CBG MEB

Public Assessment Report

Scientific discussion

Claritromycine Accord 250 mg and 500 mg film-coated tablets

(clarithromycin)

NL/H/3682/001-002/DC

Date: 21 August 2017

This module reflects the scientific discussion for the approval of Claritromycine Accord 250 mg and 500 mg film-coated tablets. The procedure was finalised on 17 February 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Claritromycine Accord 250 mg and 500 mg film-coated tablets, from Accord Healthcare Ltd.

The product is indicated for the treatment of the following bacterial infections in adults and adolescents aged 12 years and older, when caused by clarithromycin-susceptible bacteria in patients with known hypersensitivity to beta-lactam antibiotics or when beta-lactam antibiotics would be inappropriate for other reasons (see SmPC sections 4.4 and 5.1).

- Streptococcal pharyngitis
- Acute bacterial sinusitis (adequately diagnosed)
- Acute exacerbation of chronic bronchitis (adequately diagnosed)
- Mild to moderate community acquired bacterial pneumonia
- Skin infections and soft tissue infections of mild to moderate severity (e.g. impetigo, erysipelas, erythrasma)
- In appropriate combination with antibacterial therapeutic regimens and an appropriate ulcer healing agent for the eradication of *Helicobacter pylori* in patients with *Helicobacter pylori* associated ulcers (see SmPC section 4.2). This indication is restricted to adults only.

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

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Klacid 250 mg and 500 mg film-coated tablets (NL License RVG 14152 and 17902) which were registered in the Netherlands by Abbott B.V. in 1990 and 1994, respectively. The marketing authorisations have been withdrawn. Therefore, reference is made to Zeclar 250 mg and 500 mg film-coated tablets which has been registered in France by Abbott Products SAS Limited since 11 September 1991 and 28 March 1994 respectively. The innovator product is registered in several European countries under various trade names (i.e. Klaricid).

The concerned member states (CMS) involved in this procedure were Austria, Germany, Denmark, Spain, Finland, France, Ireland, Italy, Norway and Poland.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Claritromycine Accord is a film-coated tablet that contains 250 mg or 500 mg of clarithromycin as active substance.

The 250 mg strength is a light yellow coloured, oval shaped, biconvex, film coated tablet, debossed with ‘C1’ on one side.
The 500 mg strength is a light yellow coloured, oval shaped, biconvex, film coated tablet, with ‘C’ and ‘2’ debossed on either side of the break line on one side. The tablet can be divided into equal doses.

The film-coated tablets are packed in a clear PVC/PVdC-Alu blister pack.

The excipients are:
Tablet core: microcrystalline cellulose (E460), croscarmellose sodium, povidone K30, talc (E553b), colloidal anhydrous silica, magnesium stearate (E470b) and stearic acid 50.

Film-coating: Opadry Yellow (containing: Hypromellose 2910 (5mPa.s) (E464), Propylene glycol (E1520), Titanium dioxide (E171), Vanillin, Hydroxypropylcellulose (E463), Talc (E553b) and quinoline yellow (E104)).

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is clarithromycin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Clarithromycin is a semi-synthetic product derived from fermentation. It is a white or almost white crystalline powder. Clarithromycin is practically insoluble in water, soluble in acetone and in methylene chloride, slightly soluble in methanol. Clarithromycin is known to exist in four polymorphic forms. Form II is used for Claritromycine Accord.

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 general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. In-house methods are used for particle size. Batch analytical data demonstrating compliance with this specification have been provided for four batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The 500 mg tablets bears a score line to facilitate breaking in equal halves for dosing purposes. The score line of the 500 mg tablets complies with the Ph.Eur requirements at the end of shelf life. The applied overage for coating is considered acceptable. Formulation development is adequately described.

One bioequivalence study was submitted to demonstrate bioequivalence between the 500 mg strength and its corresponding reference product, Zeclar 500 mg. The bioequivalence study test batch was manufactured according to the finalised manufacturing process and composition.
Dissolution profiles of the 250 mg and 500 mg strength are similar at pH 1.2, pH 4.5 and pH 6.8. The drug release of clarithromycin at pH 1.2 is shown to be very low. The MAH adequately showed that dissolution difficulties were drug substance rather than formulation related. Hence the dissolution profile of two tablets of the 250 mg strength is shown comparable to one tablet of the 500 mg strength (same dose) in pH 6.8 phosphate buffer. The dissolution in pH 1.2 is also comparable between the formulations.

Manufacturing process
The manufacturing process is considered a standard process using wet granulation. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches per strength per manufacturing site in accordance with the relevant European guidelines.

Control of excipients
The Ph.Eur excipients comply with the relevant monographs of current edition of respective pharmacopoeia and the in-house excipient (Opadry Yellow) complies with the in-house specification and supplier own specification. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, average weight of tablet, identification, uniformity of weight, loss on drying, disintegration time, dissolution, related substances, assay and microbial examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 18 batches from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for twelve batches in accordance with applicable European guidelines. Three batches per strength per manufacturing site were stored at 40°C/75% RH for 6 months and 25°C/60% RH for 36 months. Tablets were stored in the proposed packages. The stability data show that the drug product remains stable. On basis of the data submitted, a shelf life was granted of 36 months. No specific temperature storage conditions are required, and the product does not need to be stored protected from light. Photostability studies are conducted in line with ICH requirements and confirm the tablets are not sensitive to degradation by light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Claritromycine Accord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Claritromycine Accord is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Zeclar which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

Clarithromycin is a well-known active substance with established efficacy and tolerability.
A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

For this generic application, the MAH has submitted one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Claritromycine Accord 500 mg film-coated tablets (Accord Healthcare Limited, UK) is compared with the pharmacokinetic profile of the reference product Zeclar 500 mg film-coated tablets (Abbott, France).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
The 250 mg tablets are dose-proportional with the 500 mg tablet. The tablets have been manufactured by the same manufacturing process and manufacturer. 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. Dissolution profiles were submitted at a pH of 1.2, 4.5 and pH 6.8 for the 250 and 500 mg strength. Dissolution was comparable at all three pHs. The results of the study with the 500 mg can be extrapolated to the lower strength.

Design
A single-dose, open-label, randomised, two-treatment, two-sequence, two-period cross-over bioequivalence study was carried out under fasted conditions in 42 healthy male subjects, aged 18-44 years. Each subject received a single dose (500 mg) of one of the two clarithromycin formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of seven days.

Blood samples were collected pre-dose and at 0.33, 0.67, 1.0, 1.25, 1.5, 1.75, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 16.0, 20.0, 24.0 and 36.0 hours after administration of the products.

The design (including the blood sampling scheme) is acceptable. As clarithromycin can be taken regardless of food, a study under fasting conditions is acceptable. The mean half-life of clarithromycin ranges from 2.7 to 4.8 hours. Therefore plasma sampling until 36 hours after dosing and a wash-out period of seven days is sufficient.

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
One subject discontinued from the study on his own accord. Two subjects were withdrawn from the study on the grounds of protocol non-compliance. Therefore, 39 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=39	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	29612.51 ± 7127.49	30196.49 ± 7315.03	2915.51 ± 753.30	2.25 (1.25 – 10.0)	5.18 ± 0.79
Reference	31298.43 ± 7760.59	31747.44 ± 7953.65	3015.34 ± 822.41	2.5 (1.0 – 12.0)	5.22 ± 0.78
***Ratio (90% CI)**	0.95 (0.89 - 1.00)	0.95 (0.90 - 1.01)	0.97 (0.88 - 1.07)	--	--

$AUC_{0-\infty}$ 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 on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Claritromycine Accord 500 mg is considered bioequivalent with Zeclar 500 mg.

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).

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Claritromycine Accord.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Agranulocytosis • Risk of increased toxicity in patients with severe hepatic failure in combination with renal impairment • Pseudomembranous colitis • QT prolongation/Torsades de pointes • Interaction with ergot alkaloids: risk of ergot toxicity • Interaction with statins metabolised by CYP3A4: risk of rhabdomyolysis • Interaction with midazolam and other triazolobenzodiazepines metabolised by CYP3A4: risk of excessive sedation • Interaction with colchicine: risk of colchicine toxicity • Interaction with oral anticoagulant: risk of haemorrhage • Severe immediate hypersensitivity reactions. • Antimicrobial resistance • Acute pancreatitis • Serious skin hypersensitivity reactions (SJS and TEN) • Acute renal failure • Drug related severe hepatic disorders
Important potential risks	• Cardiovascular events • Psychiatric disorders • Interaction with oral hypoglycaemic agents/insulin: risk of hypoglycaemia

Missing information	• Use during pregnancy and lactation

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Zeclar. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the content and key message of the package leaflet (PL) has been performed on the basis of a bridging report, referencing to the PL of Klaricid 250 mg and 500 mg film-coated tablets. In addition, the MAH provided a bridging report to comply the PL of Claritromycine Accord for design, layout and style of writing with the user tested PL of Mycophenolic acid 180 mg and 360 mg gastro-resistant tablets (ES/H/0183/001-002/DC). The bridging reports submitted by the MAH have been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Claritromycine Accord 250 mg and 500 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Zeclar 250 mg and 500 mg film-coated tablets. Zeclar 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 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 Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 February 2017.

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