Public Assessment Report

Scientific discussion

Esomeprazol Hetero 20 mg and 40 mg, gastro-resistant tablets
(esomeprazole magnesium)

NL/H/2824/001-002/DC

Date: 10 June 2014

This module reflects the scientific discussion for the approval of Esomeprazol Hetero 20 mg and 40 mg, gastro-resistant tablets. The procedure was finalised on 15 December 2013. 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 Esomeprazol Hetero 20 mg and 40 mg, gastro-resistant tablets from Hetero Europe S.L.

The product is indicated for:

**Adults**

**Gastroesophageal Reflux Disease (GORD)**
- treatment of erosive reflux oesophagitis
- long-term management of patients with healed oesophagitis to prevent relapse
- symptomatic treatment of gastro-oesophageal reflux disease (GORD)

In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* and
- healing of *Helicobacter pylori* associated duodenal ulcer and
- prevention of relapse of peptic ulcers in patients with *Helicobacter pylori* associated ulcers

**Patients requiring continued NSAID therapy**

Healing of gastric ulcers associated with NSAID therapy.
Prevention of gastric and duodenal ulcers associated with NSAID therapy, in patients at risk.

**Prolonged treatment after i.v. induced prevention of rebleeding of peptic ulcers.**

**Treatment of Zollinger Ellison Syndrome**

**Adolescents from the age of 12 years**

**Gastroesophageal Reflux Disease (GORD)**
- treatment of erosive reflux esophagitis
- long-term management of patients with healed esophagitis to prevent relapse
- symptomatic treatment of gastroesophageal reflux disease (GORD)

In combination with antibiotics in treatment of duodenal ulcer caused by *Helicobacter pylori*.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Nexium 20 mg and 40 mg, gastro-resistant tablets which has been registered in Sweden by AstraZeneca AB since 10 March 2000 (original product). In the Netherlands, Nexium 20 mg and 40 mg (NL License RVG 25387-25388) have been registered since 15 August 2000 by MRP SE/H/0211/001-002. In addition, reference is made to Nexium authorisations in the individual member states (reference product).

The concerned member states (CMS) involved in this procedure were Germany and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Esomeprazol Hetero 20 mg is a light pink colored, oval shaped tablet debossed with ‘H’ on one side and ‘186’ on the other side.

Esomeprazol Hetero 40 mg is a pink colored, oval shaped tablet debossed with ‘H’ on one side and ‘187’ on the other side.

The gastro-resistant tablets are packed in Alu/Alu blisters.
The excipients are:

**Tablet core** – sucrose, maize starch, hypromellose, meglumine, poloxamer, sodium lauryl sulphate, methacrylic acid copolymer, triethyl citrate, glyceryl monostearate, sodium hydroxide, silicified microcrystalline cellulose, silica, colloidal anhydrous, lactose monohydrate, maize starch, crospovidone, magnesium stearate.

**Tablet coating** - hydroxypropyl cellulose, macrogol, titanium dioxide, talc, paraffin light liquid, polysorbate, iron oxide red, iron oxide yellow.

The tablet cores are manufactured fully dose proportional.

### II.2 Drug Substance

The active substance is esomeprazole magnesium dehydrate, an established active substance however not described in the European Pharmacopoeia (Ph.Eur.). There is however a monograph for the trihydrate form. The drug substance is a white or slightly coloured powder, which is soluble in methanol, slightly soluble in water and practically insoluble in heptane. The drug substance shows polymorphism and is manufactured as Form B.

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 synthetic process for producing the active substance is described in seven chemical steps followed by chiral separation and purification. No Class 1 organic solvents or heavy metal catalysts have been used. Acceptable specifications have been adopted for the reagents and solvents.

**Quality control of drug substance**

The drug substance specification has been established in-house and is in line with the specification of the ASMF-holder. Batch analytical data demonstrating compliance with the drug substance specification have been provided on two batches.

**Stability of drug substance**

The active substance manufacturer has provided stability data on the active substance for three full-scale batches stored at 2–8°C (36 months), 25°C/60%RH (18 months), 30°C/65%RH (12 months) and 40°C/75%RH (3 months). When stored at 40°C/75%RH significant changes were seen. At the other three storage conditions no changes or trends were observed. The proposed re-test period of 12 months when stored at 2 – 8°C is justified.

### II.3 Medicinal Product

**Pharmaceutical development**

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were regarding the characterisation of the innovator product, optimization of the formulation to obtain a dissolution comparable to the innovator product and the performance of comparable dissolution studies. The excipients used in the products are well known. The choices of the packaging and manufacturing process are justified. The 40 mg test batch used in the bioequivalence study was manufactured according to the finalized manufacturing process and composition. A biowaiver for the 20 mg strength was supported by relevant dissolution data. The results of the comparative *in vitro* dissolution studies between the test and reference batch used in the bioequivalence study confirm similarity of dissolution profiles. The pharmaceutical development of the product has been adequately performed.

**Manufacturing process**

The first step of the process is the manufacture of enteric-coated pellets. For this purpose sugar spheres are first coated with a seal coating suspension, then with a suspension containing the active ingredient, then with a sub-coating, then with an enteric coating and finally with a polishing
suspension. A final blend is then prepared from the enteric coated pellets, which is compressed into tablets of either 20 mg or 40 mg. Finally, a film-coating is applied. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full-scale batches per strength.

Control of excipients
The excipients comply with the Ph.Eur. or USP-NF (silicified microcrystalline cellulose) with additional in-house requirements for some of the excipients. In-house specifications have been provided for the StarLac and Opadry film-coatings. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification (of active ingredient and colorants), average weight, water content, uniformity of dosage units, dissolution, related substances, assay, residual solvents and microbial quality. Except for related substances and water content, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three full-scale batches per strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on three full-scale batches per strength stored at 25°C/60% RH (24 months, one batch for 6 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al/Al-blisters. The results of the stability studies show an increase of some of the specified impurities at both long-term and accelerated storage conditions. Results for assay are variable but no clear trend is observed. Results for water content are variable and in general show a slight increase at both storage conditions. No trends or changes are observed for any of the other tested parameters. Based on the results of the forced degradations studies, showing no degradation upon exposure to light, it can be concluded that protection from light is not necessary. The proposed shelf-life of 24 months and storage condition ‘Store below 25°C’ are justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The lactose monohydrate present in the product is prepared from milk sourced from healthy animals in the same conditions as milk collected for human consumption. It is prepared without the use of other ruminant materials than calf rennet. The calf rennet is in accordance with Public Statement EMEA/CPMP/571/02.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Esomeprazol Hetero 20 mg and 40 mg, gastro-resistant tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Esomeprazol Hetero is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Nexium, which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.
IV. CLINICAL ASPECTS

IV.1 Introduction

Esomeprazole is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted two bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Esomeprazol Hetero 40 mg (Hetero Europe S.L., Spain) is compared with the pharmacokinetic profile of the reference product Nexiam 40 mg gastro-resistant tablets (AstraZeneca, Sweden) under fasted and fed conditions.

The choice of the reference product 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 batch is identical to the formula proposed for marketing.

The analytical methods used in both studies have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

A study under fasting and fed conditions to support this application is considered sufficient. According to the EU Bioequivalence guideline, single dose bioequivalence studies are considered sensitive enough to support proof of bioequivalence, also in case of time dependent pharmacokinetics.

Biowaiver
A biowaiver has been granted for the 20 mg strength, as the following criteria are fulfilled:
- The different strengths are manufactured by same manufacturing process.
- Esomeprazol Hetero 20 mg tablets are developed as a dose proportional formula (scale down). The ratio between amounts of excipients is similar.
- The qualitative composition of Esomeprazol Hetero tablets 20 mg and 40 mg is the same.
- Pharmacokinetics increase more than dose proportional. The highest dose is used in the bio-studies.
- The dissolution profile of Esomeprazol Hetero 40 mg tablets was demonstrated to be comparable to the 20 mg strength.

Bioequivalence studies

Bioequivalence study I – fasted conditions

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 48 healthy male subjects, aged 19-39 years. Each subject received a single dose (40 mg) of one of the 2 esomeprazole formulations. The tablet was orally administered with 240 ml water. There were 2 dosing periods, separated by a washout period of 8 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, 3.33, 3.67, 4, 4.5, 5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

The single dose, crossover study to assess bioequivalence is considered adequate.

Results
All subjects completed the study. Pharmacokinetic and statistical analysis were carried out on 48 subjects.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of esomeprazole under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=48</th>
<th>( \text{AUC}_{0-t} ) ng.h/ml</th>
<th>( \text{AUC}_{0-\infty} ) ng.h/ml</th>
<th>( \text{C}_{\text{max}} ) ng/ml</th>
<th>( t_{\text{max}} ) h</th>
<th>( t_{1/2} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>6086 ± 2950</td>
<td>6165 ± 2966</td>
<td>1892 ± 593</td>
<td>2.8 ± 1.0</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>6270 ± 3066</td>
<td>6351 ± 3106</td>
<td>1905 ± 593</td>
<td>2.5 ± 1.2</td>
<td>2.0 ± 0.7</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>0.96 (0.91-1.02)</td>
<td>--</td>
<td>0.99 (0.93-1.05)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td>17.3</td>
<td>--</td>
<td>18.0</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

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

\*In-transformed values

Bioequivalence study II – fed conditions

Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 68 healthy male subjects, aged 18-40 years. Each subject received a single dose (40 mg) of one of the 2 esomeprazole formulations. The tablet was orally administered in solid form with 240 ml water within 30 min of serving a high-fat, high-caloric breakfast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 6.5, 7, 8, 9, 10, 12, 16, 20 and 24 hours after administration of the products.

The single dose, crossover study to assess bioequivalence is considered adequate. The served high-fat, high-caloric meal is appropriate to evaluate the food interaction for delayed formulations.

Results
One subject did not report for Period II. Two subjects were found to be positive for drug abuse and were withdrawn. Pharmacokinetic and statistical analyses were carried out on 65 subjects.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of esomeprazole under fed conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=65</th>
<th>( \text{AUC}_{0-t} ) ng.h/ml</th>
<th>( \text{AUC}_{0-\infty} ) ng.h/ml</th>
<th>( \text{C}_{\text{max}} ) ng/ml</th>
<th>( t_{\text{max}} ) h</th>
<th>( t_{1/2} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>5360 ± 3791</td>
<td>5429 ± 3799</td>
<td>1383 ± 797</td>
<td>4.2 ± 1.6</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>5721 ± 3739</td>
<td>5793 ± 3759</td>
<td>1481 ± 782</td>
<td>4.3 ± 1.3</td>
<td>1.8 ± 0.6</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>0.93 (0.84-1.03)</td>
<td>--</td>
<td>0.92 (0.82-1.03)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td>34.9</td>
<td>--</td>
<td>40.2</td>
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</table>

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

\*In-transformed values
Conclusion on bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence studies Esomeprazol Hetero 40 mg is considered bioequivalent with Nexium 40 mg gastro-resistant tablets under both fasted and fed conditions.

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).

IV.3 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 Esomeprazol Hetero.

Summary table of safety concerns as approved in RMP

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Important potential risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Risk of reduced plasma levels of clopidogrel due to interaction.</td>
<td>• Increased risk of Clostridium difficile–associated diarrhea (CDAD).</td>
</tr>
<tr>
<td>• Risk of hypomagnesaemia with long-term use.</td>
<td>• Risk of pneumonia with long-term use.</td>
</tr>
<tr>
<td>• Risk of bone fracture (particularly of hip, wrist, and spine).</td>
<td>• Decrease in absorption of iron</td>
</tr>
<tr>
<td>• Risk of decrease absorption of cyanocobalamine (vitamin B12) with long-term use.</td>
<td>• Visual disturbances.</td>
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<tr>
<td></td>
<td>• Congenital cardiac malformation following in utero exposure.</td>
</tr>
</tbody>
</table>

Missing information --

No additional pharmacovigilance activities beyond routine pharmacovigilance are required.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Nexium. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Esomeprazol Krka 20 mg and 40 mg gastro-resistant capsules. The key safety message is identical. As the text is identical, it is considered that no further testing is necessary on the daughter leaflet. The design and layout of the PL is in line with a previously tested PL for Levetiracetam Hetero 750 mg. The bridging report submitted has been found acceptable.
VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Esomeprazol Hetero 20 mg and 40 mg, gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Nexium 20 mg and 40 mg, gastro-resistant tablets. Nexium 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 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 Esomeprazol Hetero 20 mg and 40 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 December 2013.

There were no post-approval commitments made during the procedure.
<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached</th>
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