PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Lansoprazol 15 Gastro-resistant capsule hard 15 mg
Lansoprazol 30 Gastro-resistant capsule hard 30 mg
Sandoz B.V., the Netherlands

lansoprazole

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/657/001-002/MR
Registration number in the Netherlands: RVG 31123, 31124

23 November 2009

Pharmacotherapeutic group: Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), Proton pump inhibitors
ATC code: A02BC03
Route of administration: oral
Therapeutic indication: treatment of duodenal and gastric ulcer, reflux oesophagitis, Zollinger-Ellison syndrome and Helicobacter pylori infections.
Prescription status: prescription only
Date of first authorisation in NL: 4 July 2005
Concerned Member States: Mutual recognition procedure with IT and PL
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 Lansoprazole 15/30 mg gastro-resistant capsule hard, from Sandoz B.V.. The date of authorisation was on 4 July 2005 in the Netherlands.

Lansoprazole is used in the treatment of patients with an ulcus duodeni, ulcus ventriculi, reflux oesophagitis or Zollinger-Ellison syndrome.

Lansoprazole is also used in combination with two suitable antibiotics for the eradication of Helicobacter pylori in patients with peptic ulcers with the objective to reduce the risk of recurrent ulcus duodeni and ulcus ventriculi, caused by this micro-organism.

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

Lansoprazole is a benzimidazole derivative that inhibits the gastric acid producing enzyme (H⁺, K⁺, ATPase) in the parietal cell. Thanks to the inhibition of the last stage in the acid production both the basal and the stimulated acid secretion in the stomach are inhibited. This rapid and effective inhibition is dose dependent and reversible. The lansoprazole has no effect on the histamine receptors and acetyl choline receptors. Two hours after a single administration of 30 mg of lansoprazole the acid production in the stomach is reduced by approximately 80%.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Prezal 15 and Prezal 30 (NL License RVG 18696 and 15420, respectively). The innovator products have been registered in the Netherlands by Sanofi Aventis the Netherlands B.V. since 16 October 1995 and 25 March 1993, respectively (original product). In addition, reference is made to Agopton, Dakar, Lanzor, Lanzo, Lansone, Ogasto and Zoton authorisations in the individual member states (reference product).

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 two bioequivalence studies in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Agopton 30 mg capsules, registered in Austria. 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 their 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, 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 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 lansoprazole, an established active substance. Lansoprazole is not described in a Ph.Eur. monograph, however a USP monograph (27) and a draft monograph in Pharmeuropa (16.4) are available. Lansoprazole is a white to off-white powder. Lansoprazole has a chiral centre (sulphur atom) which is the origin of the existence of two enantiomers.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or ‘know-how’ of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA 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.

Manufacture
A flow chart with molecular structures of the manufacturing process has been included in the Open Part of the DMF. The impurities and residual solvents are described sufficiently in the impurities section.

Specification
The active substance specification includes specifications for description, identification, appearance of solution, water, sulphated ash, related substances, assay, residual solvents, microbial contamination and particle size. The specification is considered adequate to control the quality and complies with relevant guidelines. The applied specification for the test for microbial contamination is described in the Ph.Eur. Batch analytical data demonstrating compliance with this specification have been provided for 3 production scale batches.

Stability
Stability data on the active substance have been provided for 3 batches (6 months at 40°C/75%RH and 6 years at 25°C/60%RH) in accordance with applicable European guidelines. No changes were seen in the accelerated and long-term studies. Based on the data submitted, a retest period could be granted of 5 years without specific storage requirements, in double PE bags in PE or cardboard drum.

* 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
Lansoprazol 15 and 30 mg gastro-resistant capsules contain gastro-resistant granules with as active substance 15 and 30 mg of lansoprazole, respectively.

The capsules are packed in an Al/Al blister pack.

The excipients are:
Capsule core: Saccharose, Maize starch, Hypromellose (E 464), Talc (E 553b), Titanium dioxide (E 171), Magnesium carbonate (E 504), Methacrylic acid – ethylcrylate copolymer, Macrogol 400, and Colloidal silicon (water free) (E 551).

Capsule shell: Carrageen (E 407), Potassium chloride (E 508), Titanium dioxide (E 171), and Hypromellose (E 464).

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

Lansoprazole is chemically unstable in acidic media, therefore the substance has to be administered as an enteric-coated formulation. Furthermore, lansoprazole is practically insoluble in water. Therefore, the particle size of the drug substance might have an influence on the dissolution characteristics of the finished product. In order to control this a specification has been included.

Excipients
The qualitative composition of the originator product was used as a basis for the choice of the excipients. All excipients used in the manufacturing process of the drug product are commonly used for pharmaceutical preparations with the exception of the hypromellose capsule. The MAH provides an adequate justification for the use of hypromellose capsules instead of gelatine capsules. The used excipients are safe in the proposed concentrations. The empty hypromellose capsules comply with in-house specifications, whereas all other excipients comply with the current Ph.Eur. monographs.

Clinical formulations
The dissolution profiles of the 15 and 30 mg capsules in both Simulated Intestinal Fluid (SIF) and phosphate buffer are comparable.

The composition of the Dutch and the Austrian reference products are qualitatively the same. Dissolution profiles of two batches of Lansoprazol 15/30 mg were compared with the Austrian reference product. The results show that both batches show a faster release of lansoprazole than the originator in phosphate buffer. Based upon the comparative dissolution study in SIF, it is concluded that the lansoprazole batches show similar release profiles. Furthermore, they show a similar profile as the originator products.

From literature it is known that there is a difference in dissolution rate between gelatine and hypromellose capsules. Although some minor deviations are observed between the dissolution profiles in phosphate buffer pH 6.8, this is considered of lesser importance, since it has been proven that phosphate buffer is not a bio-relevant medium.

As the SPC does not exclude the co-administration with food, in accordance with the Note for Guidance on Quality of modified release products, gastro-resistance should also be tested at a higher pH. As lansoprazole can be co-administrated with food, the gastro-resistance of the proposed product is also demonstrated at higher pH ranges (pH 2-5). Results on gastro-resistance for the 30 mg capsule are presented at pH values of 2-3-4-5 after 1 hour. When food comes into the stomach, the pH may rise up to 3.0 or 4.0 due to buffering capacity of proteins. It can be concluded that the gastro-resistance of the proposed capsules is sufficiently guaranteed when co-administered with food.
Moreover, the MAH has submitted comparative dissolution profiles of NL, UK, DE, FI and FR innovator products. The originator products are capsules which contain gastro-resistant granules. An exception is the UK where lansoprazole is administered as gastric resistant coated tablets.

Manufacturing process
The manufacturing process of lansoprazole 15 and 30 mg capsules is a common, well known and standard process, in which the active substance is coated onto a support material. Via two subsequent coating steps, the core granules are modified into gastro-resistant granules, which are finally filled into capsules.

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 batches of each strength performed in accordance with the relevant European guidelines.

Product specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on specific monographs in the Ph.Eur. and USP, and includes tests for appearance, identification, uniformity of mass, dissolution, water content, related substances, assay, and microbial contamination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 3 batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 3 batches of each strength in accordance with applicable European guidelines at 25°C/60%RH (12 months), 30°C/60%RH (12 months) and 40°C/75%RH (6 months). No significant change in their stability indicating properties were shown when stored at 25°C/60%RH up to 12 months. Under intermediate conditions the batches show no significant change in their stability indicating parameters up to 12 months. Under accelerated conditions the batches show a slight decrease in dissolution after gastric resistance, a slight decrease in assay and an increasing amount of total impurity content. On basis of the data submitted, a shelf life was granted of 18 months. The labelled storage conditions are "Do not store above 25°C" and "Store in the original packaging". After registration, a type II variation (NL/H/0657/001-002/II/012, see "steps taken after finalisation of the initial procedure" table), was approved on 21 April 2008 which added the HDPE container with PP cap as immediate packaging material for both strengths. Based on the data submitted a shelf life of “6 months when stored under 25 °C” was granted for the product stored in a HDPE container with PP cap. By a subsequent type II variation (NL/H/0657/001/II/017), approved on 6 August 2009, the shelf life of the 15 mg tablets packed in Al/Al blister was reduced to 12 months due to out-of-specification results obtained during the stability studies over 18 months. By this same variation, the shelf life of the 15 mg tablets packed in HDPE container with PP cap was changed from 6 into 12 months. Moreover, the shelf life of the 30 mg tablets packed in HDPE container with PP cap was changed from 6 into 18 months (variation NL/H/0657/002/IB/016). The storage condition remains “when stored under 25 °C” for all package forms.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.
II.2 Non clinical aspects

This product is a generic formulation of Prezal, 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 lansoprazole 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

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

For this generic application, the MAH has submitted two bioequivalence studies in which the pharmacokinetic profile of the test product Lansoprazol 30 mg capsules is compared with the pharmacokinetic profile of the reference product Agopton 30 mg capsules under fasted and fed conditions.

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.

Food effect

In the Netherlands, the SPC of Prezal states that the capsule should be taken before or after the meal, with an additional statement in section 4.5 that this should be separated by an interval of at least 0.5 hour. With this posology, it may be considered important that bioequivalence is also demonstrated under fed conditions, since it is to be expected that the absorption phase of lansoprazole coincides with the presence of food in the stomach.

For the innovator Prezal, a clear food-effect was reported in the original application, i.e. AUC and $C_{\text{max}}$ were reduced by a factor of 2 in the presence of food. The Board has decided to accept generic lansoprazole formulations even when bioequivalence is not demonstrated under fed conditions, provided that the exposure to lansoprazole from the generic formulation is not lower than that of the innovator under fed conditions, and is not increased relative to the generic exposure under fasted conditions.

Only single dose bioequivalence studies have been performed, which is acceptable for the current application, since the elimination half-life of lansoprazole is approximately 1.5 hours, and no accumulation is to be expected upon a once-daily administration.

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

Bioequivalence study 1 (fasting conditions)

A monocentre, open, randomized, single-dose, two-period crossover bioequivalence study was carried out under fasted conditions in 56 healthy male volunteers, aged from 18 to 43 years. Each subject received a single dose (30 mg) of one of the 2 lansoprazole formulations. The capsule was orally administered with 240 ml water after an overnight fast. The washout period between different periods was 10 days. Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, and 10 hours after administration of the products.

Four withdrawals were registered during the trial. One volunteer was excluded from the trial because he was not compliant, two volunteers dropped out due to vomiting, and one volunteer dropped out due to diarrhoea, abdominal pain and fever. Therefore, 52 subjects were eligible for pharmacokinetic analysis.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, $t_{\text{max}}$ (median, range)) of lansoprazole under fasted conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N=52</th>
<th>$\text{AUC}_{0-t}$</th>
<th>$\text{AUC}_{0-\infty}$</th>
<th>$C_{\text{max}}$</th>
<th>$t_{\text{max}}$</th>
<th>$t_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>2007 ± 1197</td>
<td>2080 ± 1265</td>
<td>1067 ± 432</td>
<td>1.5 (0.60-2.3)</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>2010 ± 1214</td>
<td>2083 ± 1321</td>
<td>962 ± 417</td>
<td>1.5 (0.75-3.5)</td>
<td>1.1 ± 0.4</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>1.01 (0.95-1.08)</td>
<td>1.02 (0.95-1.08)</td>
<td>1.13 (1.03-1.23)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td>19.1</td>
<td>19.1</td>
<td>27.7</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

$\text{AUC}_{0-t}$ area under the plasma concentration-time curve from time zero to t hours

$\text{AUC}_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity

$C_{\text{max}}$ maximum plasma concentration

$t_{\text{max}}$ time for maximum concentration

$\text{t}_{1/2}$ half-life

*ln-transformed values

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

Bioequivalence study 2 (fed conditions)
A monocentre, open, randomized, single-dose, two-period crossover bioequivalence study was carried out under fed conditions in 56 healthy male volunteers, aged from 18 to 44 years. Each subject received a single dose (30 mg) of one of the 2 lansoprazole formulations. The capsule was orally administered with 240 ml water, immediately after finishing a high-fat breakfast which consisted of two eggs fried in butter, 100 g sausages, two slices of toast with 25 g butter, 110 g hashed brown potatoes, and 280 g whole milk (total caloric intake 1000 kcal). The washout period between different periods was 7 days. Blood samples were collected pre-dose and at 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10 and 12 hours after administration of the products.

Three withdrawals were registered during the trial. One volunteer was dismissed from the trial due to smoking, and two volunteers dropped out due to syncope/hypotension and vomiting/hypotension, respectively. Therefore, 53 subjects were eligible for pharmacokinetic analysis.

Very low plasma levels were observed for one volunteer following administration of the reference capsule. The $\text{AUC}_{0-t}$ and $C_{\text{max}}$ following administration of the reference capsule were 16.45 ng.h/ml and 33.0 ng/ml, respectively. Due to these lower levels, the $\text{AUC}_{0-\infty}$ for the reference capsule could not be calculated for this volunteer. Still, $\text{AUC}_{0-t}$ and $C_{\text{max}}$ levels for this volunteer were used in the final statistically analyses.
Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{\text{max}} \) (median, range)) of lansoprazole under fed conditions.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{AUC}_{0-t} ) ng.h/ml</th>
<th>( \text{AUC}_{0-\infty} ) ng.h/ml</th>
<th>( \text{C}_{\text{max}} ) ng/ml</th>
<th>( t_{\text{max}} ) h</th>
<th>( t_{1/2} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td>1760 ± 1065</td>
<td>1869 ± 1172</td>
<td>854 ± 345</td>
<td>2.5 (1.25 - 4.0)</td>
<td>0.9 ± 0.6</td>
</tr>
<tr>
<td>Reference</td>
<td>1964 ± 1352</td>
<td>2141 ± 1607†</td>
<td>859 ± 352</td>
<td>2.5 (0.5 – 4.5)</td>
<td>1.0 ± 0.9</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td>0.98 (0.82 – 1.16)</td>
<td>---</td>
<td>1.02 (0.87 – 1.19)</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>CV (%)</td>
<td>57</td>
<td>---</td>
<td>50</td>
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</table>

\( \text{AUC}_{0-t} \) area under the plasma concentration-time curve from time zero to infinity
\( \text{AUC}_{0-\infty} \) area under the plasma concentration-time curve from time zero to \( t \) hours
\( \text{C}_{\text{max}} \) maximum plasma concentration
\( t_{\text{max}} \) time for maximum concentration
\( t_{1/2} \) half-life
† \( N=52 \)

*ln-transformed values

The MAH used non-parametric methods for calculation of the 90% CI for \( \text{AUC} \) and \( \text{C}_{\text{max}} \). According to the Note for Guidance on Bioavailability and Bioequivalence, this is not appropriate, and 90% CI should be calculated according to parametric methods. Still, recalculation of the 90% CI by a parametric approach by the assessor revealed that the 90% CI were within the 0.80-1.25 acceptance range, both for \( \text{AUC}_{0-t} \) and \( \text{C}_{\text{max}} \). In this calculation, data obtained from one volunteer having very low exposure after administration of the Agopton reference capsule were included.

Conclusion bioequivalence studies
Based on the pharmacokinetic parameters of lansoprazole in both studies, it can be concluded that the test Lansoprazol 30 gastro-resistant capsule hard 30 mg and reference Agopton 30 mg capsules are bioequivalent with respect to rate and extent of absorption, and fulfill the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Remarkably, the \( \text{AUC} \) and \( \text{C}_{\text{max}} \) data in the fed study are similar to those obtained in the fasted study. This is in contrast to what is normally observed, i.e., an approximately two-fold lowering of the lansoprazole exposure in combination with a high-fat meal. The MAH has discussed this matter during the procedure. It is acknowledged by the MAH that the effect of food on lansoprazole pharmacokinetics from the reference product appears small as compared to literature data. Still, the MAH indicates that, although the geometric mean values for \( \text{AUC} \) and \( \text{C}_{\text{max}} \) of the reference capsule are similar, the range of \( \text{AUC} \) and \( \text{C}_{\text{max}} \) values for the reference product is broader under fed conditions. However, the range under fed conditions appears extended to the lower end due to the deviating data for one particular volunteer. Without data for this volunteer the range for \( \text{AUC}_{0-t} \) and \( \text{C}_{\text{max}} \) is 435.09 - 6601.56 and 333.60 - 1723.00, so almost identical to the data under fasted conditions.

Therefore, the only indication that there is an effect of food for the reference capsule is the \( t_{\text{max}} \), which is increased under fed conditions, as compared to fasted conditions. The data provided by the MAH can be regarded sufficient in order to exclude dose-dumping of the test capsule under fed conditions.

The 30 mg capsules are dose proportional with the 15 mg capsules. The pharmacokinetics of the active substance are linear in the 15-60 mg dose range. The results of the bioequivalence study performed with the 30 mg capsules therefore apply to the other strengths.

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
Lansoprazole was first approved in 1990, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of lansoprazole 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. 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
For the innovator product an article 30 referral procedure was started during the procedure (EMEA/H/A-30/643). The MAH made a commitment to harmonise the SPC of NL/H/657/001-002 and NL/H/681/001-002 via a type II variation procedure with the SPC resulting from that referral immediately after a Commission Decision will be issued.

This commitment was resolved post-approval by variation NL/H/0657/001-002/II/007 (see “steps taken after finalization of the initial procedure”).

Readability test
The readability test will be performed by the MAH during the clock stop of the above mentioned type II variation.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lansoprazol 15 and 30 mg gastro-resistant hard capsules, have a proven chemical-pharmaceutical quality and are a generic form of Prezal 15 mg and 30 mg capsules. Prezal 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 SPC, package leaflet and labelling are in the agreed templates and are in agreement with other lansoprazole containing products. The MAH has made a commitment to harmonise the SPC via a variation procedure with the SPC resulting from referral EMEA/H/A/-30/643 for the innovator product.

The Board followed the advice of the assessors. Lansoprazol was authorised in the Netherlands on 4 July 2005.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Lansoprazol 15 and 30 with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 8 December 2005.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from December 2005 to December 2009.

The date for the first renewal will be: 8 December 2010.

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

Quality – drug substance
- The MAH has committed to submit the results of the uniformity of dosage unit test, which replaces the mass uniformity test.

SPC
- The MAH has committed to harmonize the SPC of NL/H/657/01-02 with the SPC resulting from referral EMEA/H/A/-30/643 by means of a type II variation immediately after a Commission Decision will be issued. The type II variation (NL/H/0657/001-002/II/007) was submitted on 6 July 2007 (see also Annex I)
- The MAH has committed to submit a harmonised package leaflet according to QRD template along with the harmonised SPC in abovementioned type II variation. See also NL/H/0657/001-002/II/007.
- The MAH has committed to re-evaluate the current studies on gastro-resistance of the medicinal products in relation to method of administration resulting from the referral.

Readability test
- The MAH has committed to perform the readability test during the clock stop of the type II variation.
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
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<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
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<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
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<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>GLP</td>
<td>Good Laboratory Practice</td>
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<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
</tr>
<tr>
<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
</tr>
<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
</tr>
<tr>
<td>PAR</td>
<td>Public Assessment Report</td>
</tr>
<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>PIL</td>
<td>Package Leaflet</td>
</tr>
<tr>
<td>PSUR</td>
<td>Periodic Safety Update Report</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
</tr>
<tr>
<td>t&lt;sub&gt;½&lt;/sub&gt;</td>
<td>Half-life</td>
</tr>
<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
</tr>
<tr>
<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
</tr>
<tr>
<td>USP</td>
<td>Pharmacopoeia in the United States</td>
</tr>
</tbody>
</table>
## STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Solid pharmaceutical forms, e.g. tablets and capsules.</td>
<td>NL/H/0657/001-002/IA/001</td>
<td>IA</td>
<td>1-5-2006</td>
<td>9-5-2006</td>
<td>Non-approval</td>
<td>N</td>
</tr>
<tr>
<td>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. All other manufacturing operations except batch release.</td>
<td>NL/H/0657/001-002/IB/002</td>
<td>IB</td>
<td>12-5-2006</td>
<td>12-6-2006</td>
<td>Approval</td>
<td>N</td>
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<tr>
<td>In order to comply to the anticipated demand of finished product, it has been decided to scale up the manufacturing process.</td>
<td>NL/H/0657/001-002/II/003</td>
<td>II</td>
<td>12-5-2006</td>
<td>11-7-2006</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Solid pharmaceutical forms, e.g. tablets and capsules.</td>
<td>NL/H/0657/001-002/IA/004</td>
<td>IA</td>
<td>18-5-2006</td>
<td>1-6-2006</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.</td>
<td>NL/H/0657/001-002/IA/005</td>
<td>IA</td>
<td>12-7-2006</td>
<td>26-7-2006</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Change in shape or dimensions of the container or closure. Other pharmaceutical forms.</td>
<td>NL/H/0657/001-002/IA/006</td>
<td>IA</td>
<td>21-2-2007</td>
<td>9-3-2007</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Update SmPC, Harmonisation PL and label</td>
<td>NL/H/0657/001-002/II/007</td>
<td>II</td>
<td>6-7-2007</td>
<td>4-9-2007</td>
<td>Approval</td>
<td>Y, Annex I</td>
</tr>
<tr>
<td>Minor change in the manufacture of the finished product.</td>
<td>NL/H/0657/001-002/IB/008</td>
<td>IB</td>
<td>18-10-2007</td>
<td>19-11-2007</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Change in the manufacturer of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance where no Ph.Eur. Certificate of Suitability is available. Change in site of the already approved manufacturer (replacement or addition).</td>
<td>NL/H/0657/001-002/IB/009</td>
<td>IB</td>
<td>---</td>
<td>11-2-2008</td>
<td>Non-approval</td>
<td>N</td>
</tr>
<tr>
<td>Deletion of any manufacturing site (including for an active substance, intermediate, or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place).</td>
<td>NL/H/0657/001-002/IA/010</td>
<td>IA</td>
<td>15-1-2008</td>
<td>29-1-2008</td>
<td>Approval</td>
<td>N</td>
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<tr>
<td>Minor change in the manufacturing process of the finished product.</td>
<td>NL/H/0657/001-002/II/011</td>
<td>II</td>
<td>21-2-2008</td>
<td>24-4-2008</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Addition of HDPE-container with PP cap as immediate packaging material. Shelf-life for product in HDPE container is 6 months.</td>
<td>NL/H/0657/001-002/II/012</td>
<td>II</td>
<td>21-2-2008</td>
<td>24-4-2008</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Change in the name of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance where no Ph.Eur.</td>
<td>NL/H/0657/001-002/IB/013</td>
<td>IB</td>
<td>3-6-2008</td>
<td>3-7-2008</td>
<td>Approval</td>
<td>N</td>
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</tbody>
</table>
Certificate of Suitability is available.

<table>
<thead>
<tr>
<th>Description</th>
<th>Code</th>
<th>Approval</th>
<th>Date</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of pharmaceutical forms.</td>
<td>NL/H/0657/001-002/IA/014</td>
<td>21-4-2009</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Submission of modules 1.6, 1.8 and 1.9 that were not yet part of the dossier.</td>
<td>NL/H/0657/001-002/II/015</td>
<td>23-6-2009</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>Change in the shelf-life of the finished product as packaged for sale. Former HDPE-container with PP cap: 6 months. Proposed: HDPE-container with PP cap: 18 months.</td>
<td>NL/H/0657/002/IB/016</td>
<td>19-8-2009</td>
<td>Approval</td>
<td>N</td>
</tr>
<tr>
<td>A reduction of shelf life packed in Al/Al blister for the strength 15 mg to 12 months due to out-of-specification results obtained during the stability studies, after 18 months. Shelf life of product in HDPE bottles with PP cap was extended from 6 to 12 months.</td>
<td>NL/H/0657/001/II/017</td>
<td>6-8-2009</td>
<td>Approval</td>
<td>N</td>
</tr>
</tbody>
</table>
ANNEX I – Type II variation (NL/H/0657/001-002/II/007)

I Recommendation
Based on the assessment of the readability test, Core SmPC, PL and labelling the RMS concludes this variation as approvable.

II Executive Summary

II.1 Scope of the variation
In December 2006 an article 30 referral by the CHMP led to a harmonized SmPC, PL and labelling for lanzoprazol 15 and 30 mg presentations. Therefore the MAH has submitted an updated SmPC together with a readability test and PL and labelling.

III Scientific Discussion

III.1 SmPC
The SmPC text (appendix A) is identical to the text of the article 30 referral text of Agopton (EMEA/H/407636/2006). This is endorsed by the RMS.

III.2 Readability test
According to article 59(3) and 61(1) of Directive 2001/83/EC as amended by Directive 2004/27/EC (Guidance concerning consultations with target patient groups for the package leaflet) it is appropriate to refer to recently approved PL for a representative medicinal product.

The MAH referred to the “parent” leaflet of:
A) Agopton (EMEA/H/407636/2006),
B) Pantoprazole Sandoz 40 mg powder for solution for injection (NL/H/0806, 0807, 0812/DC), and
C) Omeprazole Sandoz 10 mg, 20 mg, 40 mg capsules (UK/H/1022-5/DC).

The MAH concluded that for Agopton (EMEA/407636/2006) these documents must have contained results of assessments carried out in cooperation with target patients groups, however this statement can only be used for bridging if the MAH can provided crucial information regarding the date(s) of the test performance, the company that carried out the test(s).
The readability test of Omeprazole Sandoz 10 mg, 20 mg, 40 mg capsules (UK/H/1022-5/DC) can not be used as this test is still under assessment.
Pantoprazole Sandoz 40 mg powder for solution for injection (NL/H/0806, 0807, 0812/DC) was approved by day 210 of the procedure (6 April 2007) and no comments have risen.

The RMS is of the option that the latter readability test can be used for bridging the Omeprazol leaflet with the test performed for Pantoprazole Sandoz 40 mg, despite the different pharmaceutical forms, e.g injection versus capsules.

Comparison of both leaflets by the RMS led to the conclusion that the lay-out of both are identical, taking into account the minor difference in patient information (e.g. side-effect information, extra information section for health care professionals). However most important is that the (safety) information of both leaflets is provided to the patient in the same order.

The MAH is advised that in further events when they would like to brigde, that a bridging report is submitted. This should contain a detailed comparison between the leaflets used for bridging.
III.3 PIL
The leaflet text (appendix B) is similar/identical to the leaflet text of the article 30 referral text of Agopton (EMEA/H/407636/2006). This is endorsed by the RMS.

III.4 Labelling
The labelling text is provided in appendix C. No comments.

IV Overall conclusion
Based on the assessment the RMS concludes that this variation is approvable. The RMS proposes if no comments are received by the member states this variation will be ended positively by day 60 (4 September 2007) of the procedure.