Enalapril Maleate / Hydrochlorothiazide 20 mg / 12.5 mg Tablets

PL 17907/0332

UKPAR

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Lay Summary

On 27th March 2013, the MHRA granted Bristol Laboratories Limited a Marketing Authorisation (licence) for the medicinal product Enalapril maleate / Hydrochlorothiazide 20 mg / 12.5 mg Tablets (PL 17907/0332). This medicine is only available on prescription from your doctor.

Enalapril + HCTZ Tablets contain enalapril maleate and hydrochlorothiazide:

• enalapril belongs to a group of medicines known as ACE inhibitors, which work by widening your blood vessels
• hydrochlorothiazide belongs to a group of medicines known as thiazide diuretics (water tablets), which increase the volume of urine you produce.

The effect of these medicines is to lower your blood pressure. Enalapril + HCTZ Tablets are used to treat high blood pressure (hypertension). Taking both medicines, enalapril and hydrochlorothiazide can increase their effect compared to taking just one.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Enalapril maleate / Hydrochlorothiazide 20 mg / 12.5 mg Tablets outweigh the risks. Hence, a Marketing Authorisation has been granted.
Enalapril Maleate / Hydrochlorothiazide 20 mg / 12.5 mg Tablets

PL 17907/0332

SCIENTIFIC DISCUSSION

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INTRODUCTION

The MHRA granted a Marketing Authorisation for the medicinal product Enalapril maleate / Hydrochlorothiazide 20 mg / 12.5 mg Tablets (PL 17907/0332) on 27th March 2013. This prescription only medicine is used for the treatment of mild to moderate hypertension in patients who have been stabilised on the individual components given in the same proportions.

This is a national abridged application for Enalapril maleate / Hydrochlorothiazide 20 mg / 12.5 mg Tablets submitted under Article 10(1) of Directive 2001/83/EC, as amended. This product is cross referring to Innozide Tablets 20 mg/12.5 mg (PL 00025/0045), first authorised to Merck Sharp and Dohme, on 8th May 1991.

Enalapril is an orally active angiotensin-converting enzyme (ACE) inhibitor that does not contain a sulphydryl group, and that has a longer duration of action than captopril. It is a prodrug, which requires de-esterification before exhibiting ACE inhibition. Hydrochlorothiazide is a diuretic and antihypertensive agent which increases plasma renin activity. Although enalapril alone is antihypertensive concomitant administration of hydrochlorothiazide leads to greater reduction of blood pressure.

A pharmacovigilance system has been provided with this application and is satisfactory. A suitable justification for non-submission of the Risk Management Plan has been provided.
PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Nomenclature

rINN: Enalapril maleate


Structure:

![Chemical Structure of Enalapril Maleate](image)

Molecular Formula: C₂₀H₂₈N₂O₅,C₄H₄O₄

Molecular Weight: 492.5

Appearance: White or almost white, crystalline powder.

Solubility: Sparingly soluble in water, freely soluble in methanol, practically insoluble in methylene chloride. It dissolves in dilute solutions of alkali hydroxides.

Enalapril maleate is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance enalapril maleate are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

rINN: Hydrochlorothiazide

Chemical Name: 6-Chloro-3,4-dihydro-2/H-1,2,4-benzothiadiazine-7-sulphonamide 1,1 dioxide.

Structure:

![Chemical Structure of Hydrochlorothiazide](image)
Molecular Formula: C₇H₈ClN₃O₄S₂

Molecular Weight: 297.7

Appearance: White or almost white, crystalline powder.

Solubility: Very slightly soluble in water, soluble in acetone and sparingly soluble in ethanol (96%). It dissolves in dilute solutions of alkali hydroxides.

Hydrochlorothiazide is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance hydrochlorothiazide are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, maleic acid, pregelatinised starch, maize starch, yellow ferric oxide E172 and sodium stearyl fumarate.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients.

The only excipient used that contains material of animal or human origin is lactose monohydrate. The applicant has provided a declaration that the milk used in the production of lactose monohydrate is sourced from healthy animals under the same conditions as that for human consumption.

**Pharmaceutical development**

Suitable pharmaceutical development data have been provided for this application.

Comparable dissolution profiles are provided for this product versus the originator product.

**Manufacture**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. The applicant has committed to perform process validation on future commercial-scale batches.

**Finished product specification**

The finished product specifications are satisfactory. Test methods have been described and adequately validated. Batch data have been provided that complies with the release specification. Certificates of Analysis have been provided for any working standards used.
Container Closure System
The tablets are packed in aluminium / aluminium blister packs of tablets inserted into a carton package containing 10, 28, 30, 50, 56, 98 and 100 tablets.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 24 months with storage conditions “Do not store above 25°C” and “Store in the original package” are set. These are satisfactory.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically satisfactory.

User testing of the package leaflet has been accepted, based on bridging reports provided by the applicant making reference to the user-testing of the PIL for Ramipril 1.25 mg, 2.5 mg, 5 mg and 10 mg Capsules. The products are from the same therapeutic class and have similar indications. A critical analysis demonstrated that the key messages for safe and effective use for both leaflets were similar. The justification of the rationale for bridging is accepted.

The proposed artwork complies with the relevant statutory requirements. In line with current legislation the applicant has also included the name of the product in Braille on the outer packaging and has included sufficient space for a standard UK pharmacy dispensing label.

The Marketing Authorisation holder has stated that not all packs are intended to be marketed. However, they have committed to submit mock-ups of any pack size to the relevant regulatory authorities before marketing.

Marketing Authorisation Application (MAA) Forms
The MAA form is pharmaceutically satisfactory.

Expert Report
The quality overall summary is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Conclusion
There are no objections to the approval of this product from a pharmaceutical point of view.
NON-CLINICAL ASSESSMENT

The pharmacodynamic, pharmacokinetic and toxicological properties of enalapril maleate and hydrochlorothiazide are well-known. Thus, the applicant has not provided additional studies and further studies are not required.

A non-clinical overview has been provided, written by an appropriately qualified person. This is satisfactory.

Suitable justification has been provided for non-submission of an environmental risk assessment.

There are no objections to the approval of this product from a non-clinical point of view.
CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY
BIOEQUIVALENCE
To support this application, the applicant has submitted a bioequivalence study under fasting condition comparing the test product with the reference product.

This was a randomized, open label, two-treatment, two-period, two-sequence, single dose, crossover, oral bioequivalence study of Enalapril maleate / Hydrochlorothiazide 20+12.5mg tablets (IPCA Laboratories Limited, India) and INNOZIDE® containing Enalapril maleate 20 mg and Hydrochlorothiazide 12.5 mg tablets (Merck Sharp & Dohme Limited, UK) in healthy adult male human subjects, under fasting conditions.

A total of twenty four blood samples were collected during each period. The pre-dose blood sample of 5.0mL (0.00 hr) was collected within one hour before dosing. The post-dose blood samples of 5.0mL each was drawn at 0.25, 0.50, 0.75, 1.00, 1.50, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 8.00, 10.00, 12.00, 16.00, 24.00 hours and ambulatory samples at 36.00, 72.00, 120.00 and 168.00 hours following drug administration in each period. The ambulatory samples at 120.00 and 168.00 hours were drawn for enalapril and its metabolite, enalaprilat assay. Up to 10.0mL of blood sample was drawn at the end of the study for post study assessment. A washout period of 14 days was maintained between the two dosing periods in each group.

The primary Pharmacokinetic variables were $C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\text{inf}}$ for Enalapril, Enalaprilat and Hydrochlorothiazide based on which the bioavailability of the formulations was assessed. In addition, $T_{\text{max}}$, $t_{1/2}$ and $K_{\text{el}}$ were estimated.

The inclusion/exclusion criteria for study subjects were acceptable and in line with the requirements of the ‘Guideline on the Investigation of Bioequivalence’.

Results
The mean pharmacokinetic parameters and the In-transformed geometric least square means and 90% confidence interval (90% CI) and ratio of formulations Test (T) and Reference (R) (T/R%) for the pharmacokinetic parameters $C_{\text{max}}$, $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\text{inf}}$ for Enalapril, its metabolite Enalaprilat and Hydrochlorothiazide are shown in the following tables:

Summary of Geometric mean and 90% confidence intervals, for Test and Reference products (N=31)

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Ln-transformed Geometric Least Squares Mean</th>
<th>90% Confidence Interval (ln-transformed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product</td>
<td>Test Product</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>171.777</td>
<td>176.633</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (ng.h/mL)</td>
<td>269.935</td>
<td>263.616</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{inf}}$ (ng.h/mL)</td>
<td>280.277</td>
<td>274.504</td>
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</table>
Enalaprilat results

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Ln-transformed Geometric Least Squares Mean</th>
<th>90% Confidence Interval (ln-transformed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product (R)</td>
<td>Test Product (T)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>79.518</td>
<td>72.809</td>
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<tr>
<td>AUC&lt;sub&gt;0-t&lt;/sub&gt; (ng.h/mL)</td>
<td>712.618</td>
<td>663.504</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng.h/mL)</td>
<td>746.267</td>
<td>696.311</td>
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</table>

Hydrochlorothiazide results

<table>
<thead>
<tr>
<th>Parameters (Units)</th>
<th>Ln-transformed Geometric Least Squares Mean</th>
<th>90% Confidence Interval (ln-transformed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reference Product (R)</td>
<td>Test Product (T)</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>86.678</td>
<td>93.442</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-4&lt;/sub&gt; (ng.h/mL)</td>
<td>670.487</td>
<td>665.033</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (ng.h/mL)</td>
<td>708.336</td>
<td>702.256</td>
</tr>
</tbody>
</table>

The results show that the 90% confidence intervals for C<sub>max</sub>, AUC<sub>0-t</sub> and AUC<sub>0-inf</sub> fell within the acceptable range (80-125%). Bioequivalence has been demonstrated between the test formulation (Enalapril maleate and Hydrochlorothiazide 20+12.5 mg tablets) and the reference formulation (INNOZIDE<sup>®</sup> containing Enalapril maleate 20 mg and Hydrochlorothiazide 12.5 mg tablets).

**Efficacy**
No new efficacy data have been submitted and none are required for this application.

**Safety**
No new safety data have been submitted and none are required for this application.

**Expert Report**
The clinical overview is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Summary of Product Characteristics**
This is satisfactory.

**Patient Information Leaflet**
This is satisfactory.
LABELLING
This is satisfactory.

MAA FORMS
This is satisfactory.

CONCLUSIONS
There are no objections to the approval of this product from a clinical point of view.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The quality characteristics of Enalapril maleate / Hydrochlorothiazide 20 mg/12.5 mg Tablets are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY
No new data have been submitted and none are required for applications of this type. Bioequivalence has been demonstrated between the applicant’s Enalapril maleate and Hydrochlorothiazide 20+12.5 mg tablets and the reference product, INNOZIDE containing Enalapril maleate 20 mg and Hydrochlorothiazide 12.5 mg tablets.

SAFETY
No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE
The SmPC and PIL are satisfactory and consistent with those for the reference product. Satisfactory labelling has also been submitted.

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s products and the originator products are interchangeable. Extensive clinical experience with enalapril maleate and hydrochlorothiazide is considered to have demonstrated the therapeutic value of the compound. The benefit risk is, therefore, considered to be positive.
Enalapril Maleate / Hydrochlorothiazide 20 mg / 12.5 mg Tablets

PL 17907/0332

**STEPS TAKEN FOR ASSESSMENT**

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<tr>
<td>1</td>
<td>The MHRA received the Marketing Authorisation application on 5(^{th}) July 2011</td>
</tr>
<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 11(^{th}) July 2011.</td>
</tr>
<tr>
<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical and quality sections on 17(^{th}) October 2011 and 2(^{nd}) August 2012.</td>
</tr>
<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information to the clinical and quality sections on 22(^{nd}) June 2012 and 23(^{rd}) Oct 2012.</td>
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<tr>
<td>5</td>
<td>The application was determined on 27(^{th}) March 2013</td>
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Module 2
Summary of Product Characteristics

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3
Patient Information Leaflet

In accordance with Directive 2010/84/EU the Patient Information Leaflets (PIL) for products that are granted Marketing Authorisations at a national level are available on the MHRA website.
<table>
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