CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Omeprazol (als magnesium) Sandoz MUT 10 mg, 20 mg and 40 mg, gastro-resistant tablets Sandoz B.V., the Netherlands

omeprazole (as magnesium)

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/1652/001-003/DC
Registration number in the Netherlands: RVG 105000-105002

2 November 2010

Pharmacotherapeutic group:	proton pump inhibitors
ATC code:	A02BC01
Route of administration:	oral
Therapeutic indication:	(prevention of relapse of) duodenal ulcers, gastric ulcers; Helicobacter pylori (H. pylori) eradication in peptic ulcer disease; (prevention of) NSAID-associated gastric and duodenal ulcers; reflux esophagitis; long-term management of healed reflux esophagitis; treatment of symptomatic gastro-esophageal reflux disease; treatment of Zollinger-Ellison syndrome. (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	3 September 2010
Concerned Member States:	Decentralised procedure with DE, IE, LU
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 Omeprazol (als magnesium) Sandoz MUT 10 mg, 20 mg and 40 mg, gastro-resistant tablets, from Sandoz B.V. The date of authorisation was on 3 September 2010 in the Netherlands.

The product is indicated for:

Adults
- Treatment of duodenal ulcers
- Prevention of relapse of duodenal ulcers
- Treatment of gastric ulcers
- Prevention of relapse of gastric ulcers
- In combination with appropriate antibiotics, Helicobacter pylori (H. pylori) eradication in peptic ulcer disease
- Treatment of NSAID-associated gastric and duodenal ulcers
- Prevention of NSAID-associated gastric and duodenal ulcers in patients at risk
- Treatment of reflux esophagitis
- Long-term management of patients with healed reflux esophagitis
- Treatment of symptomatic gastro-esophageal reflux disease
- Treatment of Zollinger-Ellison syndrome

Paediatric use
Children over 1 year of age and ≥ 10 kg
- Treatment of reflux esophagitis
- Symptomatic treatment of heartburn and acid regurgitation in gastro-esophageal reflux disease

Children and adolescents over 4 years of age
- In combination with antibiotics in treatment of duodenal ulcer caused by *H. pylori*.

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

Omeprazole, a racemic mixture of two enantiomers reduces gastric acid secretion through a highly targeted mechanism of action. It is a specific inhibitor of the acid pump in the parietal cell. It is rapidly acting and provides control through reversible inhibition of gastric acid secretion with once-daily dosing.
Omeprazole is a weak base and is concentrated and converted to the active form in the highly acidic environment of the intracellular canaliculi within the parietal cell, where it inhibits the enzyme H+ K+-ATPase - the acid pump. This effect on the final step of the gastric acid formation process is dose-dependent and provides for highly effective inhibition of both basal acid secretion and stimulated acid secretion, irrespective of stimulus.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Mopral gastro-resistant capsules, which have been registered in France by Astra Zeneca since 15 April 1987. In the Netherlands, the innovator products Losec 10, 20 and 40, gastro-resistant capsules (NL License RVG 16745, 12438 and 14905) have been registered since 9 November 1988 (20 mg), 14 June 1991 (40 mg) and 15 February 1994 (10 mg), respectively. In addition, reference is made to Mopral and Losec authorisations in the individual member states.

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 1 single dose pilot study under fasting conditions, 1 single and multiple dose study under fasting conditions, and 1 single dose study under fed conditions, in which the pharmacokinetic profile of the 40 mg product is compared with the pharmacokinetic profile of the reference product Losec MUPS 40 mg film-coated tablets, registered in the UK. 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 its reference product.

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, as this is not required for a generic application.

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 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.

Active substance
The active substance is omeprazole magnesium, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a very fine hygroscopic powder, which is soluble in dymethylformamide and sparingly soluble in methanol. The drug substance is hygroscopic. Omeprazole magnesium is a racemate. It exists in equal amounts of both the S and R enantiomers. According to literature polymorphism is unknown.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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
In the manufacturing processes from both sources the starting material is (racemic) omeprazole, and this is included in reaction steps to result in omeprazole magnesium as a racemate. In the processes of both sources for the starting material omeprazole of Ph. Eur. quality, reflected by a CEP, is used. The manufacturing steps and applied in-process controls are well described. There are no isolated intermediates in both processes.

Quality control of drug substance
One manufacturer applies the current Ph. Eur. specifications for omeprazole magnesium. For the in-house test method on impurities, cross-validation data with the Ph. Eur. monograph’s method have been provided for demonstrating that the used method is equivalent with the corresponding monograph’s methods.
Specifications applied for omeprazole magnesium from the other DMF-holder fully comply with the Ph. Eur. monograph. For drug substance from both sources batch analysis results have been provided meeting the set (Ph.Eur.) specifications.

Stability of drug substance
One manufacturer provided long term stability data on 3 batches stored for 4 years at 25°C/60% RH. However, for internal harmonisation reasons for storage of prazole drug substances the DMF holder applies the more restrictive condition of 2-8°C, for which 3-year data are available. This lower storage temperature for the drug substance is accepted. The claimed re-test period is 3 years if stored in the proposed packaging at 2-8°C. For the drug substance from the other supplier, an appropriate re-test period of 3 years not above 25°C was granted.

** 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
Omeprazol (als magnesium) Sandoz MUT 10 mg is a light pink, oval film-coated tablet.

Omeprazol (als magnesium) Sandoz MUT 20 mg is a pink, oval film-coated tablet with a breaking notch on both sides. The tablet can be divided into equal halves.

Omeprazol (als magnesium) Sandoz MUT 40 mg is a reddish, oval film-coated tablet with a score line on both sides. The tablet can be divided into equal halves.

The gastro-resistant tablets are packed in Aluminium/aluminium blisters and Aclar/aluminium blisters.

The excipients are:
Tablet core – sucrose, maize starch, glucose, copovidone, povidone, talc, titanium dioxide (E 171), methacrylic acid-ethyl acrylate copolymer (1:1), glycerol monostearate, propylene glycol, stearic acid, polysorbate 80, simeticone, microcrystalline cellulose, macrogol 6000, crospovidone, colloidal anhydrous silica, magnesium stearate.
Tablet coating – hypromellose, macrogol 6000, titanium dioxide (E 171), talc, red iron oxide (E 172). Only 10 mg and 40 mg: yellow iron oxide (E 172).

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The gastro-resistant film-coated tablets should disintegrate rapidly into individual pellets in water or gastro-intestinal fluids. These pellets are resistant to the acidic conditions and this prevents the release of the active substance in the stomach. Bioequivalence studies have been performed with the UK reference product Losec MUPS 40 mg, marketed in the UK. The used UK reference product is essentially similar with the proposed product and has an identical composition to the NL originator product, and herewith the reference product is acceptable. Comparative dissolution profiles have been provided.
The 20 mg tablet can de discerned from the 40 mg tablet by colour (“pink” versus “reddish”), and by dimensions. The combinations are considered to be sufficiently reliable for allowing discrimination between the three tablet forms. The 20 mg and 40 mg tablets can be divided into equal halves, which has been demonstrated in breakability studies. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The product is manufactured in a five-step process. The drug-coated pellets are manufactured, an intermediate layer is applied, the insulated pellets are coated with an enteric coating suspension, compressed into pallets, and finally the tablet cores are film coated.
Validation data for 3 batches have been provided. The validation includes relevant variations of manufacturing parameters, and extensive content uniformity determinations (including uniformity of dosage units tests according to Ph. Eur.) have been performed.

Considering that the manufacturing process is not a standard manufacturing process (enteric-coated pellets embedded in an external phase) the validated maximum batch sizes are considered as the batch sizes to be registered. Process evaluations have been performed for the three pellet stages before the final blend. Uniform distribution of the active substance during tabletting and acid resistance were demonstrated. The final tabletting process has been adequately validated.

Control of excipients
All excipients except the ferric oxides are in accordance with the requirements of the corresponding Ph. Eur. monograph. For ferric oxide specifications from Directive 95/45/EC are listed. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for descriptions and dimensions; identification of the drug substance, identification of the colourants, gastro-resistance, dissolution, assay, uniformity of drug dosage units, related substances, and microbiological purity. The MAH is asked to perform a more thorough investigation for developing a method identifying the magnesium salt of the drug substance in the drug product, as a post-approval follow-up measure. Batch analysis data have been provided on all strengths. Results are available for 8 batches, demonstrating compliance with the specifications.

Stability of drug product
Three 10 mg and eight 20 mg batches have been put on stability for up to 12 months. Stability data up to 18 months were provided on 40 mg batches. Several out of specifications for assay were noted in the 10 and 20 mg tablets. These were seen in all container closure systems, *i.e.* Alu/Alu blister, the Aclar/Alu blister and the bulk tablets. The increase in assay could not be explained by the analytical method or sample preparation. It was noted that in case the assay went out of specification, assay was already very high at the initial time point. No specific trend was noted in the assay. Based on the provided data, the proposed shelf-life of 18 months could be granted for the 10 and 20 mg gastro-resistant tablets. The product in Aclar/Aluminium blister should be stored below 30°C. For the 40 mg product, a shelf life of 2 years was granted and no specific storage condition is required.

Several commitments have been made with regard to the drug product, which can be found on page 10 of this report.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Magnesium stearate, stearic acid and glycerol monostearate are of vegetable source. Also for all other excipients statements confirm that no excipients are of animal or human origin, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Losec gastro-resistant capsules, 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 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.

II.3 Clinical aspects

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

For this generic application, the MAH has submitted 1 single dose pilot study under fasting conditions, 1 single dose study under fed conditions, and 1 single and multiple dose study under fasting conditions in which the pharmacokinetic profile of the test product Omeprazol (als magnesium) Sandoz MUT 40 mg, gastro-resistant tablets (Sandoz B.V., NL) is compared with the pharmacokinetic profile of the reference product Losec MUPS 40 mg gastro-resistant tablets (Astra Zeneca, UK).

The choice of the reference product
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.

Single-dose pilot study, fasted conditions
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 16 healthy male subjects, aged 20-44 years. Each subject received a single dose (40 mg) of one of the 2 omeprazole formulations. The tablet was orally administered with 240 ml water after and overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.5, 5, 6, 8, 10 and 12 hours after administration of the products.

Analytical/statistical methods
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
All subjects completed the study entirely, and were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of omeprazole under fasted conditions.

Treatment N=16	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2088 ± 2252	2275 ± 2438	844 ± 509	2.44 ± 1.52	1.07 ± 0.56
Reference	1960 ± 1916	2010 ± 2040	961 ± 539	2.23 ± 1.02	0.94 ± 0.51
***Ratio (90% CI)**	0.97 (0.85-1.12)	1.02 (0.90-1.15)	0.79 (0.59-1.05)	--	--
CV (%)	22.8	19.1	49.3	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. The 90% confidence intervals for

C_{max} are, however, not within the acceptance range, and therefore bioequivalence has not been demonstrated.

Single-dose study, fed conditions

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fed conditions in 140 healthy subjects (87 males/53 females), aged 18-55 years. Each subject received a single dose (40 mg) of one of the 2 omeprazole formulations. The tablets were orally administered with 240 ml water, 30 min after receiving a high fat breakfast. The meal consisted of 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash brown potatoes, and 240 ml of whole milk. Subjects fasted for at least 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 14 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10, 10.5, 11, 11.5, 12, 13.5, 14, 15, 16, 18, and 24 hours after administration of the products.

Analytical/statistical methods

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

Seven subjects were withdrawn/discontinued. Six subjects withdrew or did not return for Period II check in, and 1 subject was withdrawn due to out of range viral signs prior to dosing in Period II. One subject experienced emesis 10.3 hours post-dose in Period 1 and was not withdrawn from the study. Therefore, the subject was dosed in Period 2 in error. The protocol stated that if such a volunteer nevertheless completes the study in error, results of statistical analyses were to be presented with and without this subject. However, the bioequivalence assessment should be based on the results calculated without the data of excluded subjects. Based on the above reasons the data for this subject was excluded from the main statistical analyses and bioequivalence assessment. However, additional pharmacokinetic and statistical analysis was performed including this subject data and was reported.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of omeprazole under fed conditions.

Treatment N=132	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	1251 ± 1425	1282 ± 1460	320 ± 249	6.60 ± 1.83	1.05 ± 0.72
Reference	1158 ± 1350	1183 ± 1364	366 ± 291	5.02 ± 1.92	0.94 ± 0.49
***Ratio (90% CI)**	1.13 (1.07-1.20)	--	0.90 (0.83-0.98)	--	--
CV (%)	30.5	--	41.4	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80-1.25. Based on the pharmacokinetic parameters of omeprazole under fed conditions, it can be concluded that Omeprazol (als magnesium)

Sandoz MUT 40 mg and the Losec MUPS 40 mg gastro-resistant tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Single/multiple-dose pivotal study, fasted conditions

Design

A single- and multiple-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 100 healthy subjects (86 males/14 females), aged 19-55 years. Each subject received a single dose (40 mg) of one of the 2 omeprazole formulations once daily for 7 days after an overnight fast. The tablets were orally administered with 240 ml water. For each subject there were 2 dosing periods, separated by a washout period of 8 days.
Blood samples were taken at day 1 at pre-dose and at 0.333, 0.667, 1, 1.33, 1. 67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products. At day 5, 6 and 7 at pre-dose and furthermore at day 7 at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.33, 3.67, 4, 4.33, 4.67, 5, 5.5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

Analytical/statistical methods

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

Ten subjects were withdrawn/discontinued. Eight subjects withdrew or did not return for check in, 1 subject was withdrawn because of vomiting and 1 subject because of drug abuse. A total of 92 subjects could be included in the analysis of the single dose part of the study and 90 subjects in the multiple dose part.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of omeprazole after single dose under fasted conditions.

Treatment N=92	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	2198 ± 1821	2213 ± 1829	990 ± 536	2.06 ± 0.85	1.11 ± 0.52
Reference	2105 ± 1608	2118 ± 1615	1056 ± 542	1.98 ± 0.85	1.02 ± 0.41
***Ratio (90% CI)**	1.02 (0.98-1.06)	--	0.91 (0.85-0.97)	--	--
CV (%)	15.9	--	27.0	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of omeprazole after multiple dose under fasted conditions.

Treatment N=90	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	4148 ± 2059	--	1469 ± 596	1.98 ± 0.89	--

Reference	4212 ± 2076	--	1688 ± 566	1.83 ± 0.88	--
***Ratio (90% CI)**	0.97 (0.94-1.01)	--	0.84 (0.78-0.89)	--	--
CV (%)	13.8	--	25.8	--	--

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration
$t_{1/2}$ half-life

**ln-transformed values*

Based on the pharmacokinetic parameters of omeprazole obtained after single dosing under fasting conditions, the reference and test are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_{0-t} and C_{max} were inside the normal range of acceptability (0.80-1.25).
After multiple dosing bioequivalence could only be proven for AUC. C_{max} was outside the normal acceptance range of 0.80-1.25. The MAH concluded that bioequivalence is proven based upon preset 90% CI limits of 0.75 – 1.33.
In response to objections from the member states, the MAH provided the following additional justification:

- For omeprazole there is a poor correlation between C_{max} and the degree of acid suppression in studies of omeprazole, while for AUC a correlation is observed.
- The clinical effect of omeprazole is directly correlated with the bioavailability of the drug measured as the AUC and not with the plasma concentration of the drug at any given time. As indicated the clinical efficacy of omeprazole will last much longer than expected from the current plasma concentrations.
- A linear dose-effect relationship has been demonstrated, in which gastric acid secretion decreased in a dose proportional manner and in which the duration of the effect was much longer than the omeprazole concentrations (Lind et al, Gut 24, 270-276, 1983).
- As shown by Farmovs, two formulations with a difference in C_{max} but similar AUC resulted not in a difference in intragastric pH over 24 h postdose, after single dose or multiple dose.

Widening of the C_{max} interval is herewith considered acceptable, as it is prespecified in the protocol, and sufficiently scientifically justified. Omeprazol (als magnesium) Sandoz MUT 40 mg and the Losec MUPS 40 mg gastro-resistant tablets are therefore considered bioequivalent.

From the literature it is known that food interacts with the absorption of omeprazole, but this does not influence clinical efficacy. Therefore, omeprazole may be taken without reference to food intake. The bioequivalence study under both fasting and fed conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Extrapolation to 10 mg and 20 mg tablet
The 10 and 20 mg tablets, in which enteric coated pellets are compressed, are dose-proportional with the 40 mg gastro-resistant tablet used in the bioequivalence studies. The tablets have been manufactured by the same manufacturing process. In addition, omeprazole shows linear pharmacokinetics. The results of the bioequivalence study performed with the 40 mg tablets therefore apply to the 10 mg and 20 mg products as well.

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
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 post authorisation 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
In an article 30 referral (EMA/H/A-30/1001), two harmonised SPCs and package leaflets were decided on, for the prescription only and OTC status. The MAH committed to conform the SPC and PIL to the harmonised texts as soon as the referral is finalized and the final product information is published on the EMA website. The commission has adopted the decision of the article 30 referral on 10 June 2010 and the MAH adapted the SPC to the one for Losec that has been adopted at commission level.

Readability test
The package leaflet has not been evaluated via a user consultation study. Instead, the MAH submitted a bridging study to justify reference to the readability test approved during DCPs UK/H/1023-1025 and DK/H/1457-1459 (Esmoprazol). Assessment was however not considered necessary, as the MAH committed to conform the SPC and PIL to the harmonised texts approved in the article 30 referral procedure. As the referral texts are harmonized there is no need for a complete user test. The MAH provided an overview of format, layout and design of the Omeprazol Sandoz leaflet. This was considered acceptable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Omeprazol (als magnesium) Sandoz MUT 10 mg, 20 mg and 40 mg, gastro-resistant tablets have a proven chemical-pharmaceutical quality and are generic forms of Losec gastro-resistant capsules. 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. Although the 90% CI for C_{max} after multiple dosing fell outside the normal acceptance range of 0.80-1.25, the product may be considered bioequivalent to the reference product. Widening of the acceptance range for C_{max} was predefined in the protocol. Moreover, the MAH sufficiently justified the widened CI from a scientific point of view.

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

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other omeprazole containing products.

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 Omeprazol (als magnesium) Sandoz MUT 10 mg, 20 mg and 40 mg, gastro-resistant tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 10 June 2010. Omeprazol (als magnesium) Sandoz MUT 10 mg, 20 mg and 40 mg, gastro-resistant tablets were authorised in the Netherlands on 3 September 2010. The prescription status is prescription only.

A European harmonised birth date has been allocated (15 April 1987) and subsequently the first data lock point for omeprazole is April 2012. The first PSUR will cover the period from May 2009 to April 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 22 January 2013.

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

<u>Quality - medicinal product</u>

- The MAH committed to validate the production of the pellets (the first three manufacturing steps) with at least two additional production scaled batches. At least uniform distribution of the active substance and gastro-resistance of the final pellets should be tested.
- The MAH committed to submit a variation based on appropriate validation data for higher batch scale than the validated maximum batch sizes.
- The MAH committed to develop a method identifying the magnesium salt of the drug substance in the drug product.
- The MAH committed to re-evaluate the proposed limit when further release and stability results are available and suitable to tighten the limit for total impurities again.
- The MAH committed to bring the SPC, PIL and labelling of the above procedures in accordance with the Final texts published by the Commission in case there is any difference in content. This should occur through a variation procedure.

List of abbreviations

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

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached