are used as lubricants, while in the 20 mg tablets sodium stearyl fumarate and colloidal silicium dioxide are used as lubricants. The two different manufacturing procedures are unambiguously applied for each of the two groups of bio-batches, validation batches, production batches and stability batches. For both strengths sufficient validation data have been provided.

Control of excipients
The excipients comply with Ph.Eur. and the two ferric oxide colorants with the USP. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for identification, identification of colorants, average mass and uniformity of dosage units, mass uniformity of halved tablets, dissolution, assay and related substances, water content, residual methanol, residual ethanol, microbiological purity, and hardness. Adequate specifications have been applied. Batch analysis results are provided for 3 batches of both 10 and 20 mg tablets. All results were in accordance with the set requirements.

Stability of drug product
Stability testing has been performed on 10 and 20 mg tablets packed in PVC-Alu or PVC/PVdC-Alu blisters, stored at 25°C/60% RH and 40°C/75% RH. Only 20 mg tablets are tested on hardness. No significant changes among parameters like assay and related substances have been observed; there is a
slight increase in time for impurities. One batch of each strength has been tested on photostability. The products in the primary packaging are possibly sensitive to light. Based on the results, the applicable shelf life and storage conditions are 24 months for the 10 mg strength, and 36 months for the 20 mg strength, both with the storage condition 'Store in the outer package in order to protect from light'.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

This product is a generic formulation of Zanidip, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of lercanidipine released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test products Lercanidipine HCl Torent 10 mg and 20 mg (Torrent Pharma GmbH, DE) is compared with the pharmacokinetic profile of the reference products Carmen 10 and 20 mg tablets (Berlin Chemie AG, DE). In addition, a replicate design study with the 10 mg tablets of the reference product used in the bioequivalence study was submitted. As the pharmacokinetics of lercanidipine is non-linear (more than dose proportional increase in C<sub>max</sub> and AUC) and the compositions of both tablet formulations are different, both studies are considered necessary for assessment of the bioavailability of both products.

The choice of the reference product

The choice of the reference products in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states. The formula and preparation of the bioequivalence batches is identical to the formula proposed for marketing.

Bioequivalence study I - 10 mg

Design
An open, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 18-43 years. Each subject received a single dose (10 mg) of one of the 2 lercanidipine formulations. The tablet was orally administered with 200 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

Analytical/statistical methods
The plasma samples were analysed for S- and R-enantiomers of lercanidipine. Measurement of both enantiomers is required as both products (test and reference) contain the racemate. The bioequivalence conclusion should be based on the (S)-enantiomer since the effect is mainly due to this enantiomer. The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

There was one drop-out, as one subject did not turn up for period II. Fifty-five subjects completed the study. Three volunteers were excluded from the statistical analysis of R-lercanidipine. There were insufficient samples for further repeat analysis. Hence, total 55 volunteers were evaluated for pharmacokinetic and statistical analysis of S-lercanidipine and total 52 volunteers were evaluated for pharmacokinetic and statistical analysis of R-lercanidipine.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\textsubscript{max} (median, range)) of S-lercanidipine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=55</th>
<th>AUC\textsubscript{0-4} (ng.h/ml)</th>
<th>AUC\textsubscript{0-\infty} (ng.h/ml)</th>
<th>C\textsubscript{max} (ng/ml)</th>
<th>t\textsubscript{max} (h)</th>
<th>t\textsubscript{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>10.28 ± 6.99</td>
<td>9.78 ± 6.91</td>
<td>2.75 ± 1.93</td>
<td>1.25 (0.5-4.0)</td>
<td>4.33 ± 2.14</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>8.58 ± 4.32</td>
<td>9.06 ± 4.32</td>
<td>2.29 ± 1.21</td>
<td>1.5 (0.5-6.0)</td>
<td>0.409 ± 1.26</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>1.06 (0.93 - 1.19)</td>
<td>1.07 (0.95-1.18)</td>
<td>1.10 (0.92-1.28)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td>38</td>
<td>35</td>
<td>54</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

AUC\textsubscript{0-\infty} area under the plasma concentration-time curve from time zero to infinity
AUC\textsubscript{0-4} area under the plasma concentration-time curve from time zero to t hours
C\textsubscript{max} maximum plasma concentration
\text{t}_{\text{max}} time for maximum concentration
\text{t}_{1/2} half-life

*ln-transformed values

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\textsubscript{max} (median, range)) of R-lercanidipine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=52</th>
<th>AUC\textsubscript{0-4} (ng.h/ml)</th>
<th>AUC\textsubscript{0-\infty} (ng.h/ml)</th>
<th>C\textsubscript{max} (ng/ml)</th>
<th>t\textsubscript{max} (h)</th>
<th>t\textsubscript{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>9.89 ± 6.83</td>
<td>10.4 ± 6.9</td>
<td>2.56 ± 1.72</td>
<td>1.25 (0.50-4.0)</td>
<td>4.6 ± 2.1</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>8.21 ± 3.88</td>
<td>8.74 ± 3.90</td>
<td>2.0 ± 0.99</td>
<td>1.5 (0.5-6.0)</td>
<td>4.4 ± 1.2</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>1.11 (0.98-1.27)</td>
<td>1.11 (0.98-1.24)</td>
<td>1.15 (0.96-1.36)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td>40</td>
<td>37</td>
<td>57</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

AUC\textsubscript{0-\infty} area under the plasma concentration-time curve from time zero to infinity
AUC\textsubscript{0-4} area under the plasma concentration-time curve from time zero to t hours
C\textsubscript{max} maximum plasma concentration
\text{t}_{\text{max}} time for maximum concentration
\text{t}_{1/2} half-life

*ln-transformed values
Bioequivalence has been demonstrated regarding \( \text{AUC}_{0-t} \) and \( \text{AUC}_{0-\infty} \), but not for \( C_{\text{max}} \) for S-lercanidipine as the 90% confidence interval is outside the normal acceptance range of 0.80-1.25. Remarkable is the twice higher variability in the pharmacokinetic variables with the test product compared with the reference product. The justification for being a highly variable drug is presented below in the discussion of the replicate design study (Bioequivalence study III - 10 mg, replicate design).

The 90% CI for the R-enantiomer are outside the normal acceptance range. However, as establishing bioequivalence is only based on the S-enantiomer, the 90% CI being outside the range is of no clinical significance.

**Bioequivalence study II - 20 mg**

**Design**

An open, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 56 healthy male subjects, aged 19-42 years. Each subject received a single dose (20 mg) of one of the 2 lercanidipine formulations. The tablet was orally administered with 200 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 5, 6, 9, 12, 18, 24, 48 and 72 hours after administration of the products.

**Analytical/statistical methods**

The plasma samples were analysed for S- and R-enantiomers of lercanidipine. Measurement of both enantiomers is required as both products (test and reference) contain the racemate. The bioequivalence conclusion should be based on the (S)-enantiomer since the effect is mainly due to this enantiomer. The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

**Results**

There were two drop-outs. One volunteer experienced adverse events (burning sensation in urine, abdominal pain) and was not dosed in period II. One volunteer did not turn up for period II. 54 subjects completed the study.

Three volunteers were excluded from the statistical analysis of R-lercanidipine. There were insufficient samples for further repeat analysis. Hence, total 54 volunteers were evaluated for pharmacokinetic and statistical analysis of S-lercanidipine and total 51 volunteers were evaluated for pharmacokinetic and statistical analysis of R-lercanidipine.

**Table 3.** Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of S-lercanidipine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) (ng.h/ml)</th>
<th>( \text{AUC}_{0-\infty} ) (ng.h/ml)</th>
<th>( C_{\text{max}} ) (ng/ml)</th>
<th>( t_{\text{max}} ) (h)</th>
<th>( t_{1/2} ) (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test</strong></td>
<td>25.97 ± 15.44</td>
<td>27.07 ± 15.89</td>
<td>6.25 ± 4.06</td>
<td>1.9 ± 0.7</td>
<td>10.7 ± 11.4</td>
</tr>
<tr>
<td><strong>Reference</strong></td>
<td>25.66 ± 12.28</td>
<td>26.68 ± 12.78</td>
<td>5.92 ± 3.07</td>
<td>1.9 ± 1.2</td>
<td>9.3 ± 7.3</td>
</tr>
<tr>
<td><strong>Ratio (90% CI)</strong></td>
<td>1.00 (0.90-1.10)</td>
<td>1.00 (0.90-1.10)</td>
<td>1.07 (0.93-1.21)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td><strong>CV (%)</strong></td>
<td>32</td>
<td>32</td>
<td>42</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
### Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of R-lercanidipine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} )</th>
<th>( \text{AUC}_{0-\infty} )</th>
<th>( C_{\text{max}} )</th>
<th>( t_{\text{max}} )</th>
<th>( t_{1/2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>26.86 ± 18.50</td>
<td>28.08 ± 19.26</td>
<td>5.92 ± 4.25</td>
<td>1.92 ± 0.7</td>
<td>11.7 ± 11.1</td>
</tr>
<tr>
<td>Reference</td>
<td>26.11 ± 13.02</td>
<td>27.22 ± 13.64</td>
<td>5.53 ± 2.84</td>
<td>2.0 ± 1.2</td>
<td>9.7 ± 7.4</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} )</th>
<th>( \text{AUC}_{0-\infty} )</th>
<th>( C_{\text{max}} )</th>
<th>( t_{\text{max}} )</th>
<th>( t_{1/2} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1.00 (0.89-1.10)</td>
<td>1.01 (0.90-1.11)</td>
<td>1.07 (0.92-1.21)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Reference</td>
<td>34</td>
<td>32</td>
<td>44</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*ln-transformed values

The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( C_{\text{max}} \) are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25 for both S- and R-lercanidipine. Based on the pharmacokinetic parameters of lercanidipine under fasted conditions, it can be concluded that Lercanidipine HCl Torent 20 mg and Carmen 20 mg film-coated tablets are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

**Bioequivalence study III - 10 mg, replicate design**

**Design**

This was an open label, replicate study to assess the intra-subject variability of Carmen® 10 mg Tablet of Berlin Chemie, Germany containing lercanidipine HCl 10 mg in healthy human volunteers under fasted conditions.

An open, single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 18 healthy male subjects, aged 19-42 years. Each subject received a single dose (10 mg) of one of the 2 lercanidipine formulations. The tablet was orally administered with 200 ml water under fasted conditions. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 5, 6, 9, 12, 18, 24, 48 and 72 hours after administration of the products.

**Analytical/statistical methods**

The plasma samples were analysed for S- and R-enantiomers of lercanidipine. Measurement of both enantiomers is required as both products (test and reference) contain the racemate. The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.
Results
There were no drop-outs. Hence, all 18 volunteers were evaluated for pharmacokinetic and statistical analysis of S-lercanidipine and R-lercanidipine.

Table 5. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{max}$ (median, range)) of S-lercanidipine and R-lercanidipine under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=18</th>
<th>AUC$_{0-t}$ ng.h/ml</th>
<th>AUC$_{0-\infty}$ ng.h/ml</th>
<th>C$_{max}$ ng/ml</th>
<th>$t_{max}$ h</th>
<th>$t_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S-lercanidipine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period I</td>
<td></td>
<td>10.78 ± 6.84</td>
<td>11.03 ± 6.86</td>
<td>2.70 ± 1.88</td>
<td>2.25</td>
<td>(1.0-5.0)</td>
</tr>
<tr>
<td>Period II</td>
<td></td>
<td>10.04 ± 6.93</td>
<td>10.62 ± 6.91</td>
<td>2.47 ± 1.97</td>
<td>1.75</td>
<td>(0.75-5.0)</td>
</tr>
<tr>
<td><strong>R-lercanidipine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Period I</td>
<td></td>
<td>11.70 ± 7.33</td>
<td>12.3 ± 7.36</td>
<td>2.74 ± 1.86</td>
<td>2.25</td>
<td>(1.0-3.5)</td>
</tr>
<tr>
<td>Period II</td>
<td></td>
<td>11.40 ± 8.11</td>
<td>12.02 ± 8.26</td>
<td>2.55 ± 2.03</td>
<td>1.75</td>
<td>(0.75-5.0)</td>
</tr>
</tbody>
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AUC$_{0-t}$ area under the plasma concentration-time curve from time zero to t hours
AUC$_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C$_{max}$ maximum plasma concentration
$t_{max}$ time for maximum concentration
$t_{1/2}$ half-life

*ln-transformed values

Table 6. Intra-subject and Inter-subject percentage coefficients of variance (CV %) for C$_{max}$, AUC$_{last}$ and AUC$_{INF}$ of S-lercanidipine and R-lercanidipine under fasted conditions.

The results of the duplicate design study sufficiently demonstrate high intra-individual variability for the reference product Carmen 10 mg tablets. Lercanidipine can therefore be considered a highly variable drug. Therefore, widening of the acceptance range for C$_{max}$ is acceptable considering the high intra-individual variability established with the reference product in the replicate design study. In both bioequivalence studies for the 10 mg formulation the C$_{max}$ the 90% CI is within the predefined extended range of 0.75-1.33.
Based on the additional data provided in the replicate design study, Lercanidipine HCl Torent 10 mg and Carmen 10 mg film-coated tablets are considered bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

**Food effect**
Lercanidipine should not be taken directly with food. The SPC clearly states that the tablet should be taken at least 15 minutes before meals. Oral availability of lercanidipine increases 4-fold when lercanidipine is ingested up to 2 hours after a high fat meal. Therefore bioequivalence studies under fasting conditions are considered appropriate.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

**Risk management plan**
Lercanidipine was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of lercanidipine can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

**Product information**

**SPC**
The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Zanidip.

**Readability test**
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 2 participants, followed by two rounds with 10 participants each. The 20 test subjects were volunteers of both sexes aged 18 years or older with different education levels. The test included 17 questions on the text of the leaflet. There were sufficient questions about the critical sections. The subjects were also asked to give their positive and negative feedback as well as a subjective rating of the leaflet. Before testing was started the leaflet was revised to improve readability. In round 1 and 2 all questions were located and answered correctly by at least 90% of the subjects. Therefore no changes to the leaflet were made after the first or second round. The readability test has been sufficiently performed.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lercanidipine HCl Torent 10 mg and 20 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Zanidip 10 and 20 mg film-coated tablets. Zanidip is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lercanidipine HCl Torent 10 mg and 20 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 14 April 2010. Lercanidipine HCl Torent 10 mg and 20 mg were authorised in the Netherlands on 20 May 2010.

A European harmonised birth date has been allocated (22 March 1996) and subsequently the first data lock point for lercanidipine is August 2011. The first PSUR will cover the period from April 2010 to August 2011 after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 14 April 2015.

The following post-approval commitments have been made during the procedure:

Quality - active substance
- The MAH committed to include XRD as parameter in the stability studies.
- The MAH committed to evaluate the data of the future batches till sufficient data has accumulated to tighten the optical rotation limit.
### List of abbreviations

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C\text{max}</td>
<td>Maximum plasma concentration</td>
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<tr>
<td>CMD\text{(h)}</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
</tr>
<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>t\text{½}</td>
<td>Half-life</td>
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<tr>
<td>t\text{max}</td>
<td>Time for maximum concentration</td>
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<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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