CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Claritromycine ratiopharm 250 mg and 500 mg film-coated tablets ratiopharm Nederland 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/2597/001-002/DC
Registration number in the Netherlands: RVG 111801 - 111802

23 September 2013

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 first authorisation in NL:	11 February 2014
Concerned Member States:	Decentralised procedure with DE, ES, FR, 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 ratiopharm 250 mg and 500 mg film-coated tablets, from ratiopharm Nederland B.V. The date of authorisation was on 11 February 2014 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 erysipelas

In an 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).
In The Netherlands however, both reference products were withdrawn on 31 December 2010. Therefore, for the RMS, reference is made to historical Reference medicinal products.

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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Klacid 500 mg film-coated tablets, registered in the United Kingdom. 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, 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 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
The CEPs for clarithromycin do not mention the re-test period for the drug substance. Stability data on the active substance were provided for several validation batches stored at long-term conditions (25±2°C / 60±5% RH, up to 60 months) and accelerated conditions 40±2°C / 75±5% RH (6 months). The batches remained stable under accelerated and long-term storage conditions for all parameters tested. No specific trends were observed. Based on the provided stability data, a re-test period of 60 months is acceptable.
A photostability test is performed in line with the "Note for Guidance on Photostability Testing of New Active Substances and Medicinal Products". The results show that the drug product is not light sensitive.

** 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 ratiopharm 250 mg is a yellow, oval shaped film-coated tablet, debossed with "93" on one side and "7157" on the other (length: 17mm, width: 8mm, thickness: 5-6mm).

Claritromycine ratiopharm 500 mg is a light yellow, oval shaped film-coated tablet, debossed with “93” on one side and “7158” on the other (length: 22mm, width: 11mm, thickness: 6.7-7.7mm).
The film-coated tablets are packed in blister packs of transparent or white opaque PVC or PVC/PVdC, lidded with aluminium foil.

The excipients are:
Tablet core: sodium starch glycolate (type A), microcrystalline cellulose (E460), povidone (PVP K-30) (E1201), magnesium hydroxide (E528), croscarmellose sodium, colloidal anhydrous silica, stearic acid (E570), magnesium stearate (E470b).
Film coating: hypromellose (E464), titanium dioxide (E171), macrogol 400, tartrazine lake (E102), allura red AC lake (E129), indigo carmine lake (E132), vanillin.

The excipients and packaging are usual for this type of dosage form.

Both tablet strengths are fully dose proportional, with the exception of some differences in the film coating.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. The excipients used are common in oral drug products. The product development objective was to develop a film-coated tablet that would be bioequivalent to the UK innovator product Klaricid®.
A wet granulation method was chosen and optimised during pharmaceutical development. A bioequivalence study for the 500 mg was carried out and a waiver is granted for the 250 mg.
The packaging material is commonly used for solid oral dosage forms. The suitability of the packaging material was tested in stability studies. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The tablets are manufactured by wet granulation followed by direct compression and film coating. This is considered a standard process. The manufacturing process has been adequately validated. The MAH has submitted a clear narrative description and a flow diagram. The manufacturing process has been validated according to relevant European Guidelines. Process validation data on the product was presented for three production batches of each strength for both production sites.

Control of excipients
With the exception of the coating material, all excipients comply with the European Pharmacopoeia. For the coating material, a separate specification was provided. The analytical methods are adequately described. Specifications of the excipients are acceptable.

Quality control of drug product
The drug product specification includes tests for description, identification (HPLC by assay method and HPLC by dissolution method), dissolution, uniformity of dosage units, assay, impurities and degradation products, identification of titanium dioxide, loss on drying and microbial contamination. The release and shelf life limits are identical with the exception of loss of drying. The drug product specification is acceptable.
The analytical methods were adequately described. Batch analytical data were provided for nine batches (six batches of the minimum (site I) and three batches of the maximum proposed batch size (site II)) of each strength, demonstrating compliance with the proposed release specification.

Stability of drug product
Stability data on the drug product was provided on two pilot scale batches of each strength, stored at 25°C/60% (up to 36 months), 30°C/60% (12 months) and 40ºC/75% RH (up to 6 months). The batches were stored in the proposed commercial packaging. Stability data was also provided on two production batches; one of each strength. The conditions used in the stability studies are according to the ICH stability guideline. A photostability study has been performed.

Under long-term conditions, except for a slight increase in water content, all stability indicating parameters remain stable for all batches tested. However, for the pilot batches under accelerated testing and for one production batch under accelerated as well as under intermediate conditions, the dissolution is out of specification. The results show that the drug product is not light sensitive.
In view of the provided stability data, a shelf-life of 24 months is acceptable for the product in both packagings, when stored below 25ºC.

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. 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.

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 a bioequivalence study in which the pharmacokinetic profile of the test product Claritromycine ratiopharm 500 mg film-coated tablets is compared with the pharmacokinetic profile of the reference product Klacid 500 mg tablets.

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products (if applicable) in different member states.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Design
A single-dose, 2-way crossover bioequivalence study was carried out under fasted conditions in sixty healthy male subjects, aged 19-53 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. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected at pre-dose and at 0.33, 0.67, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, and 36 hours after administration of the products.

The study design is acceptable. A GCP statement has been provided.

Analytical/statistical methods
The analytical method has been adequately validated and is 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

Two subject were withdrawn from the study after Period 1 for personal reasons and one subject was withdrawn due to a positive urine test on opiates. 57 subjects completed the study and were included in the analyses. Plasma samples were analysed for clarithromycin and its metabolite 12-OH-clarithromycin.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of clarithromycin under fasted conditions.

Treatment N=57	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	14300 ± 5273	14717 ± 5276	1787 ± 650	2.0 (0.67 – 5.0)	5.0 ± 1.7
Reference	15625 ± 257	15946 ± 6328	1983 ± 734	2.0 (1.0 – 6.0)	4.5 ± 1.1
***Ratio (90% CI)**	0.88 – 0.96	0.88 – 0.96	0.83 – 0.97	-	-
CV (%)	16%	15%	25%	-	-

$AUC_{0-\infty}$ 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*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 12-OH-clarithromycin under fasted conditions.

Treatment N=57	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	9172 ± 1719	9661 ± 1888	811 ± 225	2.0 (1.0 – 5.0)	7.8 ± 2.7
Reference	9587 ± 1876	9917 ± 1942	865 ± 231	2.0 (1.0 – 6.0)	7.1 ± 1.4
***Ratio (90% CI)**	0.92 – 1.00	0.94 – 1.01	0.88 – 1.00	-	-
CV (%)	12%	12%	21%	-	-

$AUC_{0-\infty}$ 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 and supported by the data from 12-OH-clarithromycin, it can be concluded that Claritromycine ratiopharm 500 mg film-coated tablets and the 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.

Biowaiver
A biowaiver has been granted for the 250 mg strength, based on the result of the bioequivalence study conducted with the 500 mg strength, with the following justification:

- Both strengths are manufactured by the same manufacturer and using the same manufacturing process.
- The qualitative composition of the 250 mg tablet is the same as that of the 500 mg tablet.
- The 250 mg tablets are dose proportional with the 500 mg tablets. Thus, the ratio between the amount of each excipient to the amount of active substance is the same for the two strengths.
- The dissolution profiles of the 250 mg tablets are similar to the 500 mg tablets.

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 in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. There were 23 questions in total, 20 on content and 3 on format. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Claritromycine ratiopharm 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 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 ratiopharm 250 mg and 500 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 30 May 2013 Claritromycine ratiopharm 250 mg and 500 mg film-coated tablets is authorised in the Netherlands on 11 February 2014.

The date for the first renewal will be: December 2015.

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
$t_{½}$	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