Public Assessment Report

Scientific discussion

Omeprazol “Copyfarm”
Omeprazole

DK/H/1650/001-003/MR

This module reflects the scientific discussion for the approval of Omeprazol “Copyfarm”. The procedure was finalised on 30 April 2009. 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 Omeprazol “Copyfarm” 10 mg, 20 mg and 40 mg gastro-resistant capsules, hard, from Copyfarm A/S. The date of authorisation in Denmark was on 29 November 2006.

The product is indicated for:

- Duodenal ulcers
- Benign gastric ulcers
- Reflux oesophagitis
- Maintenance treatment of reflux oesophagitis to prevent relapse
- Zollinger-Ellison syndrome
- Treatment of NSAID (Non Steroid Anti Inflammatory Drug) related gastric or duodenal ulcers
- Maintenance treatment of NSAID related gastric and duodenal ulcers to prevent relapse
- Symptomatic treatment of gastrooesophageal reflux disease

In combination with appropriate antibacterial therapeutic regimens for the eradication of Helicobacter pylori in patients with Helicobacter pylori associated peptic ulcers.

Children over 1 year of age and ≥ 10 kg:
Reflux oesophagitis. Symptomatic treatment of heartburn and acid regurgitation in gastroesophageal reflux disease.

This mutual recognition procedure concerns a generic application claiming essential similarity with the reference product Losec 10 mg, 20 mg and 40 mg gastro-resistant tablets which has been registered in Denmark by AstraZeneca A/S since 22 September 1997.

The marketing authorisation is granted based on article 10.3 of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Omeprazol “Copyfarm” 10 mg, 20 mg and 40 mg gastro-resistant capsules contains as active substance 10, 20 or 40 mg of omeprazole.

The 10 mg capsules are opaque white capsules printed “OM 10”.
The 20 mg capsules are opaque white capsules printed “OM 20”.
The 40 mg capsules are opaque white capsules printed “OM 40”.

Omeprazol “Copyfarm” is packed in HDPE containers with screw cap closure containing desiccant in pack sizes of 7, 14, 28, 50, 56 and 100 hard gastro-resistant capsules. However, not all pack sizes may be marketed.

The capsule shell consists of: Gelatin; titanium dioxide (E171) and black iron oxide (E172).
The printing ink used for the imprint of the capsules contains: Shellac, ethanol, anhydrous; isopropyl alcohol; butyl alcohol; propylene glycol; purified water; ammonia solution, concentrated; potassium hydroxide and black iron oxide (E172).
The capsules contain: Sucrose; hypromellose, talc; titanium dioxide (E171); methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30%; triethyl citrate and maize starch.
Compliance with Good Manufacturing Practice
The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type 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.

II.2 Drug Substance

The active substance is omeprazole, which is monographed in the Ph.Eur. The CEP procedure is used for the active substance. A copy of the Certificate of Suitability is presented in the documentation.

The applicant specification complies with Ph.Eur. monograph for omeprazole with additional tests for residual solvents and particle size. The specification is satisfactory. All necessary analysis methods and validations are provided. A suitable retest period has been set based on the submitted stability studies.

II.3 Medicinal Product

The product composition is adequately described. The development of the product has been satisfactorily performed and explained. Drug substance particle size is controlled to ensure a satisfactory dissolution profile. Compatibility with excipients has been demonstrated and is supported by the stability data. Excipients are otherwise common for manufacture of gastro-resistant pellets to be filled in a hard gelatin capsule. The packaging materials are standard and shown suitable by the presented stability studies.

The finished product specification is standard for the pharmaceutical form and includes relevant physicochemical, ID, assay and purity tests. Separate release and shelf-life specifications are provided, where the sole difference is a widening of the related substance limits in the shelf-life specification. Batch analysis data on a total of 21 batches (all strengths covered) prepared from different blends have been provided showing compliance with the release requirements and confirming consistency of product manufacture.

Stability data are provided for batches stored in the HDPE containers as proposed for marketing. A shelf-life of 3 years stored below 25°C is approved for the 10 mg and 20 mg strengths and 2 years stored below 25°C for the 40 mg strength.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of omeprazole are well known and on this basis, the applicant has not provided additional studies and none are required. An overview based on a literature review, as presented, is therefore appropriate and acceptable.

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 omeprazole 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.

IV. CLINICAL ASPECTS
IV.1 Introduction

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

For this generic application, the MAH has submitted 8 bioequivalence studies in which the pharmacokinetic profile of the test product Omeprazol “Copyfarm” is compared with the pharmacokinetic profile of the reference product Antra 10 mg, Astra (DE), Antra MUPS 20 mg, Astra (DE), and Antra 40 mg, Astra (DE) from AstraZeneca.

Clinical efficacy and safety
To support the application, the applicant has submitted the following studies:

<table>
<thead>
<tr>
<th>Type of study (Dose and food status)</th>
<th>Test - strength</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose, fasting</td>
<td>20 mg</td>
<td>MOPRAL 20 mg (Astra, Spain) capsules</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
<td>MOPRAL 20 mg (Astra, Spain) capsules</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
<td>Antra MUPS® 20 mg (Astra GmbH, Germany) Tablets</td>
</tr>
<tr>
<td>Repeated dose, 8 days, fasting</td>
<td>10 mg</td>
<td>ANTRA 10 mg (Astra GmbH, Germany) capsules</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
<td>MOPRAL 20 mg (Astra, Spain) capsules</td>
</tr>
<tr>
<td></td>
<td>20 mg</td>
<td>Antra MUPS® 20 mg (Astra GmbH, Germany) Tablets</td>
</tr>
<tr>
<td>Food effect</td>
<td>20 mg</td>
<td>MOPRAL 20 mg (Astra, Spain) capsules</td>
</tr>
<tr>
<td>Single dose, fed</td>
<td>20 mg</td>
<td>Antra MUPS® 20 mg (Astra GmbH, Germany) Tablets</td>
</tr>
</tbody>
</table>

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

The 10 mg and 40 mg strengths are dose proportional with the 20 mg strength. The pharmacokinetics of the active substance are linear in the oral dose range. The results of the bioequivalence study performed with the 20 mg strength therefore apply to the other strengths.

The RMS has been assured that the bioequivalence study has 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).

10 mg, steady state, fasting
The study was an open-label, randomized, replicate, two-treatment, two-sequence, two-period, crossover, multiple dose bioavailability study conducted under fasting conditions with a wash out period of 2 weeks between the administrations with the following design:

Prior to dose 1 of each period, subjects were housed from the night before and fasted for at least 10 hours. 10 mg was administered orally with 200 ml water and the subjects released 5 hours post drug administration. On the following 5 days, subjects returned, were administered their dose of 10 mg and were released immediately. For the 7th and 8th doses, subjects were housed to ensure fasting conditions. Subjects were only released after the 48 hour post dose blood draw. During housing periods, standard meals were provided 5, 11 and 14 hours post dosing.

Blood samples were collected pre-dosing and at -144, -120, -96, -72, -24, 0, 0.25, 0.5, 0.75, 1.00, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 5, 6, 8, 12 and 24.0 after the 7th drug administration. Samples were also collected at 0.25, 0.5, 0.75, 1.00, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 5, 6, 8, 12 and 24.0 after the 8th drug administration. For the 2nd, 3rd, 4th, 5th, 6th, 7th and 8th administrations, blood samples were collected within 5 minutes prior to drug administration.
Omeprazol "Copyfarm" 10 mg capsules has been compared to Antra 10 mg capsules, AstraZeneca, from the German market.

18(+4) healthy subjects (20 x Caucasian; 2 x Negroid; 11 male & 11 female; 18-47 years; 43.5-95.3 kg) participated in the study. All subjects completed the study.

Criteria for conclusion of bioequivalence:
The 90% confidence interval of the relative mean ratio was to be between 80-125% for AUCτ and between 70% and 143% for Cmax.

Results:
Pharmacokinetic parameters in steady-state (non-transformed values; arithmetic mean ± SD)
N=18

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC₀–τ ng/ml/h</th>
<th>Cmax ng/ml</th>
<th>Cmin ng/ml</th>
<th>PTF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>292.17 (182.72)</td>
<td>223.89 (127.88)</td>
<td>0.00 (0.00)</td>
<td>1967.46 (538.31)</td>
</tr>
<tr>
<td>Reference</td>
<td>281.74 (198.43)</td>
<td>199.72 (117.43)</td>
<td>0.00 (0.00)</td>
<td>1780.98 (472.11)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)

20 mg, steady state, fasting
Details as per study 10 mg, steady state, fasting with differences as follows:

The study was an open-label, randomized, replicate, two-treatment, two-sequence, two-period, crossover, multiple dose bioavailability study conducted under fasting conditions with a wash out period of 7 days between the administrations with the following design:

Prior to dose 1 of each period, subjects were housed from the night before and fasted for at least 10 hours. 20 mg was administered orally with 200 ml water and the subjects released 5 hours post drug administration. On the following 5 days, subjects returned, were administered their dose of 20 mg and were released immediately. For the 7th and 8th doses, subjects were housed to ensure fasting conditions. Subjects were only released after the 48 hour post dose blood draw. During housing periods, standard meals were provided 5, 11 and 14 hours post dosing.

Blood samples were collected pre-dosing of dose 1 (-144 hours), within 5 minutes of the 7th and 8th doses and at 0.5, 0.75, 1.00, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 5, 6, 8, 10 and 12 hours after the 7th and 8th doses.

Omeprazol “Copyfarm” 20 mg capsules has been compared to Antra MUPS 20 mg tablets, AstraZeneca, from the German market.

18(+4) healthy subjects (21 x Caucasian; 1 x Mongoloid; 11 male & 11 female; 20-45 years; 48.5-89.9 kg) participated in the study. 20 subjects completed the study. Drop-outs: 2 subjects (3 & 20) dropped out for personal reasons. Subject 3 was replaced by subject 21.

Criteria for conclusion of bioequivalence:
The 90% confidence interval of the relative mean ratio was to be between 85-125% for AUCτ, AUC∞ and between 70% and 143% for Cmax.

Results:
Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range
N=18
*ln-transformed values

40 mg, steady state, fasting
Details as per study 10 mg, steady state, fasting with differences as follows:

The study was an open-label, randomized, replicate, two-treatment, two-sequence, two-period, crossover, multiple dose bioavailability study conducted under fasting conditions with a wash out period of 14 days between the administrations with the following design:

Prior to dose 1 of each period, subjects were housed from the night before and fasted for at least 10 hours. 40 mg was administered orally with 200 ml water and the subjects released 5 hours post drug administration. On the following 5 days, subjects returned, were administered their dose of 40 mg and were released immediately. For the 7th and 8th doses, subjects were housed to ensure fasting conditions. Subjects were only released after the 24 hour post dose blood draw of the last dose. During housing periods, standard meals were provided 5, 11 and 14 hours post dosing.

Blood samples were collected pre-dosing and within 5 minutes of the 2nd, 3rd, 4th, 5th and 6th doses and 8th doses and at 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.25, 3.75, 4.0, 5.0, 6.0, 8.0, 12.0, and 24 hours after the 7th and 8th doses.

Omeprazol “Copyfarm” 40 mg capsules has been compared to Antra 40 mg capsules, AstraZeneca, from the German market.

18 (+4) healthy subjects (21 x Caucasian; 1 x Negroid; 10 male & 12 female; 21-50 years; 57.0-83.0 kg) participated in the study. 16 subjects completed the study. Drop-outs: Subjects 11, 12, 16, 19, 20 & 22 dropped out for personal reasons and/or difficulty with blood sampling. No subjects were replaced.

Criteria for conclusion of bioequivalence:
The 90% confidence interval of the relative mean ratio was to be between 85-125% for AUC\(_0-\infty\) and between 70% and 143% for C\(_\text{max}\).

Results:
Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t\(_\text{max}\) median, range N=16

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC(_0-\tau) (ng/ml/h)</th>
<th>AUC(_\infty) (ng/ml/h)</th>
<th>C(_\text{max}) (ng/ml)</th>
<th>C(_\text{min}) (ng/ml)</th>
<th>PTF%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>4036.28 (2246.78)</td>
<td>1680.47 (722.29)</td>
<td>0.31 (0.83)</td>
<td>1124.86 (323.07)</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>4180.54 (2604.74)</td>
<td>1593.35 (677.03)</td>
<td>0.14 (0.55)</td>
<td>1132.66 (464.61)</td>
<td></td>
</tr>
<tr>
<td>*Ratio (90%)</td>
<td>105</td>
<td>108</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

*In-transformed values
The study was a randomized, 4-period, 2 sequences, single dose, cross-over, replicate design conducted under fasting and fed conditions with a wash out period of 7 days between phases.

For all periods, subjects were housed for at least 10 hours prior to dosing up to 10 hours post dose. For periods 1 and 2, subjects were dosed with 1x20 mg capsule or tablet with 240 ml water. In the last two periods, subjects were fed a standardised high fat meal 30 minutes prior to dosing and then administered 1x20 mg capsule or tablet with 240ml water. Standard meals were provided 5 hours post dosing in each period.

In periods 1 & 2: Blood samples were collected pre-dosing and at 0.5, 0.75, 1.00, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, and 10 hours after drug administration.
In periods 3 & 4: Blood samples were collected pre-dosing and at 0.5, 1.00, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, and 10 hours after drug administration.

Omeprazol “Copyfarm” 20 mg capsules has been compared to Antra MUPS 20 mg tablets, AstraZeneca from the German market.

36(+4) healthy subjects (38 x Caucasian; 1 x Negroid; 1 x Mongoloid; 17 male & 23 female; 19-50 years; 44.1-103.0 kg) participated in the study. 37 subjects completed the study. Drop-outs: 3 subjects (19, 24 & 30) dropped out for personal reasons. Subject 07 was excluded from the statistical evaluation, because of problems with the plasma determination and was replaced.

Criteria for conclusion of bioequivalence:
The 90% confidence interval of the relative mean ratio was to be between 80-125% for AUCt and between 70% and 143% for Cmax.

Results:
Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) - FASTED
N=36

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC0-t ng/ml/h</th>
<th>AUC0-∞ ng/ml/h</th>
<th>Cmax ng/ml</th>
<th>tmax h</th>
<th>T1/2 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>943.92 (882.36)</td>
<td>1020.88 (959.50)</td>
<td>552.27 (351.11)</td>
<td>1.75 (0.75-6.00)</td>
<td>0.89 (0.39)</td>
</tr>
<tr>
<td>Reference</td>
<td>997.52 (828.12)</td>
<td>1045.97 (844.78)</td>
<td>621.54 (337.00)</td>
<td>1.50 (0.75-5.00)</td>
<td>0.87 (0.30)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>96 (90-102)</td>
<td>95 (89-102)</td>
<td>86 (77-96)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CV (%)</td>
<td>15.7%</td>
<td>16.3%</td>
<td>28.1%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*In-transformed values

Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, tmax median, range) - FED
N=36

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC0-t ng/ml/h</th>
<th>AUC0-∞ ng/ml/h</th>
<th>Cmax ng/ml</th>
<th>tmax h</th>
<th>T1/2 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>866.90 (802.86)</td>
<td>923.76 (833.01)</td>
<td>393.25 (266.13)</td>
<td>5.50 (2.00-10.00)</td>
<td>0.83 (0.33)</td>
</tr>
</tbody>
</table>
The study was a randomized, 2-period (4 phases), 2 sequences, single dose, cross-over, replicate design conducted under fed conditions with a wash out period of 7 days between phases.

For all periods, subjects were housed for at least 10 hours prior to dosing up to 10 hours post dose. Subjects were fed a standardised high fat meal 30 minutes prior to dosing and then administered 1x20mg capsule or tablet with 240 ml water. Standard meals were provided 5 hours post dosing in each period. Subjects were housed until 10 hours post drug administration.

Blood samples were collected pre-dosing and at 1, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8 and 10 hours after drug administration.

Omeprazol “Copyfarm” 20 mg capsules has been compared to MOPRAL 20 mg capsules, Astrazeneca , from the Spanish market.

24(+4) healthy subjects (26 x Caucasian; 2 x Negroid; 14 male & 14 female; 18-50 years; 49.5-99.3 kg) participated in the study. 21 subjects completed the study. Drop-outs: 7 subjects (1, 4, 5, 6, 14, 16 & 25) dropped out; nos. 4 and 5 for personal reasons after completing phases 4 and 3 respectively; nos. 1, 6, 14 and 25 were withdrawn due to positive urine samples for cocaine and alcohol and no. 16 prior to period 4 dosing due to low haemolysis possibly related to the study drug.

Criteria for conclusion of bioequivalence:
The 90% confidence interval of the relative mean ratio was to be between 80-125% for AUC, and between 70% and 143% for C_max.

Results:
Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_max median, range) - FED
N=23

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t} ng/ml/h</th>
<th>AUC_{0-∞} ng/ml/h</th>
<th>C_max ng/ml</th>
<th>t_max h</th>
<th>T_{1/2} h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>948.44 (944.18)</td>
<td>1233.00 (1241.54)</td>
<td>418.04 (329.15)</td>
<td>5.50 (4.00-7.50)</td>
<td>2.63 (9.82)</td>
</tr>
<tr>
<td>Reference</td>
<td>979.22 (937.74)</td>
<td>1100.07 (1135.53)</td>
<td>376.08 (288.86)</td>
<td>5.50 (2.50-7.50)</td>
<td>1.05 (0.62)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>96 (91-102)</td>
<td>95 (91-120)</td>
<td>111 (98-125)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CV (%)</td>
<td>16.26%</td>
<td>37.54%</td>
<td>33.38%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*In-transformed values
20 mg, single dose, fasting
The study was a randomized, 4-period, 2 sequences, single dose, cross-over, replicate design conducted under fasting conditions with a wash out period of minimum 6 days between administrations. The design was used AABB/BBAA as the classic AB/BA design was considered too imprecise to compare the study parameter with adequate power.

For all periods, subjects were fasted from solids for 24 hours prior to dosing until 4 hours post dosing. Subjects were dosed with 1x20 mg capsule with 125 ml water in each period. Standard meals were provided 5, 15 and 18 hours post dosing in each period.

Blood samples were collected pre-dosing and at 0.25, 0.5, 0.75, 1.00, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 and 24 hours after drug administration.

Omeprazol “Copyfarm” 20 mg capsules has been compared to MOPRAL 20 mg capsules, AstraZeneca, from the Spanish market.

18 healthy subjects (9 male & 9 female; 21-31 years; 52.1-78.8 kg) participated in the study. All subjects completed the study.

Criteria for conclusion of bioequivalence:
The 90% confidence interval of the relative mean ratio was to be between 80-125% for AUC and C_{max}.

Results:
Pharmacokinetic parameters (non-transformed values; geometric mean ± SD, t_{max} median, range)
N=18

<table>
<thead>
<tr>
<th>Treatment</th>
<th>AUC_{0-t}</th>
<th>AUC_{0-∞}</th>
<th>C_{max}</th>
<th>t_{max}</th>
<th>T_{1/2}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ng/ml/h</td>
<td>ng/ml/h</td>
<td>ng/ml</td>
<td>h</td>
<td>h</td>
</tr>
<tr>
<td>Test 1</td>
<td>625.1 (749.2)</td>
<td>648.5 (759.7)</td>
<td>362.2 (271.4)</td>
<td>- (0.50-4.00)</td>
<td>0.8 (0.3)</td>
</tr>
<tr>
<td>Test 2</td>
<td>665.3 (611.3)</td>
<td>694.1 (620.3)</td>
<td>329.2 (165.6)</td>
<td>- (0.50-4.00)</td>
<td>0.9 (0.4)</td>
</tr>
<tr>
<td>Reference 1</td>
<td>676.2 (729.1)</td>
<td>695.8 (737.7)</td>
<td>361.3 (195.7)</td>
<td>- (0.50-3.00)</td>
<td>0.8 (0.3)</td>
</tr>
<tr>
<td>Reference 2</td>
<td>611.0 (666.8)</td>
<td>633.9 (679.7)</td>
<td>332.7 (175.0)</td>
<td>- (0.50-3.00)</td>
<td>0.8 (0.3)</td>
</tr>
</tbody>
</table>

*Ratio (90% CI)
| 96 (87-106) |
| 105 (89-125) |

*ln-transformed values

20 mg, single dose and steady state, fasting
The study was a randomized, 2-period, 2 sequences, single dose, cross-over design conducted under fasting conditions with a wash out period of minimum 7 days between administrations. Subjects were fasted from solids from 12 am the previous day until 3 hours post dose on days 1 and 8 of the study. A dose of 1x20 mg capsule was administered with 125 ml water for 8 consecutive days in each period under fasting conditions. After the first dose, subjects were released 30 minutes after dose administration. Subjects were rehoused from the evening of day 7 until 24 hours after the last administered dose. Water was allowed ad libitum from 2 hours post dose. Standard meals were provided 6, 9 and 12 hours post dosing on days 1 and 8 in each period.

Day 1: Blood samples were collected pre-dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 12 hours after drug administration.
Days 2-7 inc: Samples collected pre-dose
Day 8: Samples collected pre-dosing and at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8 and 12 hours after drug administration. Day 9: 24 hour after the last dose.

Omeprazol “Copyfarm” 20 mg capsules has been compared to MOPRAL 20 mg capsules, AstraZeneca, from the Spanish market.

36 healthy subjects (19 male & 17 female; 18-34 years; 50-90.8 kg) participated in the study. 34 subjects completed the study. Drop-outs: Subject 13 dropped out for personal reasons on day 3 of period 1. Subject 22 was withdrawn due to positive drug testing for at day 0 and was not replaced.

Criteria for conclusion of bioequivalence:
The 90% confidence interval of the relative mean ratio was to be between 80-125% for $AUC_t$ and $C_{max}$.

Results:
Pharmacokinetic parameters (non-transformed values; geometric mean ± SD, $t_{max}$ median, range) – SINGLE DOSE, DAY 1
N=34

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-t}$ ng/ml/h</th>
<th>$AUC_{0-\infty}$ ng/ml/h</th>
<th>$C_{max}$ ng/ml</th>
<th>$t_{max}$ h</th>
<th>$T_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>608.6 (760.8)</td>
<td>-</td>
<td>325.0 (214.4)</td>
<td>-</td>
<td>0.83 (0.59)</td>
</tr>
<tr>
<td>Reference</td>
<td>568.9 (687.8)</td>
<td>-</td>
<td>318.4 (226.8)</td>
<td>-</td>
<td>0.77 (0.46)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>110 (100-120)</td>
<td>-</td>
<td>107 (94-122)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*In-transformed values

Pharmacokinetic parameters (non-transformed values; geometric mean ± SD, $t_{max}$ median, range) – STEADY STATE, DAY 8
N=34

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$AUC_{0-t}$ ng/ml/h</th>
<th>$AUC_{0-\infty}$ ng/ml/h</th>
<th>$C_{max}$ ng/ml</th>
<th>$t_{max}$ h</th>
<th>$T_{1/2}$ h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>991.0 (829.2)</td>
<td>-</td>
<td>580.5 (301.6)</td>
<td>-</td>
<td>0.90 (0.48)</td>
</tr>
<tr>
<td>Reference</td>
<td>899.3 (858.3)</td>
<td>-</td>
<td>526.6 (344.4)</td>
<td>-</td>
<td>0.96 (0.48)</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>114 (105-124)</td>
<td>-</td>
<td>117 (102-135)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*In-transformed values

Conclusion
The primary pharmacokinetic variables evaluated for single dose studies were $AUC_{0-t}$ and $C_{max}$ and for steady state, $AUC_t$ and $C_{max}$. Bioequivalence was determined based on limits of 80-125% for $AUC_t$ and 70-143% for $C_{max}$.

Based on the pharmacokinetic parameters of omeprazole, it can be concluded that Omeprazol “Copyfarm” and Losec/Antra tablets from AstraZeneca are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.
IV.2 Risk management plan & Pharmacovigilance system

Omeprazole was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of omeprazole 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.

The Pharmacovigilance system described fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the identification and notification of any a potential risks occurring either in the Community or in a third country.

V. PRODUCT INFORMATION

SmPC and Package leaflet
The content of the SmPC and package leaflet approved during the mutual recognition procedure is in accordance with that accepted for the reference product Losec marketed by AstraZeneca.

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 language used for the purpose of user testing the PIL was English. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Omeprazol “Copyfarm” 10 mg, 20 mg and 40 mg gastro-resistant capsules, hard has a proven chemical-pharmaceutical quality and is a generic form of Losec gastro-resistant tablets. Losec 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 SmPC, package leaflet and labelling are in the agreed templates and are in agreement with other omeprazole containing products.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Omeprazol “Copyfarm” with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 30 April 2009.
A European harmonised birth date has been allocated 1987-04-15. The next PSUR will be submitted with the DLP of 2012-04, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 29 November 2011.

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

1. A commitment to present batch analysis data on genotoxic impurities within a period of 6 months after the end of this MRP procedure is made.

2. The finished product manufacturer commits to perform the in use stability testing on one batch towards the end of the finally proposed shelf life.