PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Lanzatol 15, gastro-resistant capsules
Lanzatol 30, gastro-resistant capsules
Focus farma 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/0827/01-02/MR
Registration number in the Netherlands: RVG 33545, 33546

2 June 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 authorisation in NL: 18 April 2006
Concerned Member States: Mutual recognition procedure with EE (30 mg only), IT, LT (30 mg only), LV (30 mg only) and NO
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.
INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Lanzatol 15 and Lanzatol 30, gastro-resistant capsules from Focus farma B.V., the Netherlands. The date of authorisation was on 18 April 2006 in the Netherlands.

The product is indicated for:
- Treatment of duodenal and gastric ulcer;
- Treatment of reflux oesophagitis;
- Prophylaxis of reflux oesophagitis;
- Zollinger-Ellison syndrome;
- Treatment of NSAID-associated benign gastric and duodenal ulcers in patients requiring continued NSAID treatment;
- Prophylaxis of NSAID-associated gastric ulcers and duodenal ulcers in patients at risk requiring continued therapy;
- Symptomatic gastroesophageal reflux disease;
- Eradication of *Helicobacter pylori* (*H.pylori*) concurrently given with appropriate antibiotic therapy for treatment of *H.pylori*-associated ulcers.

Due to the existence of a European patent on the use of benzimidazol derivates for the preparation of medicinal product for the treatment of Helicobacter pylori infections, the last indication is not included in the SPC and Package Leaflet approved for this product in the Netherlands. In the Dutch Package Leaflet, the following information is added:

"Lansoprazole which is contained in Lanzatol is also authorised to treat other illnesses, which are not mentioned in this leaflet. Ask your doctor, pharmacist or other healthcare professional if you have further questions" to inform the patient accordingly.

As agreed in the CMD, the texts used in the MRP will contain all indications and the member states will decide on a national level whether or not the indications for which a usage patent is applicable will be implemented in the national texts.

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

Lansoprazole is a gastric proton pump inhibitor. It inhibits the final stage of gastric acid formation by inhibiting the activity of H⁺/K⁺-ATPase of the parietal cells in the stomach. The inhibition is dose-dependent and reversible, and the effect applies to both basal and stimulated secretion of gastric acid. Lansoprazole is concentrated in the parietal cells and becomes active in their acidic environment, whereupon it reacts with the sulphhydryl group of H⁺/K⁺-ATPase causing inhibition of the enzyme activity.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator products Prezal 15 and Prezal 30 (NL License RVG 18696 and 15420 respectively). The innovator products have been registered in the Netherlands by Sanofi-Aventis Netherlands B.V. since 16 October 1995 and 25 March 1993, respectively. 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 applicant has submitted two bioequivalence studies in which the pharmacokinetic profile of the product is compared.
with the pharmacokinetic profile of the reference product Zoton 30 mg, registered in the United Kingdom.
Zoton is the British name for the innovator product Prezal. 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 with respect to this product.

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.

Drug substance
There is no Ph.Eur.* monograph available for the drug substance lansoprazole, but there is a USP
monograph. The drug substance is an off-white to light brown powder. There is one chiral centre and the
substance exists as a racemic mixture. The drug substance manufacturer produces the polymorphic form
Lansoprazole I, which is controlled by the IR spectrum.

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 diagram is enclosed: lansoprazole is manufactured via a 3-step process.

Specification
The drug substance specification is in line with the USP, with additional requirements for heavy metals,
chromatographic purity, residual solvents, particle size and bulk density. The specification is acceptable in
view of the route of synthesis and the various ICH guidelines. Batch analysis data demonstrating
compliance with this specification have been provided for 3 batches.

Stability
Stability data has been obtained during storage at 25°C/60% RH and 40°C/75% RH. The drug substance
was packaged in the proposed packaging. The solid drug substance is stable with respect to degradation.
The only trends were observed at accelerated conditions: a decrease of assay up to 1 %, a slight
coloration and a slight increase in water content.
Based on the data provided, the recommended retest period of 24 months is justified.

* 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.
Drug product
The 15 mg capsules are yellow hard gelatine capsules, size 3, with the inscription “L15” on both halves of the capsule.
The 30 mg capsules are purple/blue hard gelatine capsules, size 1, with the inscription “L30” on both halves of the capsule.

The excipients are:
*Capsule-content* - Hydroxypropylmethylcellulose (E464), metacrylic acid/ethyl acrylate copolymer (1:1), talc (E553b), titanium dioxide (E171), macrogol, colloidal anhydrous silica, sugar spheres (sucrose, starch, talc, kaoline).
*Capsule-shell 30 mg* - gelatin, azorubine (E 122), indigo carmine (E 132), titanium dioxide (E171).
*Capsule-shell 15 mg* - gelatin, chinoline yellow (E 104), yellow iron oxide (E 172), titanium dioxide (E 171).
*Inc* - shellac glaze (E904), black iron oxide (E172), soya lecithine (E322), antifoam DC 1510.

The excipients comply with Ph.Eur. monographs or in-house specifications. The dissolution of the bioequivalent batch was not comparable with the innovator products. However, the bioequivalence study showed bioequivalence.

Manufacture of the product
The drug substance is layered to sugar spheres, followed by a barrier coating and an enteric coating. The process is validated on 5 batches at the commercial production scale of enteric coated pellets. This is considered the most important part of the process. Per strength 2 batches of capsule filling have been validated.

Product specification
Adequate dissolution specifications have been set for both dissolution in acidic liquid and in alkaline liquid. Additionally, the product specification includes tests for identification and assay of lansoprazole, identification of colorants, appearance, average and uniformity of fill, loss of drying, related substances and microbial quality. Desoxy-lansoprazole is the major degradation product and also the active metabolite of lansoprazole. The requirements for the degradation products are acceptable in view of the relevant ICH Guideline and the results of the stability studies. Batch analysis results of two batches of each strength have been provided. Compliance with the release requirements has been demonstrated.

Stability of the product
Data of stability studies performed at 25°C/60% RH, 30°C/60% RH and 40°C/75% RH have been submitted that justify the shelf-life of 18 months at storage conditions below 25°C. The enteric coated pellets were tested at 25°C/60% RH with a storage time of 6 months. The pellets show some decrease in dissolution but the requirement was met. Furthermore, a slight increase in loss on drying is seen (1%), related substance and assay results showed no significant changes.

The studies on capsules showed a significant change at the accelerated condition (40°C/75% RH), so 30°C/60% RH studies were performed as well. At 30°C/60% RH an increase is seen in loss on drying (2%), as well as an increase in related substances, but much less pronounced than at 40°C/75% RH. The capsules should be stored in the original Al/Al blister or Al blister pack (Al laminated with LDPE). Therefore, the labelled storage conditions are: “Do not store above 25°C, store in the original package in order to protect from moisture”.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The only excipient for animal origin is gelatine. Reference is made to the Ph.Eur. for gelatine. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the
Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

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 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 Lanzatol 30 mg capsule is compared with the reference product Zoton 30 mg capsule (United Kindom). One bioequivalence study was carried out under fasting conditions (BE-057-LANS-2003) and the other bioequivalence study under fed conditions (BE-163-04).

The same test batch was used for both bioequivalence studies. The formula and preparation of the bioequivalence batch was identical to the formula proposed for marketing.

Bioequivalence study 1: fasting conditions, BE-057-LANS-2003
A randomised, open-label, two-treatment, two-sequence, two-period, single-dose, cross-over, bioequivalence study was carried out under fasted conditions in 48 healthy male volunteers, aged 18-32 years. Each subject received after an overnight fast a single dose (20 mg) of one of the 2 lansoprazole formulations with 240 ml water. For each subject there were 2 dosing periods, separated by a washout period of 12 days. Blood samples were taken predose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 4, 5, 6, 7, 8, 10, 12, 16, 20 and 24 hours after administration of the products. There was one dropout before the beginning of period II, because of fever not related to treatment. As stated in the protocol, the pharmacokinetic data of the first 46 volunteers were analysed.
Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, \( t_{max}\) (median, range)) of lansoprazole under fasted conditions

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{N=46} )</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_{max} ) h</th>
<th>( t_{1/2} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>4489 ± 3152</td>
<td>4644 ± 3272</td>
<td>1233 ± 408</td>
<td>1.75 (1.0-6.0)</td>
<td>2.1 ± 1.1</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>4404 ± 2950</td>
<td>4526 ± 3030</td>
<td>1214 ± 479</td>
<td>1.75 (1.0-5.0)</td>
<td>2.0 ± 1.2</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>1.03 (0.94-1.12)</td>
<td>1.03 (0.95-1.12)</td>
<td>1.06 (0.96-1.17)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td>25.7%</td>
<td>24.7%</td>
<td>29.1%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</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
\( t_{max} \): time for maximum concentration
\( t_{1/2} \): half-life

*ln-transformed values

The 90% confidence intervals calculated for \( \text{AUC}_{0-t} \), \( \text{AUC}_{0-\infty} \) and \( \text{C}_{\text{max}} \) 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 lansoprazole under fasted conditions, it can be concluded that Lanzatol 30 mg capsule and the reference Zoton 30 mg capsule are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study 2: fed conditions, BE-163-04

A randomised, open-label, two-treatment, two-sequence, two-period, single-dose, cross-over, bioequivalence study was carried out under fed conditions in 49 healthy male volunteers, aged 18-37 years. Each subject received after a high fat meal (approximately 1000 kcal) a single dose (20 mg) of one of the 2 lansoprazole formulations with 240 ml water. For each subject there were 2 dosing periods, separated by a washout period of 8 days. Blood samples were taken predose and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 10, 12, 16, 20 and 24 hours after administration of the products. There were five dropouts: two subjects were not taken up into the study, because of having superficial fungal infection of the skin, and having a high blood pressure at the time of clinical examination during check-in. One was given the wrong investigational product, one was febrile and complained of generalised boy pains during clinical examination for check-in for period 2, and one was withdrawn because of violation of the registration procedure. Therefore, pharmacokinetic data of 44 volunteers were analysed.

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>( \text{N=46} )</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_{max} ) h</th>
<th>( t_{1/2} ) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test</td>
<td></td>
<td>5007 ± 3674</td>
<td>5251 ± 4063</td>
<td>860 ± 390</td>
<td>5.0 (3.0-10)</td>
<td>2.7 ± 1.5</td>
</tr>
<tr>
<td>Reference</td>
<td></td>
<td>2242 ± 2488</td>
<td>2364 ± 2514</td>
<td>409 ± 408</td>
<td>4.5 (2.0-15)</td>
<td>2.6 ± 1.6</td>
</tr>
<tr>
<td>*Ratio (90% CI)</td>
<td></td>
<td>3.45 (2.60-4.57)</td>
<td>3.30 (2.51-4.35)</td>
<td>3.34 (2.45-4.56)</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>CV (%)</td>
<td></td>
<td>92.1%</td>
<td>88.1%</td>
<td>105.1%</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>
The 90% confidence intervals calculated for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{\text{max}}$ are in agreement with those calculated by the MAH. The 90% CI are far outside the 0.80-1.25 acceptance range for bioequivalence, and data indicate that the exposure under fed conditions is significantly higher with the test lansoprazole formulation than with the reference formulation.

In order to investigate if the exposure for the reference formulation has decreased, or the exposure for the test formulation has increased, the data from the fasted study BE-057-LANS-2003 are compared with data from the fed study in the table below.

<table>
<thead>
<tr>
<th>Lansoprazole</th>
<th>30 mg Lanzatol test capsule</th>
<th>30 mg Zoton® reference capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fasted</td>
<td>Fed</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (ng.h/ml)</td>
<td>4489 ± 3152</td>
<td>5007 ± 3674</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (ng.h/ml)</td>
<td>4644 ± 3272</td>
<td>5251 ± 4063</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (NG/ML)</td>
<td>1233 ± 408</td>
<td>860 ± 390</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (h)</td>
<td>1.75 (1.0-6.0)</td>
<td>5.0 (3.0-10)</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>2.1 ± 1.1</td>
<td>2.7 ± 1.5</td>
</tr>
</tbody>
</table>

From this comparison it appears that the exposure (AUC) of the reference Zoton® lansoprazole capsule decreases markedly under high-fat fed conditions, whereas exposure (AUC) from the test lansoprazole capsule is hardly affected. $C_{\text{max}}$ from both the test and reference capsule decreases, in line with the delayed $t_{\text{max}}$ under fed conditions. However, also in this case, the effect for the reference capsule is much more pronounced.

In conclusion, the effect of a high-fat meal appears much more pronounced for the Zoton® reference capsule than for the lansoprazole test capsule, and the exposure from the test capsule under fed conditions appears not increased as compared to fasted conditions. Therefore, under fed conditions, efficacy as well as safety of the lansoprazole test capsule is not expected to be affected negatively.

**Conclusion**

Bioequivalence with the reference lansoprazole capsule has been demonstrated under fasted conditions. Furthermore, the effect of a high-fat meal is much more pronounced for the Zoton reference capsule than for the lansoprazole test capsule, and the exposure from the test capsule under fed conditions appears not increased as compared to fasted conditions and not under fed conditions. Therefore, under fed conditions, efficacy as well as safety of the Lanzatol 30 mg is not expected to be affected negatively.

Only the 30 mg dose, and not the 15 mg dose, has been tested for bioequivalence. This is considered acceptable, since the 15 mg capsule is dose-proportional to the 30 mg capsule, and lansoprazole pharmacokinetics have been demonstrated to be linear in the 15-60 mg dose range. Additional requirements as indicated in section 5.4 of the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98, are met as well. Therefore, conclusions on the 30 mg bioequivalence study are valid for the 15 mg capsule 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
Lansoprazole was first approved in 1993, 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 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 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 Risk Management Plan is not necessary for this product.

Product information

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test was diagnostic and a first test was performed with 10 participants. After these 10 participants, the data were reviewed for the presence of major comments, which would require rewriting of the PIL. Since this was not the case, the test was continued with the same PIL and the same questions on a second run of 10 participants.

The readability test had demonstrated that the tested PIL scores well on the tested elements: findability, understandability and applicability of the provided information. In both tests it was easy to determine which results are linked to which conclusions. The conclusions are clear, concise and clearly presented. The patient information leaflet has been adapted sufficiently taking into account the results of the test.

Package Leaflet
Due to the existence of a European patent on the use of benzimidazol derivates for the preparation of medicinal product for the treatment of Helicobacter pylori infections, the indication “Eradication of Helicobacter pylori concurrently given with 2 appropriate antibiotics (see Chapter 4.2) in patients with peptic ulcers with the intention to prevent relapse of duodenal ulcers and gastric ulcers in patients with H.pylori associated ulcers” is not included in the PIL approved for this product in the Netherlands. In the Dutch PIL, the following information is added: “Lansoprazole which is contained in Lanzatol is also authorised to treat other illnesses, which are not mentioned in this leaflet. Ask your doctor, pharmacist or other healthcare professional if you have further questions” to inform the patient accordingly.

As agreed in the CMD, the texts used in the MRP will contain all indications and the member states will decide on a national level whether or not the indications for which a usage patent is applicable will be implemented in the national texts.

SPC
The content of the SPC approved during the mutual recognition procedure is in accordance with the SPC for Prezal harmonised via art. 30 (EMEA/H/A-30/643) of the Directive 2001/83/EC procedure decided on by the European Commission on 13 December 2006.

Due to the existence of a European patent on the use of benzimidazol derivates for the preparation of medicinal product for the treatment of Helicobacter pylori infections, the indication “Eradication of Helicobacter pylori concurrently given with 2 appropriate antibiotics (see Chapter 4.2) in patients with peptic ulcers with the intention to prevent relapse of duodenal ulcers and gastric ulcers in patients with H.pylori associated ulcers” is not included in the SPC approved for this product in the Netherlands.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Lanzatol 15 and Lanzatol 30 have a proven chemical-pharmaceutical quality and are generic forms of Prezal 15 mg and Prezal 30 mg, respectively. 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 is harmonised with that of the innovator's SPC according to the CHMP referral opinion (EMEA/H/A-30/643).

Satisfactory chemical-pharmaceutical documentation has been provided, assuring consistent and sufficient quality of the product.

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. Braille conditions are met by the MAH.

The Board followed the advice of the assessors. No discussion in a Board meeting was deemed necessary. Lanzatol 15 and Lanzatol 30 were authorised in the Netherlands on 18 April 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 2 November 2006. The concerned member states, on the basis of the data submitted, considered that bioequivalence has been demonstrated for Lanzatol 15 and Lanzatol 30 capsules with the reference product, and have therefore granted a marketing authorisation.

The PSUR submission cycle is 3 years.

The date for the first renewal will be: 10 November 2008.

There were no post-approval commitments made during the procedure.
### 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>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
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<tr>
<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
</tr>
<tr>
<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
</tr>
<tr>
<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
</tr>
<tr>
<td>CV</td>
<td>Coefficient of Variation</td>
</tr>
<tr>
<td>EDMF</td>
<td>European Drug Master File</td>
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<tr>
<td>EDQM</td>
<td>European Directorate for the Quality of Medicines</td>
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<tr>
<td>EU</td>
<td>European Union</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GLP</td>
<td>Good Laboratory Practice</td>
</tr>
<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference of Harmonisation</td>
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<tr>
<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<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>
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<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>Change in the name of the medicinal product in Norway.</td>
<td>NL/H/0827/001-002/IB/001</td>
<td>IB</td>
<td>6-6-2007</td>
<td>12-10-2007</td>
<td>Approval</td>
<td>N</td>
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<tr>
<td>Change in the printing ink.</td>
<td>NL/H/0827/001-002/IA/002</td>
<td>IA</td>
<td>20-3-2008</td>
<td>3-4-2008</td>
<td>Approval</td>
<td>N</td>
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<td>Minor change in the manufacturing process of the active substance.</td>
<td>NL/H/0827/001-002/IB/003</td>
<td>IB</td>
<td>16-5-2008</td>
<td>16-6-2008</td>
<td>Approval</td>
<td>N</td>
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<td>Change to comply with Ph.Eur. or with the national pharmacopoeia of a Member State. Change of specification(s) of a former non-European pharmacopoeial substance to comply with Ph.Eur. or with the national pharmacopoeia of a Member State. Active substance.</td>
<td>NL/H/0827/001-002/IB/004</td>
<td>IB</td>
<td>16-5-2008</td>
<td>16-6-2008</td>
<td>Approval</td>
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<td>Addition of a batch release site.</td>
<td>NL/H/0827/002/IA/005</td>
<td>IA</td>
<td>24-9-2008</td>
<td>8-10-2008</td>
<td>Approval</td>
<td>N</td>
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<td>Change to batch release arrangements and quality control testing of the finished product. Replacement or addition of a manufacture responsible for batch release. Including batch control/testing.</td>
<td>NL/H/0827/001-002/IA/006</td>
<td>IA</td>
<td>23-9-2008</td>
<td>7-10-2008</td>
<td>Approval</td>
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<td>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.</td>
<td>NL/H/0827/002/IA/007</td>
<td>IA</td>
<td>13-10-2008</td>
<td>27-10-2008</td>
<td>Approval</td>
<td>N</td>
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