CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Itomed10/20/40 mg gastro resistant capsules Chemo Iberica S.A., Barcelona, Spain

omeprazole

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/0974/001-003/MR
Registration numbers in the Netherlands: RVG 32670,32614,32671

5 August 2009

Pharmacotherapeutic group:	proton pump inhibitors
ATC code:	A02BC01
Route of administration:	oral
Therapeutic indication:	Duodenal ulcers, Benign gastric ulcers, Reflux oesophagitis, Maintenance treatment of reflux oesophagitis to prevent relapse, Zollinger-Ellison syndrome, NSAID (Non Steroid Anti Inflammatory Drug) related gastric and duodenal ulcers, Maintenance treatment of NSAID related gastric and duodenal ulcers to prevent relapse, Symptomatic treatment of gastro-oesophageal reflux disease in combination with appropriated antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* in patients with *Helicobacter pylori* associated with peptic ulcers.
Prescription status:	prescription only
Date of authorisation in NL:	21 August 2006
Concerned Member States	Mutual recognition procedure with DE, DK, EL, ES, FI, HU, LT, NO, PL, SE, SI, SK (all strenghts), CZ, IT (only 20 mg), PT (only 20 and 40 mg).
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) (20 mg) and 10(3) (10 and 40 mg)

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 Itomed 10/20/40 mg gastro resistant capsules, from Chemo Iberica S.A, Spain. The first date of authorisation was on 21 August 2006 in the Netherlands.

The product is indicated for the treatment of:

- 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 and duodenal ulcers
- Maintenance treatment of NSAID related gastric and duodenal ulcers to prevent relapse
- Symptomatic treatment of gastro-oesophageal reflux disease
- In combination with appropriate antibacterial therapeutic regimens for the eradication of *Helicobacter pylori* in patients with *Helicobacter pylori* associated peptic ulcers.

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

Omeprazole, a substituted benzimidazole, is a gastric proton pump inhibitor, i.e. omeprazole directly and dose-dependently inhibits the enzyme H^+,K^+-ATPase, which is responsible for the gastric acid secretion in the gastric parietal cells. Due to this selective intracellular mode of action and the low affinity for other membrane-bound receptors (such as the histamine H_2, muscarine M_1 or gastrinergic receptors), omeprazole has been assigned to a separate class of acid-inhibiting agents, which block the final step of acid production. As a consequence of its mode of action, omeprazole leads to an inhibition of both basal and stimulable acid secretion, irrespective of the stimulus type. Thus, omeprazole increases the pH-value and reduces the volume of gastric acid secretion.

Legal basis
The marketing authorisation is granted based on article 10(1) (generic application) (for the 20 mg strength) of Directive 2001/83/EC and 10(3) hybrid application (for the 10 and 40 mg strengths). Since bioequivalence is shown for the 20 mg strength capsules with the 20 mg innovator product, the application for the 20 mg strength is based on article 10(1) generic application. For the 20 and 40 mg strength the application is based on article 10(3) (hybrid application) since for these product bioequivalence is based on dose-proportionality with, and extrapolation of the results achieved with the 20 mg strength.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Mopral 20 mg capsules which has been registered in France by Astrazeneca since 1988 (original product). In addition, reference is made to Losec and Mopral authorisations in the individual member states (reference product).

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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of Spanish and French reference product, Mopral 20 mg capsules. 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. This generic product 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.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

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

Active substance
The active substance is omeprazole. Omeprazole is well known and described in de Ph.Eur*. It is a white to almost white powder. It is slightly soluble in water, soluble in methylene chloride and sparingly soluble in ethanol. It shows polymorphism. Omeprazole is a mixture of two enantiomers.

Manufacture
The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitablity concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia. The MAH justifies the particle size/density parameters.

Specification
The drug substance complies with the specifications as stated in the Ph.Eur., on the CEP and in the USP. These are therefore sufficiently justified.

Stability
The packaging material and the re-test period (3 years) if stored between 2ºC and 8ºC are as described by the CEP.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Medicinal Product

Composition
The drug product is formulated as a hard gelatin capsule containing twice coated pellets: the outer coating is a gastro resistant layer; the inner coating contains the active substance. The capsules will be marketed in three strengths: 10, 20 and 40 mg Itomed. The capsules differ in color or in size or in both.

The capsules are packed in Alu-Alu blister packaging and, alternatively, in HDPE containers with plastic caps containing a silica gel desiccant. These types of packaging are considered to be appropriate for the product; omeprazole.

The excipients are:

Capsule core: sugar spheres (consisting of corn starch and sucrose), sodium laurilsulfate, anhydrous, isodium phosphate, mannitol, hypromellose, macrogol 6000, talc, polysorbate 80, titanium dioxide, methacrylic acid-ethyl acrylate copolymer (1:1) dispersion 30 per cent.

Capsule shell:
10 and 20mg capsules: gelatin, quinoline yellow, titanium dioxide.
40mg capsules: gelatin, indigo carmine, titanium dioxide.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The development of the product has been extensively described, including a physio-chemical study of each chosen component as well as their compatibility, study of loading and coating suspensions and treatment of the parameters and processing conditions relevant for the process. The MAH has sufficiently justified the batch used in the bioequivalence study.

The contents of the 3 tablet formulations, 10, 20 and 40 mg, are dose proportional. The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs.

Manufacturing process
Sugar spheres are coated with an omeprazole suspension, which in turn are coated by a gastro-resistant layer. These pellets are filled into hard gelatin capsules. The process has been adequately described. Adequate validation data has been provided.

Product specification
The drug product specification includes tests on appearance, content uniformity, uniformity of mass, identification, water content, disintegration time, assay, gastro resistance, dissolution rate, related substances, appearance of the pellets and microbiological purity.
The methods used have been adequately described and validated.
Batch analysis data have been provided for all pellet production lines and all three capsule strengths. Compliance with release specifications is demonstrated.

Stability tests on the finished product
Stability data have been obtained during storage at 25ºC/60%RH, 30º/65%RH and 40ºC/75%RH. The capsules were packed in Alu-Alu blisters or in HDPE-bottles. Stability data have been included for pilot batches as well as up-scaled batches. A slow increase of water content and an increase in some impurities are observed in all batches tested.
In view of the results the proposed shelf life (3 years) and storage conditions (store below 25ºC) are acceptable for both packaging materials. In addition, the labelled storage condition for the Aluminium/Aluminium blister pack is: *"Store in the original ……* and for the HDPE bottle: *"Keep the bottle tightly closed ..."*

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
For all excipients there are statements by suppliers that no TSE or other transmissible agents can be present in their products. The empty capsules are made of gelatin. The risk of TSE is covered by CEP's for each of the four sources of gelatin used by the manufacturer of the empty capsules.

II.2 Non clinical aspects

This product is a generic formulation of Losec 20 mg capsules, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone pre-clinical 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 3 bioequivalence studies in which the pharmacokinetic profile of the test Itomed 20 mg capsules is compared with the pharmacokinetic profile of the reference product Mopral® 20 mg capsules, under fasting and fed conditions.

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 MAH has provided dissolution profiles comparing the 10 and 40 mg presentation to the 20 mg presentation. The dissolution profiles for all three strengths were similar. Moreover, omeprazole pharmacokinetics is considered linear up to a dose of 40 mg.

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

Bioequivalence study 1 (single and multiple-dose, fasted conditions)

Test: Itomed 20 mg gastro resistant capsule (Chemo Iberica S.A., Spain)
Reference: Mopral 20 mg capsule (Astra Espana, Spain)

The Spanish Mopral reference capsule is identical to the Dutch innovator capsule Losec.

A randomized, single and multiple-dose, 3-way crossover, comparative bioequivalence study was carried out under fasted conditions in 36 healthy male volunteers, aged 18-45 years. Each subject received a daily dose (20 mg) of one of the 2 omeprazole formulations for a period of 5 days. The capsule was orally administered with 240 ml water. At day 1 and 5, capsules were taken after a 10 h fasting period. For each subject there were 3 dosing periods, separated by a washout period of 7 days.

In a third arm an Losec formulation from a third country was investigated. As the results obtained for this Losec formulation obtained from a non-European country is not relevant for this EU application, these results are not listed.

Blood samples were taken at day 1 and 5, predose and at 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 hours after administration of the products. All 36 subjects were eligible for pharmacokinetic analysis. The method for analyzing plasma samples was validated and a validation report was provided for all three bioequivalence studies. Also the statistical analysis is acceptable.

Table 1. Pharmacokinetic parameters day 1 (non-transformed values; arithmetic mean ± SD, t_{max}(median, range)) of omeprazole under fasted conditions.

Treatment n=36	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	545 ± 441	559 ± 453	327 ± 183	2.0 ± 1.1	0.8 ± 0.3
Reference	527 ± 439	540 ± 451	278 ± 131	2.3 ± 1.3	0.8 ± 0.3
***Ratio (90% CI)**	1.02 (0.95-1.09)	1.02 (0.95-1.09)	1.12 (1.01-1.25)	---	---
CV (%)	17.5 %	17.0%	26.9%	---	---

$AUC_{0-\infty}$	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 2. Pharmacokinetic parameters day 5 (non-transformed values; arithmetic mean ± SD, t_{max}(median, range)) of omeprazole under fasted conditions.

Treatment n=36	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	937 ± 799	967 ± 853	479 ± 260	2.3 ± 1.3	1.0 ± 0.6
Reference	974 ± 786	997 ± 816	486 ± 243	1.5 ± 1.6	0.9 ± 0.5
***Ratio (90% CI)**	0.96 (0.90-1.02)	0.96 (0.90-1.02)	0.96 (0.86-1.07)	---	---
CV (%)	15.1%	15.0%	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

Bioequivalence study 2 (single dose, fed conditions)

Test: Itomed 20 mg (Chemo Iberica S.A., Spain)
Reference: Mopral 20 mg (Astra, France)

The French Mopral reference capsule is identical to the Dutch innovator capsule Losec.

A two–period, two-sequence, cross-over, controlled, block randomized, single dose bioequivalence study was carried out in 36 healthy volunteers (15 males, 21 females), aged 21 to 41 years. Each subject received a single dose (20 mg) of one of the 2 omeprazole formulations. The capsule was orally administered with 200 ml water after the consumption of a breakfast consisting of 2 croissants, 1 cereal bar, 20 g of butter, 200 ml orange juice, and 200 ml whole milk, with a total amount of 660 calories. There were 2 dosing periods, separated by a washout period of 1 week.

Blood samples were taken predose and at 1, 2, 2.5, 3, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.25, 6.5, 7, 7.5, 8, 10, and 12 hours after administration of the products. All 36 subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max}(median, range)) of omeprazol under fed conditions.

Treatment n=36	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	654 ± 769	681 ± 863	318 ± 200	3.75 (1.0–6.25)	0.8 ± 0.5
Reference	665 ± 762	687 ± 841	300 ± 197	3.0 (1.0 -6.5)	0.8 ± 0.5
***Ratio (90% CI)**	0.92 (0.83-1.01)	0.92 (0.83-1.01)	1.04 (0.88-1.22)	---	---
CV (%)	24.4%	24.0%	42.3%	---	---

$AUC_{0-\infty}$ 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

Bioequivalence study 3 (single dose, fed conditions, high fat)

Test: Itomed 20 mg (Chemo Iberica S.A., Barcelona, Spain)
Reference: Mopral 20 mg (Astra Espana, Spain)

The Spanish Mopral reference capsule is identical to the Dutch innovator capsule Losec.

A randomized, 2-way crossover bioequivalence study was carried out under fed conditions in 36 healthy volunteers (33 males, 3 females), aged 18 to 45 years. By protocol, the samples of the first 30 volunteers who completed the study were intended to be analyzed. Each subject received a single dose (20 mg) of one of the 2 omeprazole formulations. The capsule was orally administered with 180 ml water after the consumption of a high-fat breakfast consisting of buttered English muffin, one fried egg, 2 strips of bacon, one slice of American cheese, hash brown potatoes, 240 ml whole milk, and 180 ml orange juice (approximately 800 to 1000 calories). There were 2 dosing periods, separated by a washout period of 1 week.
Blood samples were taken predose and at 1, 2, 2.5, 3, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.25, 5.5, 5.75, 6, 6.25, 6.5, 7.5, 8, 10, and 12 hours after administration of the products.

One volunteer was excluded from analysis due to unallowed investigational drug administration within 28 days prior to omeprazole administration. Therefore, the volunteer was by protocol replaced by nr 31 (28 males, 2 females).

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max}(median, range)) of omeprazole under fed conditions (high-fat breakfast).

Treatment n=36	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	471 ± 577	517 ± 681	227 ± 137	4.9 (3.0-8.0)	1.0 ± 0.7
Reference	550 ± 771	575 ± 743	273 ± 187	4.5 (2.0-5.0)	1.4 ± 1.4
***Ratio (90% CI)**	0.90 (0.81-0.98)	0.91 (0.83-1.00)	0.83 (0.70-0.99)	---	---
CV (%)	22.1%	21.6%	40.1%	---	---

$AUC_{0-\infty}$ 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*

Discussion clinical aspects
Based on the pharmacokinetic parameters of omperazole under fasting conditions in Study 1 the reference product Mopral 20 mg capsules, Astra Zeneca, and the test product are considered bioequivalent with respect to the extent and rate of absorption. The 90% confidence intervals calculated for AUC_{inf}, 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.

Also under fed conditions in Study 2 (36 volunteers), the reference capsule (Mopral 20 mg, Astra, France) and test capsule were demonstrated to be bioequivalent with respect to the extent and rate of absorption, with 90% CI for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} within the 0.80-1.25 acceptance range.
However, results from the food-effect Study 3, using 30 volunteers, only demonstrated that the test capsule and the Spanish reference capsule are bioequivalent with respect to the extent of absorption under fed conditions, but not with respect to the rate of absorption, with 90% CI for the C_{max} 0.70-0.99. The reason for the different outcome of these two studies is not readily available, although the higher power of Study 2 may contribute to this difference. The RMS considered bioequivalence under fed conditions proven via Study 2.

However, during the procedure a potential serious risk to public health was raised with regard to the demonstration of bioequivalence with the formulation that is on the national market. A request for

referral to the CMD(h) was submitted: *Bioequivalence is demonstrated against the reference product (Losec gastro-resistant capsules) and not against Losec MUPS enterotablets. Losec gastro-resistant capsules is no longer registered in the member state referring these applications.*

In the CMD-meeting of 19 June 2007, the RMS presented its view and the MAH's written responses were discussed. Many innovator products have different pharmaceutical forms on the market in a single Member State. Generic companies are not required to develop generic presentations from all pharmaceutical forms of the innovator. They have the freedom to choose a reference medicinal product and are required to demonstrate bioequivalence with that reference medicinal product only. Following the discussion in the CMD all involved member states could agree that a bioequivalence study comparing the test product vs. Losec MUPS enterotablets is not required, since bioequivalence only has to be demonstrated against the reference product. However, the MAH committed to submit additional dissolution profiles (i.e. including all strengths) of the test product and Losec MUPS enterotablets.

The two additional dissolution studies that are to be submitted concern;
1. Losec 10 mg MUPS marketed in Finland versus Itomed 10 mg capsules and
2. Losec 40 mg MUPS marketed in the Netherlands versus Itomed 40 mg capsules.
   The Dutch board will provide the Dutch reference product composition to the Finnish authorities and the Finnish authorities will compare these data with the composition of the Finnish Losec 40 mg MUPS.
3. The similarity factors will be submitted.

The MAH has committed to submit these studies after agreement of this proposal, and within 2 months after the Finnish authorities have compared the composition of the Losec 40 mg MUPS (AstraZeneca) and the Losec 40 mg MUPS (AstraZeneca) from the Dutch market.

Additionally, the MAH has committed to compare the Finnish reference products (Losec MUPS) and the reference products used in the bioequivalence study (Losec capsules from Spain and France, both Astrazenica). If the reference batches are not available to the MAH anymore, the certificates of analysis of these batches will be compared with the batch results of the Finnish reference product.

The 10 mg and 40 mg capsules are dose-proportional with the 20 mg capsule. Therefore, no bioequivalence studies are needed for these strengths, as the results obtained for the 20 mg capsule can be extrapolated to the 10 mg and 40 mg capsule. Omeprazole pharmacokinetics is considered linear up to a dose of 40 mg.

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 postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The applicant has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for other generic applications e.g. NL/H/0519-0521/001-003/MR.

Readability test
A readability test was performed in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC.
The qualitative method was used. Fourteen educated subjects (7 females, 7 males; age 25-60 years) were interviewed by means of an in depth interview (face-to-face, 30 min.). Age distribution: 25-30 years, 3 subjects; 30-35 years, 4 subjects; 35-40 years, 4 subjects and 40-45 years, 3 subjects. All subjects had experience with the illness.

As the outcome of the readability test suggested minor changes to the PIL, i.e. alphabetic order of subsection “taking other medicines”, a second readability was not conducted as only minor changes were applied. It was suggested by the respondents to include a table with indications and dosage in order to easily get an overview and quickly find the right doses in section “How to take Itomed 10/20/40 mg capsules”.
It was also suggested by the respondents that in section 2 “Before you take Itomed 10/20/40 mg capsules; subsection “important information about some of the ingredients of Itomed 10/20/40 mg capsules”, should be placed directly under subsection “Do not take Itomed 10/20/40 mg capsules” as this information was found to be most important.
Moreover, the RMS proposed to put the texts regarding *Children, Patients with hepatic* ***and renal*** *function disorders* under a new subheading “Special patient groups”. The text has been adapted accordingly.
These suggestions were applied in the current attached PIL. The readability test was sufficiently performed and there was no need for a second test as no major changes were applied to the leaflet.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Itomed 10/20/40 mg capsules have a proven chemical-pharmaceutical quality and are generic forms of Losec 10/20/40 mg 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 European guidance documents. The SPC is consistent with that of the reference product. The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for other generic applications e.g. NL/H/0519-0521/001-003/MR.

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.

The Board followed the advice of the assessors. Itomed 10/20/40 mg capsules was authorized in the Netherlands on 21 August 2006.

During the procedure a potential serious risk to public health was raised with regard to the demonstration of bioequivalence with the formulation that is on the national market. A request for referral to the CMD(h) was submitted*: "Bioequivalence is demonstrated against the reference product (Losec gastro-resistant capsules) and not against Losec MUPS enterotablets. Losec gastro-resistant capsules is no longer registered in the member state referring this application"*

Following the discussion in the CMD(h) meeting of 19 June 2007, all involved member states could agree that a bioequivalence study comparing the test product vs. Losec MUPS enterotablets is not required, since bioequivalence only has to be demonstrated against the reference product. Moreover, the MAH committed to submit additional dissolution profiles (i.e. including all strengths) of the test product and Losec MUPS enterotablets. See for a more extensive discussion on the post-approval commitments section II.3 Clinical aspects.

On the basis of the data submitted, the concerned member states considered that essential similarity has been demonstrated for Itomed 10/20/40 mg capsules with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 11 April 2007.

A European harmonised birth date has been allocated (15 April 1987), and subsequently the first data lock point for the PSUR cycle is April 2009. The first PSUR will cover the period from February 2005 to April 2009. Thereafter, a 3-yearly PSUR interval is proposed.

The date for the first renewal will be: April 2012

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
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
Submission of a new or updated PH. Eur Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a new manufacturer (replacement or addition). Other substances.	NL/H/0974/ 001-003/IA/ 001	IA	26-11-2007	10-12-2007	Approval	N
Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an excipient. From a manufacturer currently approved or a new manufacturer (replacement or addition).	NL/H/0974/ 001-003/IA/ 002	IA	11-2-2008	25-2-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Primary packaging site. Solid pharmaceutical forms, e.g. tablets and capsules.	NL/H/0974/ 002-003/IA/ 003	IA	10-4-2008	24-4-2008	Approval	N
Change in the name of the medicinal product.	NL/H/0974/ 001-002/IB/ 004	IB	18-3-2008	17-4-2008	Approval	N
To fulfil commitments that were agreed during the MRP and to make a minortypographical correction to 3.2.P.5.1.	NL/H/0974/ 001-003/II/ 005	II / Post-approval committment	22-5-2008	21-7-2008	Approval	N
Change in the name and/or address of the MAH.	NL/H/0974/ 001-003/IA/ 006	IA	10-4-2008	24-4-2008	Approval	N
Change in the name and/or address of the MAH.	NL/H/0974/ 001-002/IA/ 007	IA	20-5-2008	3-6-2008	Approval	N
Change in pack size of the finished product. Change in the number of units (e.g. tablets, ampoules etc.) in a pack. Change within the range of the currently approved pack sizes. Addition of bottle size of 100 capsules.	NL/H/0974/ 001-003/IA/ 008	IA	27-1-2009	10-2-2009	Approval	N
Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an excipient. From a manufacturer currently approved or a new manufacturer (replacement or addition).	NL/H/0974/ 001-003/IA/ 009	IA	25-5-2009	8-6-2009	Approval	N
Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an excipient. From a manufacturer currently approved or a new manufacturer (replacement or addition).	NL/H/0974/ 001-003/IA/ 010	IA	25-5-2009	8-6-2009	Approval	N
Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an excipient. From a manufacturer currently approved or a new manufacturer (replacement or addition).	NL/H/0974/ 001-003/IA/ 011	IA	25-5-2009	8-6-2009	Approval	N
Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an excipient. From a manufacturer currently approved or a new manufacturer (replacement or addition).	NL/H/0974/ 001-003/IA/ 012	IA	25-5-2009	8-6-2009	Approval	N
Submission of a new or updated TSE Ph. Eur. Certificate of Suitability for an excipient. From a manufacturer currently approved or	NL/H/0974/ 001-003/IA/ 013	IA	25-5-2009	8-6-2009	Approval	N

a new manufacturer (replacement or addition).						
Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a site where batch control/testing takes place.	NL/H/0974/ 001-003/IA/ 014	IA	30-6-2009	14-7-2009	Approval	N