IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Clarithromycin 250 mg film-coated tablets
Clarithromycin
PA0281/250/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

This product was initially authorised under procedure number UK/H/4546/1-2/DC with the UK as RMS. The responsibility of RMS was transferred to Ireland on 24/01/2019 under procedure number IE/H/0934/1-2/DC.
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0281/250/001-002
Marketing Authorisation Holder: Pinewood Laboratories Ltd

The current Summary of Product Characteristics (SmPC) for this medicinal product is available on the HPRA website at www.hpra.ie.

The UK public assessment report published at the time of the initial marketing authorisation is provided herein.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the applications for Clarithromycin 250mg and 500mg film-coated tablets (PL 29831/0476-7; UK/H/4546/001-2/DC) could be approved. These applications were submitted via the decentralised procedure, with the UK as Reference Member State (RMS) and Malta as Concerned Member State (CMS). These products are prescription-only medicines (POM).

Clarithromycin 250mg and 500mg film-coated tablets are indicated for the treatment of the following infections caused by clarithromycin susceptible organisms:

- • Bacterial pharyngitis
- • Mild to moderate community-acquired pneumonia
- • Acute bacterial sinusitis (adequately diagnosed)
- • Acute exacerbation of chronic bronchitis
- • 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 (see section 4.2 of the SmPC).

These applications were submitted according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be generic medicinal products of Klaricid 250 mg and 500 mg Film-Coated Tablet (Pl 00037/0211 and 0254), which were first authorised to Abbott Laboratories Limited, UK on 09 April 1991 and 24 March 1994 respectively.

Clarithromycin belongs to a group of medicines called macrolides. It is a semi-synthetic derivative of erythromycin and exerts its antibacterial action by binding to the 50s ribosomal sub-unit of susceptible bacteria and suppresses protein synthesis. Clarithromycin 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.

No new non-clinical studies were conducted, which is acceptable given that the products are intended to be generic medicinal products of originator products that have been licensed for over 10 years.

One bioequivalence study (single dose) was submitted to support these applications, comparing the test product Clarithromycin 500mg film-coated tablets (Wockhardt UK Ltd) with the reference product Klaricid 500 mg Film-Coated Tablet (Abbott Laboratories Limited, UK).

With the exception of the bioequivalence study, no new clinical studies were conducted, which is acceptable given that the applications were for products that are intended to be generic medicinal products of originator products that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these product types at all sites responsible for the manufacture, assembly and batch release of these products.

The RMS and CMS considered that the applications could be approved with the end of procedure (Day 169) on 12 September 2011. After a subsequent national phase, the licences were granted in the UK on 11 October 2011.

II. QUALITY ASPECTS

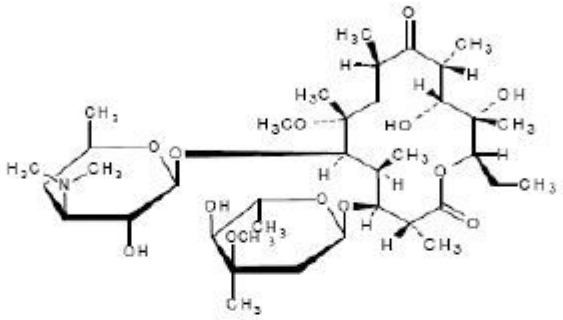
III.1 QUALITY ASPECTS

S. Active substance

INN: Clarithromycin

Chemical name: (3R,4S,5S,6R,7R,9R,11R,12R,13S,14R)-4-[(2,6-Dideoxy-3-Cmethyl-3-O-methyl[-α-L-ribo-hexopyranosyl)oxy]-14-ethyl-12,13-dihydroxy-7-methoxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2,10-dione (6-O-methylerythromycin A)

Structure:



Molecular formula: $C_{38}H_{69}NO_{13}$

Molecular mass: 748

Appearance: Clarithromycin is a white or almost white crystalline powder. It is practically insoluble in water, soluble in acetone and methylene chloride and slightly soluble in methanol.

Clarithromycin is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated to support a suitable retest period when stored in the proposed packaging.

P. Medicinal Product

Other Ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, cellulose microcrystalline, sodium starch glycolate (Type A), hydroxypropyl cellulose, colloidal silicon dioxide, talc, magnesium stearate, purified water and Opadry Y-1-7000 White.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of Opadry Y-1-7000 White which complies with a suitable in-house specification and is in compliance with current EU directives concerning the use of colouring agents. Satisfactory certificates of analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

With the exception of lactose monohydrate, none of the excipients contain materials of animal or human origin. The supplier of lactose monohydrate has confirmed that the lactose is sourced from healthy animals under the same conditions as milk for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of these products.

Pharmaceutical Development

The objective of the development programme was to formulate stable, robust, immediate-release tablets containing 250mg or 500mg clarithromycin, which could be considered generic medicinal products of Klaricid 250 mg and 500 mg Film-Coated Tablet (Abbott Laboratories Limited, UK).

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* dissolution and impurity profiles have been provided for the proposed and originator products.

Manufacturing Process

Satisfactory batch formulae have been provided for the manufacture of product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The proposed finished product specifications are acceptable. Test methods have been described and have been adequately validated. Batch data have been provided, which comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Container-Closure System

All strengths of the finished product are packaged in polyvinylchloride/polyvinylidene chloride/ blister strips in pack sizes of 14 tablets.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

Stability of the product
Stability studies were performed in accordance with current guidelines on batches of finished product packed in the packaging proposed for marketing. The data from these studies support a shelf-life of 24 months with no special storage conditions.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) form
The MAA forms are satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
There are no objections to the approval of these products from a pharmaceutical viewpoint.

III. NON-CLINICAL ASPECTS

III.2 NON-CLINICAL ASPECTS
As the pharmacodynamic, pharmacokinetic and toxicological properties of clarithromycin are well-known, no new non-clinical studies are required and none have been provided.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant pharmacology and toxicology.

Suitable justification has been provided for non-submission of an environmental risk assessment. As these products are intended for generic substitution with other products already on the market, it is not considered to increase the environmental risk. Thus, the applicant's justification is accepted.

There are no objections to the approval of these products from a non-clinical viewpoint.

IV. CLINICAL ASPECTS

III.3 CLINICAL ASPECTS
Pharmacokinetics
In support of these applications, the marketing authorisation holder has submitted the following bioequivalence study:

An open label, randomised, single-dose, two-treatment, two-period, two-sequence, crossover, study to compare the pharmacokinetics of the test product Clarithromycin 500mg film-coated tablets (Wockhardt UK Ltd) versus the reference product Klaricid

500 mg Film-Coated Tablet (Abbott Laboratories Limited, UK) in healthy adult volunteers under fasted conditions.

All volunteers received a single oral dose of either the test or reference product as a 1 x 500 mg tablet administered with 240 ml of water after an overnight fast. Blood samples were taken for the measurement of pharmacokinetic parameters at pre- and up to 48 hours post dose. The washout period between treatment periods was at least 7 days.

The pharmacokinetic results for clarithromycin are presented below (log-transformed values; geometric least squares mean, ratios and 90% confidence intervals):

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml
Test (mean)	21701.2392	22620.3112	2469.4665
Reference (mean)	23281.4345	23943.6389	2639.6366
Ratio (90% CI)	93.21 (86.22-100.78%)	94.47 (87.63-101.86%)	93.55 (82.39-106.23%)

$AUC_{0-\infty}$ 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

The pharmacokinetic results for metabolite 14-hydroxy clarithromycin are presented below (log-transformed values; geometric least squares mean, ratios and 90% confidence intervals):

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml
Test (mean)	10355.3525	10581.4095	784.7246
Reference (mean)	10324.1547	10553.2708	760.2625
Ratio (90% CI)	100.30 (94.40-106.58%)	100.27 (94.37-106.53%)	103.22 (93.88-113.48%)

$AUC_{0-\infty}$ 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

The 90% confidence intervals for AUC and C_{max} for test versus reference product for clarithromycin and its metabolite 14-hydroxy clarithromycin are within predefined acceptance criteria specified in the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1). Thus, the data support the claim that the test product is bioequivalent to the reference product.

As the 250mg and 500mg strengths of the product meet the criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev1), the results and conclusions of the bioequivalence study on the 500mg strength can be extrapolated to the 250mg strength.

Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for these applications.

Efficacy
No new efficacy data were submitted and none were required for these applications.

Safety
With the exception of the data generated during the bioequivalence study, no new safety data were submitted and none were required for these applications. No new or unexpected safety issues were highlighted by the bioequivalence data.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
The SmPCs, PIL and labels are acceptable. The SmPCs are consistent with that for the originator products. The PIL is consistent with the SmPCs and in line with current guidelines. The labelling is in-line with current guidelines.

Clinical Expert Report
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

Pharmacovigilance System and Risk Management Plan
The Pharmacovigilance System, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Suitable justification has been provided for not submitting a Risk Management Plan for these products.

Conclusion
There are no objections to the approval of these products from a clinical viewpoint.

V. OVERALL CONCLUSIONS

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The quality characteristics of Clarithromycin 250mg and 500mg film-coated tablets are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for applications of this type. The pharmacodynamic, pharmacokinetic and toxicological properties of clarithromycin are well-known.

EFFICACY
With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type.

Bioequivalence has been demonstrated between the applicant's Clarithromycin 500mg film-coated tablets and its respective reference product (Klaricid 500 mg Film-Coated Tablet, Abbott Laboratories Limited, UK). As the 250mg and 500mg strength of the product meets the biowaiver criteria specified in the *Notes for Guidance on the Investigation of Bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98 Rev 1), the results and conclusions of the bioequivalence study on the 500mg strength can be extrapolated to the 250mg strength.

SAFETY

With the exception of the bioequivalence study, no new data were submitted and none are required for applications of this type. As the safety profile of clarithromycin is well-known, no additional data were required. No new or unexpected safety concerns arose from the safety data from the bioequivalence study.

PRODUCT LITERATURE

The SmPCs, PIL and labelling are satisfactory and consistent with that for the reference products, where appropriate, in line with current guidelines.

BENEFIT-RISK ASSESSMENT

The quality of the products is acceptable and no new non-clinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant's products and the originator products are interchangeable. Extensive clinical experience with clarithromycin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

VI. REVISION DATE

02/03/2022

VII. UPDATES

This section reflects the significant changes following finalisation of the initial procedure.

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From UK/H/4546/1-2/DC to IE/H/0934/1-2/DC			