Public Assessment Report

Scientific discussion

Claritromycine Aurobindo 250 mg and 500 mg, film-coated tablets

(clarithromycin)

NL/H/3076/001-002/MR

Date: 22 September 2014

This module reflects the scientific discussion for the approval of Claritromycine Aurobindo 250 mg and 500 mg, film-coated tablets. The procedure was finalised on 18 April 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 10-12.

I. INTRODUCTION

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

The product is indicated for the treatment of the following bacterial infections, when caused by clarithromycin-susceptible bacteria:

- Bacterial pharyngitis
- Mild to moderate community acquired pneumonia
- Acute bacterial sinusitis (adequately diagnosed)
- Acute exacerbation of chronic bronchitis
- 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 Helicobacter pylori associated ulcers.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
A comprehensive description of the indications and posology is given in the SmPC.

This mutual recognition 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) 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 The marketing authorisations have been withdrawn.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 Klaricid 250 mg and 500 mg tablets, marketed by Abbott Laboratories, UK.

The concerned member states (CMS) involved in this procedure were Czech Republic, Denmark, France, Ireland, Malta, Romania, Sweden, Spain and the United Kingdom (all strengths). Additionally, for the 500 mg strength Cyprus, Estonia, Latvia and Lithuania were involved.

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

II. QUALITY ASPECTS

II.1 Introduction

Claritromycine Aurobindo 250 mg is a light yellow coloured, oval shaped, biconvex film-coated tablet, with ‘D’ debossed on one side and ‘62’ on the other side.
Claritromycine Aurobindo 500 mg is a light yellow coloured, oval shaped, biconvex film-coated tablet, with ‘D’ debossed on one side and ‘63’ on the other side.

The film-coated tablets are packed in PVC/ PVdC/Aluminium blisters.

The excipients are:
Core - microcrystalline cellulose, croscarmellose sodium, povidone, colloidal anhydrous silica, magnesium stearate.
Coating - hypromellose, propylene glycol, titanium dioxide, hydroxypropyl cellulose, vanillin, sorbic acid, yellow iron oxide (ready to use coating material).

The tablets 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, which is practically insoluble in water, soluble in acetone and methylene chloride, slightly soluble in methanol, dehydrated alcohol and acetronitrile. Clarithromycin has ten chiral centers in the main macrolide ring and can exist in various crystalline forms. The provided data ensure that the drug substance manufacturer consistently yields polymorphic 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 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 CEP requirements. The specification is acceptable in view of the CEP and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches used for the manufacture of the finished product.

Stability of drug substance
Stability data on the active substance have been provided for five full-scale batches stored at 25°C/60% RH (12, 24 and 48 months) and 40°C/75% RH (6 months). The claimed re-test period of 48 months is justified. The claimed storage condition that the drug substance "does not require any special storage conditions" was also granted.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. It was aimed to develop dose and weight proportional tablets with a formulation similar to the innovator product Klaricid 250 mg and 500 mg tablets, marketed by Abbott Laboratories, UK. Comparative dissolution data of Claritromycine Aurobindo 250 mg and 500 mg test with reference product from various European member states (NL and UK - 500mg only, Italy and Portugal) have been provided. The results were similar. The use of the UK innovator product in the bioequivalence study is therefore acceptable.
Feasibility and optimisation trials of various formulations and production processes are evaluated, finally leading to the final proposed formulation and manufacturing by wet granulation approach. A film coat is applied, which is in line with the innovator product. The 500 mg batch used for bioequivalence testing is made in accordance with the final proposed formulation at the proposed manufacturing site. A biowaiver is requested for the 250 mg strength. From a chemical-pharmaceutical view, the biowaiver request is acceptable. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The tablets are manufactured by a wet granulation method, which includes preparation of the granules, compression of lubricated blend and coating of the compressed tablets. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for 3 batches of the common blend as well as three batches per tablet strength. The product is manufactured using conventional manufacturing techniques.

Control of excipients
All excipients comply with their specifications of the Ph.Eur. monographs and additional requirements. For the Opadry coating an acceptable in-house specification is provided.

Quality control of drug product
The product specification includes tests for description, identity, average weight, dissolution, uniformity of dosage units, assay, related substances, thickness, microbial contamination, loss on drying and identification of titanium dioxide and iron oxide.
Release and end of shelf-life specification are identical except for thickness and loss on drying. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on two production-scale batches of each strength, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided for 4 full-scale batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVdC-aluminium blister packs as well as a simulated bulk pack. Results stayed within limits. Forced degradation studies showed no sensitivity to light. A shelf-life of 3 years was granted based on the provided data; the product does not require any special storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
0There 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 Aurobindo 250 mg and 500 mg 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 Aurobindo 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 Klacid tablets, which is available on the European market. Reference is made tot 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 Board agreed that no further clinical studies are required.

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

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Claritromycine Aurobindo 500 mg (Aurobindo Pharma B.V., NL) is compared with the pharmacokinetic profile of the reference product Klaricid 500 mg tablets (Abbott, UK).

The choice of the reference product 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 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 4.5 (acetate buffer), 5.0 (acetate buffer) and pH 6.8 (phosphate buffer) for the 250 and 500 mg tablet. Dissolution was comparable at all three pHs. The results of the study with the 500 mg can be extrapolated to the lower strength.

Bioequivalence studies

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 36 (+2 stand by) healthy male subjects, aged 19-42 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 overnight fasting. Fasting was continued for 4 hours after dosing. There were 2 dosing periods, separated by a washout period of 8 days.

Blood samples were collected pre-dose and at 0.5, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 30, 36 and 48 hours after administration of the products.

A single dose, crossover study to assess bioequivalence is considered adequate.

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

All subjects completed the study entirely. Results of 36 subjects, as per protocol, were included in the analysis and evaluation.

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

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	22001 ± 6895	22367 ± 6910	2450 ± 703	2.0 (1.0 – 5.0)	5.2 ± 0.9
Reference	22807 ± 7383	23193 ± 7396	2449 ± 759	1.88 (1.0 – 6.0)	5.2 ± 1.0
***Ratio (90% CI)**	0.97 (0.90 - 1.03)	0.97 (0.90 - 1.03)	1.01 (0.92 - 1.11)	--	--
CV (%)	17.5	17.0	23.4	--	--

$AUC_{0-\infty}$ 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 14-OH-clarithromycin under fasted conditions.

Treatment N=36	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Test	12575 ± 3114	12937 ± 3196	1017 ± 271	2.38 (1.0 – 5.0)	7.7 ± 2.5
Reference	12639 ± 3239	13125 ± 3539	973 ± 288	2.25 (1.0 – 4.0)	8.8 ± 6.0
***Ratio (90% CI)**	1.00 (0.95 - 1.05)	0.99 (0.94 - 1.05)	1.05 (0.98 - 1.13)	--	--
CV (%)	13.3	13.7	17.1	--	--

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

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, supported by data on 14-OH-clarithromycin, it can be concluded that Claritromycine Aurobindo 500 mg and Klaricid 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.

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 Aurobindo.

Summary of Safety Concerns	
Important identified risks	- Risk of QT prolongation, ventricular tachycardia, and torsade de pointes - Use in patients with hypokalaemia - Use in patients with hepatic impairment. - Use in patients with renal impairment - Risk of fatal hepatic failure - Antibiotic-associated diarrhea, including *Clostridium difficile-associated diarrhea(CDAD)* and Pseudomembranous colitis - Exacerbation of symptoms of myasthenia gravis - Acute renal failure and renal failure - Eosinophilic pneumonia - Emerging resistance, including cross resistance between clarithromycin and other macrolide drugs as well as lincomycin and clindamycin. - Severe acute hypersensitivity reactions such as anaphylaxis, Stevens-Johnson Syndrome, and toxic epidermal necrolysis - Psychiatric ADRs such as psychotic disorder and depersonalization are sometimes irreversible - Drug-drug-interactions (Concomitant use with astemizole, cisapride, pimozideand, terfenadine, HMG-CoA reductase inhibitors (statins) , ergotamine or dihydroergotamine, colchicines, triazolobenzodiazepines such as triazolam, midazolam, other ototoxic drugs(especially with aminoglycosides), oral hypoglycemic agents and/or insulin, warfarin and cytochrome CYP3A4 enzyme inducers).
Important potential risks	- Use in immunocompromised patients
Missing information	- Use in Pregnancy and lactation

The member states agree that no additional pharmacovigilance activities beyond routine measures are required.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Klacid 250 mg and 500 mg tablets. 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

The package leaflet (PL) has not been evaluated via a user consultation study. Reference is made to the successfully user tested PL for another clarithromycin product, authorized through procedure UK/H/1662/001/DC. Both products contain the same active substance. The leaflets therefore contain the same key messages for safe use. Both PLs have the same layout and design. Separate user testing for the leaflet of Claritromycine Aurobindo is not required.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Claritromycine Aurobindo 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 Board followed the advice of the assessors. Claritromycine Aurobindo 250 mg and 500 mg, film-coated tablets were authorised in the Netherlands on 12 October 2011.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, recognized the assessment of the MEB, and have therefore granted a marketing authorization. The mutual recognition procedure was finalised with a positive outcome on 18 April 2014.

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

Summary Public Assessment Report

Generics

Claritromycine Aurobindo 250 mg and 500 mg, film-coated tablets

(clarithromycin)

NL/H/3076/001-002/MR

Date: 22 September 2014

Summary Public Assessment Report

Generics

Claritromycine Aurobindo 250 mg and 500 mg, film-coated tablets

Active substance: clarithromycin

This is a summary of the public assessment report (PAR) for Claritromycine Aurobindo 250 mg and 500 mg, film-coated tablets. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Claritromycine Aurobindo.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Claritromycine Aurobindo and what is it used for?
Claritromycine Aurobindo is a 'generic medicine'. This means that it is similar to a 'reference medicine' already authorised in the European Union (EU) called Klaricid 250 mg and 500 mg tablets.

Clarithromycin is an antibiotic that is used to treat following infections:

- Chest infections such as bronchitis and pneumonia,
- Throat and sinus infections,
- Skin and soft tissue infections,
- *Helicobacter pylori* infections associated with duodenal ulcers.

How does this medicine work?
The active substance clarithromycin belongs to a group of medicines called macrolide antibiotics. Antibiotics stop the growth of bacteria which cause infections. This medicine prevents bacteria from making certain proteins. Bacteria cannot develop without these proteins.

How is this medicine used?
The medicine can only be obtained with a prescription. The tablets may be taken with or without food. The recommended dose depends on the type of infection. Usually one tablet of 250 mg or 500 mg is taken twice a day.

How has this medicine been studied?
Because Claritromycine Aurobindo is a generic medicine, studies in patients have been limited to tests to determine that it is bioequivalent to the reference medicine, Klaricid. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the possible side effects of this medicine?
Because Claritromycine Aurobindo is a generic medicine and is bioequivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.
For the full list of restrictions, see the package leaflet.

Why is this medicine approved?
It was concluded that, in accordance with EU requirements, this medicine has been shown to have comparable quality and to be bioequivalent to the reference medicine. Therefore, the Medicines Evaluation Board of the Netherlands decided that, as for Klaricid, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of this medicine?
A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Claritromycine Aurobindo, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about this medicine
In the Netherlands, the marketing authorisation for Claritromycine Aurobindo 250 mg and 500 mg, film-coated tablets was granted on 12 October 2011.

The full PAR for this medicine can be found on the website http://mri.medagencies.org/Human.
For more information about treatment with Claritromycine Aurobindo, read the package leaflet (http://mri.medagencies.org/download/NL_H_3076_001_FinalPL.pdf) or contact your doctor or pharmacist.

This summary was last updated in September 2014.