CBG MEB

Public Assessment Report

Scientific discussion

Panclamox 40/500/1000 mg, gastro-resistant tablet/film-coated tablet/film-coated tablet

(pantoprazole/clarithromycin/amoxicillin)

NL/H/2449/001/DC

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This module reflects the scientific discussion for the approval of Panclamox 40/500/1000 mg/gastro-resistant tablet/film-coated tablet/film-coated tablet. The procedure was finalised on 12 September 2013. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Panclamox 40/500/1000 mg/gastro-resistant tablet/film-coated tablet/film-coated tablet, from Sandoz B.V.

The product is indicated for combination therapy for the eradication of *Helicobacter pylori* in adults with peptic ulcers, with the objective of reducing the frequency of recurrence of duodenal ulcers and gastric ulcers caused by this microorganism.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product ZacPac which has been registered in Germany by Nycomed since 2000 (original product). The Dutch reference product is PantoPac (NL License RVG 23316), which has been registered by Takeda Nederland b.v. since 1999 via the national procedure.

The reference products for the individual tablets are:
- Clamoxyl 1 g tablets, registered since 1979 by SmithKline-Beecham Pharma in Germany
- Klacid 500 mg tablets, registered since 1994 by Abbott in the Netherlands
- Pantoloc 40 mg gastro-resistant tablets, registered since 1994 by Altana Pharma in Germany.

The concerned member states (CMS) involved in this procedure were Austria and Slovakia.

The separate products included in ZacPac and the application for the combination package of Panclamox 40/500 /1000 mg all concern generic products based on the same reference products. Therefore the legal basis article 10(1) of Directive 2001/83/EC for Panclamox 40/500/1000 mg is acceptable as a generic application to the reference product ZacPac.

II. QUALITY ASPECTS

II.1 Introduction

Panclamox 40/500/1000 is a combination pack, consisting of 14 tablets each of a pantoprazole 40 mg gastro-resistant tablet, a clarithromycin 500 mg film-coated tablet and a amoxicillin 1000 mg film-coated tablet.

The tablets are packed in PVC-PVDC/Al blister packs. One blister contains two tablets of each tablet formulation, sufficient for one day dosing.

The pantoprazole gastro-resistant tablet is a yellow, oval, coated tablet and contains as active substance 45.1 mg pantoprazole sodium sesquihydrate corresponding to 40 mg pantoprazole.
The excipients are:
Tablet core - sodium carbonate, anhydrous; microcrystalline cellulose; crospovidone (type A); hydroxypropylcellulose; silica, colloidal anhydrous; and calcium stearate.
Coating - hypromellose; titanium dioxide; macrogol 400; quinolone yellow aluminium lake; ferric oxide yellow (E172); Ponceau 4R aluminium lake (E124), methacrylic acid – ethyl acrylate copolymer (1:1); polysorbate 80; sodium laurilsulfate; and triethyl citrate.
Printing ink – macrogol 600; shellac; povidone; ferric oxide black (E172); ferric oxide red (E172); and ferric oxide yellow (E172).

The clarithromycin film-coated tablet is a light yellow, oval tablet and contains as active substance 500 mg clarithromycin.
The excipients are:
Tablet core – croscarmellose sodium; microcrystalline cellulose; povidone; magnesium stearate; silica, colloidal anhydrous; and talc.

Coating – hypromellose; propylene glycol; titanium dioxide; hydroxypropylcellulose; sorbitan monooleate; quinolin yellow (E104); and vanillin.

The amoxicillin film-coated tablet is a white to cream-coloured, oval, biconvex tablet and contains as active substance 1148 mg amoxicillin trihydrate, corresponding to 1000 mg amoxicillin.
The excipients are:
Tablet core – magnesium stearate; polyvidone (K25); sodium starch glycolate type A; and microcrystalline cellulose.
Coating – titanium dioxide; talc; and hypromellose.

II.2 Drug Substance

Pantoprazole sodium sesquihydrate

Pantoprazole in the form of pantoprazole sodium sesquihydrate is an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is freely soluble in water. The active substance exists in different hydrate forms. Three manufacturers are used for the production of pantoprazole. For all active substance manufacturers the CEP procedure is used.

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 suitability 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 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.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEPs, with no additional requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for one full scale batch from two suppliers. This is acceptable since the CEP procedure is used for all suppliers and no additional requirements are applied by the applicant.

Stability of drug substance
For one of the suppliers stability data on the active substance have been provided for eight full-scale batches stored at 25°C/60% RH (24 - 60 months). For three of these batches stability data were also provided for the storage condition 40°C/75% RH (6 months). Stability data demonstrating that the sesquihydrate nature of pantoprazole sodium does not change during storage has been provided. Based on the data provided, the re-test period of 60 months can be granted. A photostability study has been preformed in accordance with the relevant NfG. No changes in related substances were observed. For the second manufacturer, the active substance is stable for 5 years when stored between 2°C and 8°C. For the third manufacturer, the active substance is stable for 4 years. Assessment of the stability data was part of granting the CEPs and has been granted by the EDQM.

Clarithromycin

Clarithromycin is an established active substance described in the European Pharmacopoeia. The active substance is practically insoluble in water. Clarithromycin exists in different polymorphic forms which can be distinguished by IR. The active substance is form II, Two manufacturers are used for the production of clarithromycin. For both active substance manufacturers the CEP procedure is used.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the CEPs, with additional requirements for particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full scale batches from both suppliers.

Stability of drug substance
Stability data from both suppliers are provided.
For the first supplier, stability data on the active substance have been provided for four full scale batches stored at 25 - 30°C (36 months) and 40°C/75% RH (6 months). A slight decrease in assay and a slight increase in related substances were observed after 36 months. The deviant long term storage condition has been adequately justified.
For the second supplier, stability data on the active substance have been provided for three full scale batches stored at 25°C /60% RH (48 months) and 40°C/75% RH (6 months). With the exception of a slight increase in water content under the accelerated condition, no trends are observed.
Based on the submitted stability data a re-test period of 36 months, when stored in the original container is granted for both drug substance manufacturers.

Amoxicillin trihydrate

Amoxicillin in the form of amoxicillin trihydrate is an established active substance described in the European Pharmacopoeia. The active substance is slightly soluble in water. One manufacturer is used, which uses the CEP procedure.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance specification is in line with the CEP, with additional requirements for bulk density, tapped density and particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scale batches.

Stability of drug substance
Stability data on the active substance have been provided for six full scale batches stored at 25 - 30°C (24 - 60 months) and 40°C/75% RH (6 months). A slight decrease in assay and a slight increase in related substances were observed after 60 months. The deviant long term storage condition has been adequately justified.
Based on the stability data provided a re-test period of 36 months and the storage condition ‘Store below 30°C’ are granted.

II.3 Medicinal Product

Pantoprazole 40 mg gastro-resistant tablets

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were formulation studies and dissolution studies. Bioequivalence studies were performed with a batch of the drug product with the same composition and manufactured in the same way as the commercial batches. The dissolution profiles of the biobatches are not comparable. The generic formulation showed faster dissolution than the innovator. However, since test and reference product were demonstrated to be bioequivalent *in vivo*, no objections were made.

Manufacturing process
The manufacturing process is divided into the following steps: wet granulation, drying, sifting, blending, compression, film-coating, enteric coating, imprint and packaging.

The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches of all batch sizes from both manufacturing sites. The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the Ph.Eur. with the exception of the coating agents. In-house specifications have been provided. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification of pantoprazole, quinolone yellow, titanium dioxide and ferric oxide, uniformity of dosage units, disintegration, dissolution, gastro-resistance, related substances, microbial purity and assay. The release and shelf-life limits are identical except for related substances and assay. The drug product specification is acceptable.
The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production sites have been provided on three full scale batches, demonstrating compliance to the release specification.

Stability of drug product
Stability data on the product has been provided for two batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in blisters similar to the marketing packaging.
Out-of-specification results were observed at accelerated conditions for assay and impurities. At long term conditions no specific trends were observed. Stability was not tested at intermediate conditions.
Based on the stability data provided, a shelf life of 24 months is granted for the pantoprazole gastro-resistant tablets in the proposed blister, with the following storage condition: Store below 25°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalo-pathies
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.

Clarithromycin 500 mg film-coated tablets

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were formulation studies and dissolution studies. The dissolution profiles of the clarithromycin batches used in the bioequivalence study are considered similar.
Bioequivalence studies were performed with a production scale batch of the drug product, with the same composition and the same manufacturing process as the future commercial batches.
The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is divided into the following steps: wet granulation, drying, sifting, blending, compression, film-coating and packaging.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for five production scale batches.
The product is manufactured using conventional manufacturing techniques.

Excipients
The excipients comply with the Ph.Eur. with the exception of the coating agents. In-house specifications have been provided. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, identification of clarithromycin, quinolone yellow and titanium dioxide, loss on drying, average mass, uniformity of dosage units, related substances, dissolution, microbial purity, related substances and assay. The release and shelf-life limits are identical except for loss on drying. The drug product specification is acceptable.
The analytical methods have been adequately described and validated.

Batch analytical data from the proposed production site have been provided on three full scale batches, demonstrating compliance to the release specification.

Stability of drug product
Stability data on the product has been provided three batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in blisters similar to the marketing packaging.
An increase in loss on drying was observed at both conditions. The increase was more pronounced at accelerated conditions than at long term conditions. Based on the photostability data provided the proposed storage condition 'Keep blister in the outer carton in order to protect from light' is considered acceptable.
Based on the stability data provided, a shelf life of 24 months can be granted for the clarithromycin film-coated tablet in the proposed blister.

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.

Amoxicillin 1000 mg film-coated tablets

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were the characterisation of the originator product, comparative dissolution studies and optimising the formulation.
Bioequivalence studies were performed with a full scale batch of the drug product. The comparative dissolution profiles of test and reference product are considered essentially similar.

Manufacturing process
The manufacturing process is divided into the following steps: wet granulation, drying, sifting, blending, compression, film-coating and packaging.
The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the final blend has been presented for five production scale batches. Furthermore process validation on the product has been presented for two production scale batches.
The product is manufactured using conventional manufacturing techniques.

Control of excipients
The excipients comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, odour, identification of amoxicillin and titanium dioxide, disintegration, dissolution, uniformity of dosage units, water content, microbial purity, related substances, ethanol content and assay. The release and shelf-life limits are identical except for total impurities and assay. The drug product specification is acceptable.
The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three full scale batches, demonstrating compliance to the drug product specification.

Stability of drug product
Stability data on the product has been provided three batches stored at 25°C/60% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in blisters similar to the marketing packaging.
An increase in related substances was observed at both conditions. The increase was more pronounced at accelerated conditions than at long term conditions. At accelerated conditions a decrease in assay was observed.
Based on the stability data provided, a shelf life of 24 months without special storage conditions can be granted for the amoxicillin film-coated in the proposed blister.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

In the manufacture of amoxicillin materials of animal origin are used. 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.

Final drug product (combination pack)

Stability of drug product
Based on the stability data of the least stable tablet (i.e. pantoprazole gastro-resistant tablet) a shelf life of 24 months with the following storage condition is granted: Store below 25°C. Based on the photostability results obtained with the clarithromycin tablet the following condition is also applicable: Keep blister in outer carton in order to protect from light.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that the three different tablets, as well as the combination pack Panclamox 40/500/1000 mg, gastro-resistant tablet/film-coated tablet/film-coated tablet, have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

The following post-approval commitments were made:

- The MAH committed to continue the on going long-term stability studies up to 24 months.
- The MAH committed to place the first three industrial scale batches on long term and accelerated stability studies.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Panclamox 40/500/1000 mg is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.1 Discussion on the non-clinical aspects

This product concerns a combination pack containing generic formulations of the innovator products Clamoxil 1000 mg, Klacid 500 mg, and Pantoloc 40 mg which are available on the European market. Reference is made tot the preclinical data obtained with the innovator products. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Pantoprazole, clarithromycin and amoxicillin are well-known active substances with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted bioequivalence studies, which are discussed below.

IV.2 Pharmacokinetics

Pantoprazole

The MAH conducted three bioequivalence studies in which the pharmacokinetic profile of the test product pantoprazole 40 mg, gastro-resistant tablet (Sandoz B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Pantoloc 40 mg (Altena Pharma, Denmark). The product was studied once under fasted conditions and twice under fed conditions.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in the bioequivalence studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence studies

Bioequivalence study I – pantoprazole under fasted conditions
Design

A single-dose, randomised, two-way crossover bioequivalence study was carried out under fasted conditions in 40 healthy male subjects, aged 20-55 years. Each subject received a single dose (40 mg) of one of the 2 pantoprazole formulations. The tablet was orally administered with 240 ml water after a 10 hour fast. There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and at 0.5, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.33, 3.67, 4.0, 4.5, 5.0, 6.0, 8.0,10.0, and 12.0 hours after administration of the products.

The design of this single-dose, crossover study to assess bioequivalence is considered adequate. The washout period of 7 days, considering the elimination half-life of approximately 1.5 hour is considered sufficient

Results
Two subjects withdrawn and did not attend for period 2 for personal reasons. The remaining 38 subjects completed the study entirely and were included in the pharmacokinetic and statistical analysis.

Table 1. Pharmacokinetic parameters (arithmetic mean ± SD, tmax as median, (range)) of pantoprazole under fasted conditions.

Treatment N=38	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5561 ± 792	6331 ± 1257	2423 ± 126	2.67 (1.33-5.0)	1.53 ± 0.23
Reference	5619 ± 786	6498 ± 1319	2631 ± 146	2.33 (1.33 4.5)	1.59 ± 0.25
***Ratio (90% CI)**	0.99 (0.95-1.04)	0.99 (0.94-1.03)	0.93 (0.88-0.99)	-	-
CV (%)	11.8	11.3	14.3	-	-

**Ln-transformed values*

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

the pharmacokinetic parameters of pantoprazole, it can be concluded that the pantoprazol 40 mg gastro-resistant tablets and Pantoloc 40 mg gastro-resistant tablets are bioequivalent under fasted conditions with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Bioequivalence study II – pantoprazole under fed conditions

Design

A single-dose, randomised, two-way crossover bioequivalence study was carried out under fed conditions in 44 healthy male subjects, aged 19-54 years. Each subject received a single dose (40 mg) of one of the 2 pantoprazole formulations. The tablet was orally administered with 240 ml water after a high-fat breakfast, consisting of 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash brown potatoes, and 240 ml whole milk. There were 2 dosing periods, separated by a washout period of at least 7 days.

Blood samples were collected pre-dose and at 1.0, 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 14.5, 15.0, 15.5, 16.0, 17.0, 18.0, 19.0, and 20 hours after administration of the products.

Results

Two subjects were withdrawn, one because of adverse events in period 1, which were judged unrelated to the study medication, and one did not attend for period 2 due to personal reasons. The remaining 42 subjects completed the study entirely. Eleven subjects were excluded from the pharmacokinetic and statistical analysis because the absorption phase was not covered in these patients for one or both of the tested medicinal products.

In principle a single-dose, crossover study to assess bioequivalence is considered adequate. Also the composition of the high-fat breakfast is considered appropriate. However, the study design is not considered acceptable because the sampling scheme is inadequate (see conclusion).

Table 2. Pharmacokinetic parameters (arithmetic mean ± SD, tmax as median, (range)) of pantoprazole under fed conditions.

Treatment N=31	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	6217 ± 1040	7551 ± 1638	2551 ± 154	6.5 (3-13.5)	2.2 ± 0.4
Reference	6850 ± 1257	8004 ± 1802	2623 ± 172	6.5 (3-16)	2.5 ± 0.6
***Ratio (90% CI)**	0.94 (0.84-1.05)	0.95 (0.86-1.05)	0.99 (0.83-1.17)	-	-
CV (%)	26.6	23.3	40.4	-	-

**Ln-transformed values*

Conclusion

In this study it has not been shown adequately that pantoprazole 40 mg gastro-resistant tablets and Pantoloc 40 mg gastro-resistant tablets are bioequivalent under fed conditions. The study design is not considered acceptable since the sampling schedule was not adequate. The purpose of a fed study for gastro-resistant formulation is to exclude the possibility of dose-dumping. The absorption phase was not covered in 11 out of 42 evaluable volunteers. It can not be excluded that the complete absence of pantoprazole plasma exposure is caused by dose dumping and subsequent acid degradation of pantoprazole in the stomach.

Notably, in 10 out of 11 excluded volunteers the test product was absorbed too late, which was the case in 5 out of 11 for the reference product. (in 4 cases both test and reference). Overall, absorption of the test product under fed conditions appears later than that of the reference product. Additional studies are required to demonstrate bioequivalence under fed conditions (see below).

Bioequivalence study III – pantoprazole under fed conditions

Design

A single-dose, randomised, two-way crossover bioequivalence study was carried out under fed conditions in 74 healthy male subjects, aged 20-55 years. Each subject received a single dose (40 mg) of one of the 2 pantoprazole formulations. The tablet was orally administered with 240 ml water after a high-fat breakfast, consisting of 2 eggs fried in butter, 2 strips of bacon, 1 English muffin with 11 g of butter, 4 ounces of hash brown potatoes, and 240 ml whole milk. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 2.0, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10.0, 10.5, 11.0, 11.5, 12.0, 12.5, 13.0, 13.5, 14.0, 15.0, 16.0, 17.0, 18.0, 18.5, 19.0, 19.5, 20.0, 20.5, 21.0, 21.5, 22.0, 23.0, 24.0, 26.0, 28.0, and 30.0 hours after administration of the products.

The design of this single-dose, crossover study to assess bioequivalence under fed condition is considered appropriate. The composition of the high-fat breakfast is considered adequate.

Results
Six subjects were withdrawn from the study: three due to adverse events (vomiting, rash, and hyperhidrosis and syncope) and three did not attend for period 2 for personal reasons. The remaining 68 subjects completed the study entirely and were included in the pharmacokinetic and statistical analysis.

Table 3. Pharmacokinetic parameters (arithmetic mean ± SD, tmax as median, (range)) of pantoprazole under fed conditions.

Treatment N=68	**AUC_{0-t}** ng/ml/h	**$AUC_{0-\infty}$** ng/ml/h	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	5565 ± 4534	5970 ± 5916	2453 ± 751	7.0 (2.0-22.0)	1.6 ± 1.5
Reference	5977 ± 4853	6327 ± 6137	2768 ± 771	6.0 (3.0-22.0)	1.5 ± 1.5
***Ratio (90% CI)**	0.93 (0.91-0.95)	0.93 (0.91-0.96)	0.88 (0.83-0.92)	-	-
CV (%)	61.8	65.2	25.0	-	-

**Ln-transformed values*

Conclusion
The 90% confidence intervals calculated for $AUC_{0-t,}$ $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of pantoprazole, it can be concluded that the pantoprazol 40 mg gastro-resistant tablets and Pantoloc 40 mg gastro-resistant tablets are bioequivalent under fed conditions with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Overall conclusion of the bioequivalence studies for pantoprazole 40 mg, gastro-resistant tablets
Based on bioequivalence studies I and III it can be concluded that the pantoprazol 40 mg gastro-resistant tablets and Pantoloc 40 mg gastro-resistant tablets are bioequivalent under both fasted and fed conditions with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Clarithromycin
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product clarithromycin 500 mg, film-coated tablet (Sandoz B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Klacid 500 mg tablet (Abbott B.V., the Netherlands).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in the bioequivalence studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable. However, the proposed broadening of the CI interval for Cmax is not considered acceptable, as a high intra-subject variability for Cmax is not shown. But as the results of the statistical analysis showed that AUC and Cmax are within the acceptable limits of 0.80-1.25, this issue is not relevant and the study design is accepted.

Design
A single-dose, randomised, two-way crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects, 18 males and 18 females, aged 21-41 years. Each subject received a single dose (500 mg) of one of the 2 clarithromycin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 6 hours after dosing. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.0, 1.33, 1.67, 2.0, 2.33, 2.67, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0 and 48.0 hours after administration of the products.

The design of this single-dose, crossover study under fasted conditions to assess bioequivalence is considered adequate. Clarithromycin may be taken without reference to food intake. Therefore a study under fasting condition is sufficient.

Results
One subject withdrew from the study. The remaining 35 subjects completed the study entirely and were included in the pharmacokinetic and statistical analysis.

Table 4. Pharmacokinetic parameters (arithmetic mean ± SD) of clarithromycin under fasted condition.

Treatment N=35	**AUC_{0-t}** mcg/ml/h	**$AUC_{0-\infty}$** mcgi/ml/h	**C_{max}** mcg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	13.9 ± 4.4	14.1 ± 4.5	1.85 ± 0.61	1.70 ± 0.70	4.5 ± 1.3
Reference	13.7 ± 4.3	13.8 ± 4.4	1.79 ± 0.71	1.55 ± 0.72	4.6 ± 1.4
***Ratio (90% CI)**	1.02 (0.96-1.08)	1.02 (0.96-1.08)	1.06 (0.95-1.19)	-	-
CV (%)	14.9	14.4	28.3	-	-

**Ln-transformed values*

Conclusion
The 90% confidence intervals calculated for $AUC_{0-t,}$ $auc_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of clarithromycin under fasted conditions, it can be concluded that clarithromycin 500 mg, film-coated tablets and Klacid 500 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

Amoxicillin
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product amoxicillin 1000 mg, film-coated tablet (Sandoz B.V., the Netherlands) was compared with the pharmacokinetic profile of the reference product Clamoxyl 1 g tablets (SmithKline-Beecham Pharma, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods

The analytical methods have been adequately validated and are considered acceptable for analysis of the plasma samples. The methods used in the bioequivalence studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Design
A single-dose, randomised, two-way crossover bioequivalence study was carried out under fasted conditions in 20 healthy subjects, aged 19-36 years, two alternates were included. Each subject received a single dose (1000 mg) of one of the 2 amoxicillin formulations. The tablet was orally administered with 240 ml water after an overnight fast. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of at least 14 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0 and 10.0 hours after administration of the products.

The design of this single-dose, crossover study under fasted conditions to assess bioequivalence is considered adequate. Fasting conditions were applied, which is appropriate as food does not influence the absorption of amoxicillin.

Results
One subject withdrew from the study and was replaced by one of the alternates in the analyses. 21 subjects completed the study entirely, 20 subjects were included in the pharmacokinetic and statistical analysis.

Table 5. Pharmacokinetic parameters (arithmetic mean ± SD) of amoxicillin under fasted condition.

Treatment N=20	**AUC_{0-t}** mcg/ml/h	**$AUC_{0-\infty}$** mcgml/h	**C_{max}** mcg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	43.3 ± 9.7	44.9 ± 10.2	14.9 ± 3.8	1.5 ± 0.4	1.2 ± 0.4
Reference	44.1 ± 11.7	45.5 ± 11.9	15.0 ± 3.8	1.4 ± 0.3	1.2 ± 0.6
***Ratio (90% CI)**	1.00 (0.93-1.07)	-	1.00 (0.93-1.07)	-	-
CV (%)	12.4	-	13.6	-	-

**Ln-transformed values*

Conclusion
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80–1.25. Based on the pharmacokinetic parameters of amoxicillin under fasted conditions, it can be concluded that amoxicillin 1000 mg, film-coated tablets and Clamoxyl 1 g tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

The MEB has been assured that all 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).

Overall conclusion bioequivalence of the combination pack
For the combination pack consisting of a 40 mg pantoprazol gastro-resistant tablet, a 500 mg clarithromycin tablet, and a 1000 mg amoxicillin tablet, bioequivalence has been shown with the individual reference products, i.e. Pantoloc 40 mg gastro-resistant tablet (Altena Pharma, Denmark), Klacid 500 mg (Abbott B.V., the Netherlands), and Clamoxil 1000 mg (SmithKline-Beecham Pharma, Germany) respectively. For the pantoprazole gastro-resistant tablet bioequivalence has been shown under fasting and fed conditions.

IV.3 Risk Management Plan

The MAH has not submitted a risk management plan for Panclamox 40/500/1000 mg/gastro-resistant tablet/film-coated tablet/film-coated tablet, as this was not required at the time of dossier submission. Routine pharmacovigilance activities in accordance with EU regulations will be undertaken whilst the product is authorized. As the safety profiles of the products included in the combination pack are well-established, a Risk Minimisation Plan is not considered necessary.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product ZacPac. No new clinical studies were conducted. The MAH demonstrated through bioequivalence studies that the pharmacokinetic profiles of the products included in the combination pack are similar to the pharmacokinetic profiles of the three reference products for the individual tablets. The pharmacovigilance system of the MAH fulfils the requirements. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging study between Panclamox 40/500/1000 mg/gastro-resistant tablet/film-coated tablet/film-coated tablet and Helicomp Sandoz (omeprazole/amoxicillin/clarithromycin 20/1000/500 mg). Bridging is acceptable because both medicinal products belong to the same therapeutic class, are used for the same indication and the method of administration is identical. Additional text which had to be included due to product-specific information is derived from other readability-approved PLs. Further, regarding layout reference is made to the successfully user tested PLs for other products of the same MAH. The user tests for these leaflets confirm that the MAH's house style does not affect readability of the PL. The bridging report has been found acceptable. Separate user testing is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The three individual tablets in Panclamox 40/500/1000 mg/gastro-resistant tablets/film-coated tablets/film-coated tablets have a proven chemical-pharmaceutical quality. The product is a generic form of ZacPac. ZacPac and its individual components are well-known medicinal products with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents for all three tablet formulations.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Panclamox 40/500/1000 mg/gastro-resistant tablets/film-coated tablets/film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 September 2013.

The MAH committed to adapt the product information in accordance with the final text resulting from the article 30 referral that will be initiated for amoxicillin.

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	Assess-ment report attached
Update of SPC and PIL to align texts with P-RMS FAR IE/H/PSUR/0020/002	NL/H/2449/001/IB/ 001	IB variation	13 January 2014	21 March 2014	Approved	N
New certificate of suitability from a new manufacturer	NL/H/2449/001/IA/ 002	IA variation	4 March 2014	3 April 2014	Valid	N
Deletion imprint "imprinted 40 in black" on the yellow oval coated tablet.	NL/H/2449/001/IA/ 003	IA variation	5 June 2014	5 July 2014	Valid	N
Update SmPC and PI in order to include Pantoprazole DE/H/ PSUR/0039/001.	NL/H/2449/001/IB/ 004	IB variation	24 June 2014	24 July 2014	Approved	N