CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Claritromycine Sandoz 125 mg/5 ml and 250 mg/5 ml, granules for oral suspension 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/2099/001-002/DC
Registration number in the Netherlands: RVG 108098-108099

2 May 2012

Pharmacotherapeutic group:	antiinfectives for systemic use, macrolides
ATC code:	J01FA09
Route of administration:	oral
Therapeutic indication:	acute and chronic infections, when caused by clarithromycin susceptible organisms in adults, adolescents and children, 6 months to 12 years (see next page)
Prescription status:	prescription only
Date of first authorisation in NL:	20 January 2012
Concerned Member States:	Decentralised procedure with BE, BG, EE, EL, IT, LT, PL, RO, SK
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 125 mg/5 ml and 250 mg/5 ml, granules for oral suspension from Sandoz B.V. The date of authorisation was on 20 January 2012 in the Netherlands.

The product is indicated in adults, adolescents and children, 6 months to 12 years, for the treatment of the following acute and chronic infections, when caused by clarithromycin susceptible organisms.

- Infections of the upper respiratory tract such as tonsillitis/pharyngitis, as an alternative when beta lactam antibiotics are not appropriate.
- Acute otitis media in children.
- Infections of the lower respiratory tract such as community acquired pneumonia.
- Sinusitis and acute exacerbation of chronic bronchitis in adults and adolescents over 12 years of age
- Skin infections and soft tissue infections of mild to moderate severity.

In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing medicinal product for the eradication of *Helicobacter pylori* in adult patients with *H. 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 anti-bacterial 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 *Haemophilus 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 product Klacid. The first registration was for Klacid 250 mg tablet (NL License RVG 14152) was obtained in the Netherlands by Abbott B.V. on 20 November 1990 (original product). Klacid 125 mg/5 ml and 250 mg/5 ml, granules for suspension (NL License RVG 105868, 16752) are registered in the Netherlands since 15 October 1993 and 17 October 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 studies in which the pharmacokinetic profile of the products is compared with the pharmacokinetic profile of the reference products Klacid 125 mg/5 ml and 250 mg/5 ml oral suspension, registered in the Netherlands. 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.*). The drug substance 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 can be distinguished in the manufactured form. The active substance is form II.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of 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
A CEP has 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 CEP. Batch analytical data demonstrating compliance with the drug substance specification have been provided.

Stability of drug substance
Stability studies were conducted on three clarithromycin powder batches and two clarithromycin microfine batches, packed into the commercial packaging under long-term (36 months) and accelerated (6 months) conditions.
Under long term and accelerated stability conditions all results stayed within specifications. Based on these observations a retests period of 36 months and the proposed storage conditions (at room temperature) were granted.
The MAH committed to place 3 batches of clarithromycin under long-term ICH conditions.

** 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
Claritromycine Sandoz 125 mg/5 ml and 250 mg/5 ml are white to beige granules, after reconstitution with water resulting in a white to beige suspension.

After reconstitution 1 ml oral suspension contains either 25 or 50 mg clarithromycin, 5 ml oral suspension contains 125 or 250 mg clarithromycin.

The granules are packed in 60 ml, 120 ml and 240 ml HDPE bottles with child resistant PP-screw closures, an oral PE/PP-measuring syringe (5 ml) with filling marks at 2.5 ml, 3.75 ml and 5.0 ml and a PE/PP-measuring spoon with filling marks at 1.25 ml, 2.5 ml and 5.0 ml.

Pack sizes:
125 mg/5 ml
1 bottle contains 34.1 g granules for oral suspension for 50 ml ready-for-use suspension (required water amount: 29.5 g) or
41.0 g granules for oral suspension for 60 ml ready-for-use suspension (required water amount: 35.4 ml) or
54.6 g granules for oral suspension for 80 ml ready-for-use suspension (required water amount: 47.2 ml) or
68.3 g granules for oral suspension for 100 ml ready-for-use suspension (required water amount: 59.0 ml) or
81.9 g granules for oral suspension for 120 ml ready-for-use suspension (required water amount: 70.8 ml).

250 mg/5 ml
1 bottle contains 34.1 g granules for oral suspension for 50 ml ready-for-use suspension (required water amount: 28.5 ml) or
41.0 g granules for oral suspension for 60 ml ready-for-use suspension (required water amount: 34.2 ml) or
54.6 g granules for oral suspension for 80 ml ready-for-use suspension (required water amount: 45.6 ml) or
68.3 g granules for oral suspension for 100 ml ready-for-use suspension (required water amount: 57.0 ml).

The excipients are: poloxamer 188, povidone K 30 (E1201), hypromellose (E464), macrogol 6000, titanium dioxide (E171), methacrylic acid – ethyl acrylate copolymer (1:1), triethyl citrate (E1505), glycerol monostearate, polysorbate 80 (E433), sucrose, maltodextrin, potassium sorbate (E202), colloidal anhydrous silica (E551), xanthan gum (E415), fruit punch flavouring (natural and artificial flavouring substances including maltodextrin, modified starch and maltol).

The finished dosage form consists of coated micro pellets containing the drug substance clarithromycin, which are embedded in a suspension base with powdered sucrose as the main component. The total weight of both strengths is identical. The total weight of both strengths is identical. For the 125 mg/5 ml form half the amount of micro pellets is used, which is compensated by the carrier maltodextrin. Both strengths are fully dose proportional with the exception of some differences in the excipients of the granules.

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. A 5% filling overage of the final granules in the plastic bottles is used in order to comply with the requirement on deliverable volume of the USP.
Two bioequivalence studies were performed, both strengths were included. The batches used in the bioequivalence studies have the same composition and are manufactured in the same way as the commercial batches. For the comparative dissolution studies the MAH used three different pH values other than those described in the applicable guideline. However, an acceptable explanation was given: as the use of the gastric resistance coating will prevent dissolution of the drug substance at lower pH values.

Manufacturing process

The manufacturing process of the granules includes the production of coated and taste-masked micropellets, followed by the manufacturing of the granules.
Validation protocols and reports for qualifying batches of five micropellet batches, three coated micropellet batches, and three granules batches have been provided. The validation of the commercial production was carried out with 10 commercial batches of micropellets manufactured at one production site and 3 commercial batches of granules manufactured at another site.

Control of excipients
All the excipients, except for fruit punch dry flavouring, comply with the Ph.Eur. The specifications for testing the fruit punch dry flavouring were established in-house. These specifications are acceptable.

Microbiological attributes
Potassium sorbate was chosen as preservative in a common concentration of 20 mg/dose unit. The same excipient is used by the originator in the same dosage range. The anti-microbial effectiveness test was conducted with and without citric acid using the fixed quantity of potassium sorbate. Both variants met the specifications. The test is repeated at the beginning and the end of shelf-life of the stability batches.
The test on efficacy of antimicrobial preservation was performed according to Ph.Eur., Category 3 (oral preparations). All the samples i.e. with preservative (potassium sorbate) concentrations of 70%, and 100% of declared content comply with the requirements for the test of efficacy of antimicrobial preservation for oral preparations as per Ph.Eur.

Quality control of drug product
The product specification includes tests for appearance, identification, average and individual filling mass, loss on drying, suspensibility, resuspensibility, dissolution, viscosity, pH, assay, related substances and microbial contamination. The release and end of shelf-life requirements are identical, except for assay of potassium sorbate.
The analytical methods have been satisfactory validated. The MAH has analyzed a sufficient number of batches produced at each manufacturing site. Batch analytical data provided comply with the specifications. The MAH committed to test the taste masking capabilities according to the protocol.

Stability of drug product
Stability data on the product has been provided for three (125 mg) and seven (250 mg) pilot-scale batches and seven full-scale batches (125 and 250 mg) stored at 25°C/60% RH (36 and 24 months), 30°C/60% RH (12 months), 30°C/70% RH (36 months), 40°C/75% RH (6 months) and 30°C/65% (24 months) packed in HPDE bottles. Also data has been provided for five batches of the micropellets stored at 25°C/60% RH (12 and 24 months) and at 40°C/75% RH (6 months) packed in compound pack.
With the exception of the assay of potassium sorbate, all tested parameters are within specifications and no clear trend or significant changes are observed. For the assay of potassium sorbate a clear downward trend is observed at both long term and intermediate conditions. In several cases for batches stored at 30°C/70%RH for 36 months, the end of shelf-life limits are exceeded.
Based on the provided data a re-test period of 36 months and the claimed storage conditions of “do not store above 25 °C” can be granted.
The MAH committed to submit the photostability report post approval.

Ready for use stability study
Ready for use stability study has been performed on the granules. Testing points were, 0, 7, 10 and 14 days after reconstitution. Products were tested at the beginning and at the end of the stability test program. The following parameters were investigated: appearance, suspensibility, pH, assay (Clarithromycin and potassium sorbate), related substances and microbial contamination. The preservative effectiveness test is performed at the beginning and the end of the shelf-life. No clear trend or significant changes in any of the tested parameters was observed. The product remains stable throughout the test period. The claimed shelf-life of 14 days for the ready to use suspension is justified.

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, 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 125 mg/5 ml and 250 mg/5 ml (Sandoz B.V., NL) is compared with the pharmacokinetic profile of the reference product Klacid 125 mg/5 ml and 250 mg/5 ml granules for oral suspension (Abbott B.V., NL).

The choice of the reference products
The choice of the reference products in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states.
The formula and preparation of the bioequivalence batches 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 studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I – 125 mg/5 ml
Design
A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy subjects (20 males, 12 females), aged 21-43 years. Each subject received a single dose (125 mg/5 ml) of one of the 2 clarithromycin formulations. The suspension was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 6 hrs 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.

Results
All subjects completed the study and results of the 32 subjects were included in the analysis.

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

Treatment N=32	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h

Test	6.95 ± 2.21	7.09 ± 2.26	1.10 ± 0.30	2.10 ± 0.88	3.6 ± 0.8
Reference	7.61 ± 2.10	7.74 ± 2.14	1.22 ± 0.30	2.99 ± 0.77	3.8 ± 0.7
***Ratio (90% CI)**	0.91 (0.87-0.94)	0.90 (0.85-0.95)	0.88 (0.83-0.95)	--	--
CV (%)	12.6	12.5	14.1	--	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

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 125 mg/5 ml and Klacid 125 mg/5 ml granules for oral suspension 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 – 250 mg/5 ml

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 32 healthy subjects (17 males, 15 females), aged 21-44 years. Each subject received a single dose (250 mg/5 ml) of one of the 2 clarithromycin formulations. The suspension was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 6 hrs 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.

Results

All subjects completed the study and results of the 32 subjects were included in the analysis.

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD) of clarithromycin under fasted conditions.

Treatment N=32	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	17.4 ± 4.8	17.6 ± 4.8	2.19 ± 0.61	2.30 ± 0.73	4.8 ± 1.0
Reference	17.5 ± 4.5	17.7 ± 4.5	2.42 ± 0.59	3.38 ± 0.95	4.5 ± 1.0
***Ratio (90% CI)**	0.99 (0.95-1.03)	0.99 (0.95-1.03)	0.90 (0.86-0.94)	--	--
CV (%)	9.9	9.8	10.6	--	--

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

**ln-transformed values*

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 250 mg/5 ml and Klacid 250 mg/5 ml granules for oral suspension 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 study has 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 another recently approved clarithromycin product.

Readability test

The package leaflet has not been evaluated via a user consultation study. Instead, a bridging report has been provided with reference to another PIL that has been successfully user tested. The explanation of differences in lay-out have been adequately dealt with and pose no difficulties with respect to readability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Claritromycine Sandoz 125 mg/5 ml and 250 mg/5 ml, granules for oral suspension have a proven chemical-pharmaceutical quality and are generic forms of Klacid 125 mg/5 ml and 250 mg/5 ml, granules for suspension. 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 is consistent with that of the reference product. 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 125 mg/5 ml and 250 mg/5 ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 7 November 2011. Claritromycine Sandoz 125 mg/5 ml and 250 mg/5 ml, granules for oral suspension were authorised in the Netherlands on 20 January 2012.

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

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

Quality - active substance
- The MAH committed to place 3 batches of clarithromycin under long-term ICH conditions.

Quality - medicinal product
- The MAH committed to test the taste masking capabilities according to the protocol.
- The MAH committed to submit the photostability report for the granules for oral suspension.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

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