

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

**Clarithromycine Sandoz 250 mg and 500 mg, film-coated tablets
Sandoz B.V., the Netherlands**

clarithromycin

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/2087/001-002/DC
Registration number in the Netherlands: RVG 107886, 107902**

17 November 2011

Pharmacotherapeutic group:	Macrolides
ATC code:	J01FA09
Route of administration:	oral
Therapeutic indication:	acute and chronic bacterial infections caused by micro-organisms susceptible to clarithromycin in adults and adolescents 12 years and older (see next page)
Prescription status:	prescription only
Date of authorisation in NL:	23 September 2011
Concerned Member States:	Decentralised procedure with BE, BG, EL, ES, PL, RO, SK, additionally for 500 mg only - LU
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Claritromycine Sandoz 250 mg and 500 mg, film-coated tablets from Sandoz B.V. The date of authorisation was on 23 September 2011 in the Netherlands.

The product is indicated in adults and adolescents 12 years and older for the treatment of the following infections, when caused by clarithromycin-susceptible bacteria (see sections 4.4 and 5.1 of the approved SPC):

- Bacterial pharyngitis
- Acute bacterial sinusitis
- Acute bacterial exacerbation of chronic bronchitis
- Mild to moderate community acquired pneumonia
- Skin infections and soft tissue infections of mild to moderate severity, for example folliculitis, cellulitis and erysipela
- in appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing medicinal product for the eradication of *Helicobacter pylori* in patients with *Helicobacter pylori* associated ulcers.

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

Clarithromycin, a semi-synthetic derivative of erythromycin, exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin are generally two-fold lower than the MICs of erythromycin.

The 14-hydroxy metabolite of clarithromycin also has antimicrobial activity. The MICs of this metabolite are equal or two-fold higher than the MICs of the parent compound, except for *H. influenzae* where the 14-hydroxy metabolite is two-fold more active than the parent compound.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Klacid 250 mg and 500 mg film-coated tablets (NL License RVG 14152 and 17902 respectively) which have been registered in the Netherlands by Abbott B.V. since 1990 and 1994, respectively. In addition, reference is made to Klacid 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 study in which the pharmacokinetic profile of the 250 mg and 500 mg products is compared with the pharmacokinetic profile of the reference products Klaracid 250 mg and Klacid 500 mg film-coated tablets, registered in the UK and the Netherlands, respectively. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

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

Active substance

The active substance is clarithromycin, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white crystalline powder, which is soluble in acetone and methylene chloride, slightly soluble in methanol, ethanol and acetonitrile and practically insoluble in water. Clarithromycin appears in different polymorphic forms which are distinguished by X-ray diffraction. The polymorphic form used is form II.

The CEP procedure is used for both suppliers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of 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 new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

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 of the MAH is in line with the Ph.Eur. monograph and the additional requirements from the two CEPs. Batch analytical data demonstrating compliance with the drug substance specification have been provided on four batches.

Stability of drug substance

For one manufacturer, stability studies were conducted on six batches under long-term (36 months) and accelerated conditions. For the other supplier, stability studies were conducted on three batches under long-term (36 months) and accelerated conditions.

Based on the submitted stability data the claimed re-test period of 36 months was granted for the active substance from both manufacturers.

* *Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition

Clarithromycine Sandoz 250 mg is a dark yellow, film-coated capsule shaped tablet (15.6 x 7.9 mm).

Clarithromycine Sandoz 500 mg is a light yellow, film-coated oval shaped tablet (18.8 x 8.8 mm).

The film-coated tablets are packed in PVC/PVDC aluminium blisters.

The excipients are:

Core - croscarmellose sodium (E 468), microcrystalline cellulose (E 460), povidone, magnesium stearate (E 572), colloidal anhydrous silica (E 551), talc (E 553b)

Coating - hypromellose (E 464), propylene glycol (E 1520), titanium dioxide (E171), hydroxypropylcellulose (E 463), sorbitan monooleate (E494), quinolin yellow (E104), vanillin.

The tablet cores are fully dose proportional.

Pharmaceutical development

The pharmaceutical development of the product has been described, the choice of excipients is justified and their functions explained. The main development studies performed were comparative dissolution studies and optimising the manufacturing process.

Two bioequivalence studies were performed: one for each tablet strength. The batches used in the bioequivalence studies have the same composition and are manufactured in the same way as the commercial batches. Dissolution comparison tests have only been done at two pH levels. This was accepted, as the drug products were unstable at a third pH level.

The pharmaceutical development has been described in sufficient detail.

Manufacturing process

The tablets are manufactured by wet granulation followed by direct compression and film coating. This considered a standard process. The manufacturing process has been adequately validated. The MAH has submitted a clear narrative description and a flow diagram. Validation protocols and reports for two qualifying batches of each strength and three production-scale batches of each strength have been provided.

Control of excipients

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

Quality control of drug product

The product specification includes tests for appearance, identification, average mass, uniformity of dosage units, loss on drying, dissolution, assay, related substances and microbial contamination. The release and end of shelf-life requirements are identical, except for loss of drying, where a slightly higher end of shelf-life specification is applied. This difference is justified.

The analytical methods have been satisfactorily validated. Batch analytical data have been provided on on three batches of each strength, demonstrating compliance with the specifications.

Stability of drug product

Stability data on the product has been provided for four pilot-scale batches and six full-scale batches (three of each strength) stored at 25°C/40%RH (60 and 36 months), 30°C/65%RH (60 and 36 months) and 40°C/25%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. All tested parameters remained within specification. In general, an increase for the loss of drying was noted at accelerated and long-term conditions in the earlier batches, however the commercial scale batches show a less pronounced trend. For the other tested parameters no clear trend is observed. Photostability testing was performed in accordance with ICH requirements and demonstrated that a small increase in impurity content. Therefore, the drug product should be stored protected from light and kept in the outer carton.

Based on the data provided, the proposed shelf-life of 36 months was granted; the drug product should be stored in the outer carton in order to protect it from light.

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 Klacid tablets, 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 clarithromycin 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

Clarithromycin 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 products Claritromycine Sandoz 250 mg and Claritromycine Sandoz 500 mg (Sandoz B.V., NL) is compared with the pharmacokinetic profile of the reference products Klaricid 250 mg (Abbott, UK) and Klacid 500 mg tablets (Abbott, NL).

The choice of the reference product

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

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

Bioequivalence study I – 250 mg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects (18 males/18 females), aged 18-43 years. Each subject received a single dose (250 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 at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 16, 24 and 36 hours after administration of the products.

Analytical/statistical methods

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

Results

All subjects completed the study and results of 36 subjects were included in the analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean \pm SD) of clarithromycin under fasted conditions.

Treatment N=36	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/ml	t _{max} h	t _{1/2} h
Test	5.77 \pm 2.91	5.95 \pm 2.91	0.91 \pm 0.46	1.82 \pm 2.06	4.3 \pm 1.8
Reference	5.66 \pm 1.90	5.79 \pm 1.92	0.92 \pm 0.33	1.33 \pm 0.71	3.9 \pm 1.1
*Ratio (90% CI)	0.99 (0.92-1.08)	1.00 (0.93-1.08)	0.95 (0.84-1.07)	--	--
CV (%)	20.1	19.5	30.8	--	--

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

**In-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, AUC_{0-∞} 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 Clarithromycine Sandoz 250 mg and Klaricid 250 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.

Bioequivalence study II – 500 mg tablet

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects (18 males/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 at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 12, 16, 24, 36 and 48 hours after administration of the products.

Analytical/statistical methods

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

Results

There was one drop-out. The remaining 35 subjects completed the study and were included in the analysis.

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

Treatment N=35	AUC _{0-t} µg.h/ml	AUC _{0-∞} µg.h/ml	C _{max} µg/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	--	--

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

**In-transformed values*

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 Claritromycine Sandoz 500 mg 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.

Clarithromycin may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of clarithromycin. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

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

Clarithromycin was first approved in 1989, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of clarithromycin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product. Furthermore, the text has been updated conform the agreed Core Safety Profile (CSP).

Readability test

The package leaflet has been evaluated via a user consultation study. Instead, a bridging report was submitted. Reference is made to a successfully user tested PIL for a clarithromycin 250 mg product (parent PL).

The bridging report presents a side by side comparison of the leaflet text from the user-tested parent PL and the daughter PL. The textual differences for each section are discussed where applicable. The small differences are not considered to negatively influence the readability of the PL.

Overall, the leaflet content of parent and daughter PL is considered to be sufficiently similar to allow bridging. The MAH's house style has passed user tests in a substantial number of recently approved procedures. The layout and style of the daughter PL is considered acceptable. No separate user testing is required.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Clarithromycine Sandoz 250 mg and 500 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Klacid 250 mg and 500 mg film-coated tablets. Klacid 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 MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

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

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Claritromycine Sandoz 250 mg and 500 mg with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 August 2011. Claritromycine Sandoz 250 mg and 500 mg, film-coated tablets were authorised in the Netherlands on 23 September 2011.

The date for the first renewal will be: 22 January 2016.

There were no post-approval commitments made during the procedure.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
t _{1/2}	Half-life
t _{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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