CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Claritromycine Apotex 250 mg, film-coated tablets
Claritromycine Apotex 500 mg, film-coated tablets
Apotex Europe 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/1029/001-002/DC
Registration number in the Netherlands: RVG 34920, 34921

22 July 2009

Pharmacotherapeutic group:	Macrolides
ATC code:	J01FA09
Route of administration:	oral
Therapeutic indication:	acute and chronic bacterial infections caused by micro-organisms susceptible to clarithromycin
Prescription status:	prescription only
Date of authorisation in NL:	18 March 2008
Concerned Member States:	Decentralised procedure with CZ, IT, PL, UK
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 Apotex 250 mg, film-coated tablets and Claritromycine Apotex 500 mg, film-coated tablets, from Apotex Europe B.V.. The date of authorisation was on 18 March 2008 in the Netherlands.

The product is indicated for the treatment of the following acute and chronic bacterial infections caused by micro-organisms susceptible to clarithromycin:

- upper respiratory tract infections such as tonsillitis/pharyngitis, as an alternative when beta lactam antibiotics are not appropriate.
- acute otitis media in children.
- lower respiratory tract infections such as community-acquired pneumonia.
- sinusitis and acute exacerbation of chronic bronchitis in adults and adolescents over 12 years of age.
- skin 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 Helicobacter pylori associated ulcers.

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

Clarithromycin is a semi-synthetic derivative of erythromycin A. It exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and inhibits RNA-dependent bacterial 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 film-coated tablets and Klacid 500 mg film-coated tablets (NL 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 and Zeclar 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 a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Zeclar 500 mg tablets, registered in France. 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.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types 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
General information
The active substance is clarithromycin, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The drug substance is a white to off-white powder that is soluble in acetone and practically insoluble in water. There are three polymorphic forms described in literature. In the manufacturing process only one polymorphic form is produced, form II. Form II is thermodynamically stable compared to the other forms. A separate identity reaction on the polymorphic form is included.

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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Manufacturing process
The manufacturing process is covered by the CEP.

Specification
The active substance specification is considered adequate to control the quality. The MAH has adopted the Ph. Eur. specifications as well as additional release specifications for residual solvents, particle size, X-ray diffraction and crystallinity. Batch analytical data demonstrating compliance with these specifications have been provided for 3 batches.

Stability of drug substance
Clarithromycin is susceptible to light in solution, but also in solid state an increase in seen in solid state after exposure to light. Stability data have been provided for 6 batches stored at 25°C/60% RH and 40°C/75% RH. The drug substance was packaged in the commercial packaging during the stability testing. A small increase in total amount of impurities is observed. No other clear up- or downward trends are observed during 36 months storage. All parameters remain within specification. The proposed re-test period of 36 months could therefore be granted with the additional storage condition: ‘Store in well-closed, light-resistant containers’.

** 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 Apotex 250 mg contains as active substance 250 mg of clarithromycin, and are pale yellow, oval, film-coated tablets, engraved "CLA250" on one side and "APO" on the other side.

Claritromycine Apotex 500 mg contains as active substance 500 mg of clarithromycin, and are pale yellow, capsule-shaped, film-coated tablets, engraved "CLA500" on one side and "APO" on the other side.

The film-coated tablets are packed in are packaged in white, opaque HDPE bottles or blisters consisting of PVC/PVdC clear film backed with aluminium foil.

The excipients are:

Tablet core
Croscarmellose sodium (E468), microcrystalline cellulose PH 102, magnesium stearate (E572), silica colloidal anyhydrous (E551).

Tablet coating
Hypromellose 2910 E5 (E464), macrogol 8000 , titanium dioxide (E171), yellow ferric oxide (E172).

The two tablets are completely dose proportional.

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The objective was to develop a product that would be essentially similar to the innovator products Zeclar and Klacid tablets. The tablets were coated to mask taste and for aesthetic reasons. The tablets had to be bioequivalent to the brand and should meet general physical and chemical specifications for a solid dosage form. The MAH wanted to achieve a proportional formulation for the 250 and 500 mg strengths.

The formulation development has been adequately described.

Excipients
The chosen excipients are widely used in pharmaceutical preparations. The excipients were chosen to allow rapid disintegration and dissolution. The different functions of the excipients are well described. Ph. Eur. specifications are used for all excipients with the exception of ferric oxide. For ferric oxide the US-NF specifications are used.

Manufacturing process
The MAH has submitted a clear narrative description and a flow diagram of the manufacturing process, including mixing times and speed. The applicant has clearly described the in-process controls, including the tests and acceptance criteria. The tablets are produced by direct compression followed by film coating. The MAH provided process validation data for pilot-scale batches. Process validation for full-scale batches have been presented.

Specification
The finished product specifications are adequate to control the relevant parameters for the dosage form. Most of the specifications are based on the USP. These specifications are either similar or tighter compared to the European Pharmacopoeia. These are therefore acceptable. The specification includes tests for average weight, identification, loss on drying, microbial testing, dissolution, uniformity of dosage units, degradation products and assay.

The methods for the testing of the drug product are described in detail. The Ph. Eur. is referred to where applicable. The MAH has adequately validated the following methods: assay, identification and content uniformity, dissolution, degradation products, identification of titanium dioxide, identification of ferric oxide and the microbial limit test.

Batch analytical data from 3 batches for each strength have been provided, demonstrating compliance with the specification, except for appearance. The imprints used for the submission batches were different than the proposed commercial batches. This has been sufficiently justified.

Stability tests on the finished product
During the stability studies the tablets have been stored at 25ºC/60%RH, 30ºC/65%RH and 40ºC/75%RH. For each strength, two batches were stored up to 18 months, while one batch was stored up to 24 months. Significant change occurred in the tablets stored at 40ºC. Since the tablets are fully dose proportional the submitted data is regarded as sufficient to grant a shelf life of 24 months, as two batches cover a period of 24 months and the other batches are regarded as supportive (covering a shelf life of 18 months). The MAH has performed a photostability study. During this study no degradation occurred. The labelled storage condition is “Store below 30ºC”.

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 a bioequivalence study in which the pharmacokinetic profile of the test product Claritromycine Apotex 500 mg is compared with the pharmacokinetic profile of the French reference product Zeclar 500 mg and with Klacid 500 mg from the Australian market. Only the French reference product, Zeclar 500 mg, is considered relevant for this application, as the Australian reference product is not registered in Europe. Therefore, only the data of the French reference product were used for assessment.

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

The choice of the French reference product in the bioequivalence study has been justified by comparison of dissolution results (NL, FR, CZ, UK, IT, PL) and compositions of reference products in different member states.

Design
A single-dose, 3-way crossover bioequivalence study was carried out under fasted conditions in 36 healthy subjects, 18 males and 18 females, aged 20-55 years. Eleven subjects were smokers (less than 10 cigarettes per day). Each subject received a single dose (500 mg) of one of the 3 clarithromycin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting was continued for 4 hours after dosing. There were 3 dosing periods, separated by a washout period of 7 days. Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, and 36 hours after administration of the products.

The analytical method is considered adequate validated and acceptable for analysis of the plasma samples.
The applied statistical method by the applicant is acceptable**.** However broadening of the interval for C_{max} as mentioned in the protocol is not considered acceptable. The justification is insufficient:clarithromycin is not a highly variable drug for which a broadening of the 90% CI may be applied. But, the results obtained were all within the normal acceptance range

Results
One subject was withdrawn from the study before the third dosing period, because of a positive drug test. Thirty-five subjects were eligible for pharmacokinetic analysis.

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

Treatment N=35	**AUC_{0-t}** µg.h/ml	**$AUC_{0-\infty}$** µg.h/ml	**C_{max}** µg/ml	**t_{max}** h	**$t_{1/2}$** h
Test	16.69 ± 5.74	17.12 ± 5.83	2.14 ± 0.73	2.0 (0.67-6.0)	4.7 ± 1.1
Reference	16.84 ± 6.08	17.35 ± 6.22	1.96 ± 0.60	2.0 (0.67-12.0)	5.2 ± 1.3
***Ratio (90% CI)**	0.99 (0.94-1.04)	0.99 (0.94-1.03)	1.08 (0.97-1.19)	-	-
CV (%)	12.3%	12.3%	26.1%	-	-
$AUC_{0-\infty}$ 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*

Conclusion and discussion
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 Apotex 500 mg tablets and Zeclar 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.

Dose proportionality
The 250 mg tablets are dose proportional with the 500 mg tablets. Clarithromycin shows non-linear pharmacokinetics. AUC and C_{max} increases more than dose proportional due to saturation of metabolism, especially above the 500 mg dose. Although pharmacokinetics is not linear, the bio-study is carried out with the highest strength, which is considered to be most sensitive in this case.
The results of the bioequivalence study performed with the 500 mg tablets therefore apply to the other strengths.

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. Claritromycine has a well-recognised efficacy and an acceptable

level of safety in the indications approved for Klacid 250 and 500 mg film-coated tablets, and corresponding products have been widely used in many countries. Therefore, it is accepted that routine pharmacovigilance will be performed by the MAH. However, based on the results of the CLARICOR study, the MAH should monitor cardiovascular outcomes and present cumulative overviews in the upcoming PSURs.. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. The MAH committed to present cumulative overviews in the upcoming PSURs.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance with the SPC approved for the procedures NL/H/571-572/003/MR, concerning Clarithromycin, granulate for oral suspension.

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. Before the actual readability test commenced, a so-called “Audience Design Step” was performed. In this Step, an “Expert Patient” (person with experience of the indication for use of the leaflet being tested) critically read the leaflet in order to refine the contents and design of the leaflet.
The questionnaire was tested in pilot interviews and was found not to raise problems. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
Two cohorts of 10 participants were recruited of sufficiently diverse demographic and sociologic criteria. The test results were presented for the complete number of participants and not for each cohort. The PIL successfully passed in the first cohort of 10 persons and no changes in the PIL were needed. The user test showed that the leaflet enabled 90% of participants to find, and 90% of those to express in their own words each piece of information tested.
The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Claritromycine Apotex 250 mg, film-coated tablets and Claritromycine Apotex 500 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms of Klacid 250 mg film-coated tablets and Klacid 500 mg film-coated tablets, respectively. 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 pharmcovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other clarithromycin containing products. The content of the SPC is in accordance with the SPC of the procedures NL/H/571-572/003/MR.

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 Apotex 250 mg, film-coated tablets and Claritromycine Apotex 500 mg film-coated tablets with the reference products, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 13 January 2008. Claritromycine Apotex 250 mg, film-coated tablets and Claritromycine Apotex 500 mg film-coated tablets were authorised in the Netherlands on 18 March 2008.

A European harmonised birth date has been allocated (17-07-1989) and subsequently the first data lock point for clarithromycin is April 2009. The first PSUR will cover the period from March 2008 to April 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 December 2012.

The following post-approval commitment has been made during the procedure:

Pharmacovigilance

- The MAH commits to monitor cardiovascular outcomes and present cumulative overviews in the upcoming PSURs, based on the results of the CLARICOR study.

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
US-NF	United States National Formulary
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
Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance from a manufacturer currently approved.	NL/H/1029/ 001-002/IA/001	IA	26-1-2009	9-2-2009	Approval	N
Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance. Addition of a new test parameter to the specification of an active substance.	NL/H/1029/ 001-002/IB/002	IB	26-1-2009	25-2-2009	Approval	N
Change in source of an excipient or reagent from a TSE risk to a vegetable or synthetic material.	NL/H/1029/ 001-002/IA/003	IA	26-1-2009	9-2-2009	Approval	N
Change in test procedure of the finished product. Minor change to an approved test procedure.	NL/H/1029/ 001-002/IA/004	IA	2-2-2009	16-2-2009	Approval	N
Change in the name and/or address of a manufacturer of the finished product	NL/H/1029/ 001-002/IA/005	IA	26-1-2009	9-2-2009	Approval	N
Change in the name and/or address of the marketing authorisation holder	NL/H/1029/ 001-002/IA/006	IA	26-1-2009	9-2-2009	Approval	N
Change in the test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance. Minor change to an approved test procedure.	NL/H/1029/ 001-002/IA/007	IA	2-2-2009	16-2-2009	Approval	N
Change in test procedure of the finished product. Minor change to an approved test procedure.	NL/H/1029/ 001-002/IA/008	IA	3-6-2009	17-6-2009	Approval	N