Public Assessment Report
Scientific discussion

Olmesartan/Hydrochlorothiazide Alter 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg, 40 mg/25 mg

Atolme Plus 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg, 40 mg/25 mg Film-Coated Tablets

(Olmesartan Medoxomil and Hydrochlorothiazide)

Registration number in Spain:
80653, 80651, 80658, 80650
80741, 80738,80740,80739

ES/H/0322/001-004/DC
ES/H/0323/001-004/DC

Applicant: Laboratorios Alter, S.A.

This module reflects the scientific discussion for the approval of **Olmesartan/Hydrochlorothiazide Alter 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg, 40 mg/25 mg and Atolme Plus 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg, 40 mg/25 mg Film-Coated Tablets**. The procedure was finalised on January 2016. For information on changes after this date please refer to the module 'Update'.

INTRODUCTION

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Olmetec Plus® film-coated tablets (Daiichi Sankyo España S.A). Olmetec Plus® film-coated tablets has been registered in Europe since 2005.

The legal basis of the application is Article 10(1) of Directive 2001/83/EC.

The Concerned Member State involved in this procedure is PT.

The product is indicated for the treatment of essential hypertension in patients whose blood pressure is not adequately controlled with olmesartan medoxomil in monotherapy.

A comprehensive description of the product information is given in the SmPC.

RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member States have granted a marketing authorisation for **Olmesartan/Hydrochlorothiazide Alter 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg, 40 mg/25 mg** and **Atolme Plus 20 mg/12.5 mg, 20 mg/25 mg, 40 mg/12.5 mg, 40 mg/25 mg Film-Coated Tablets** for Laboratorios Alter S.A.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Active substances

Olmesartan medoxomil and hydrochlorothiazide are known active substances described in European Pharmacopoeia. Ph. Eur. Certificates of Suitability have been submitted to support the quality of both active ingredients.

The hydrochlorothiazide CEP include re-test period for the drug substance. The olmesartan medoxomil CEP does not include re-test period but stability data have been included in the dossier to support the proposed the re-test period.

Finished product

Description of the product

The product are olmesartan medoxomil / hydrochlorothiazide film-coated, biconvex tablets without grooves, with different shape, dimensions and colour depending on the dosage:

- 20 mg / 12.5 mg tablets are yellow and round (11 mm diameter).
- 20 mg / 25 mg tablets are light pink and oblong (17 x 7.5 mm).
- 40 mg / 12.5 mg tablets are yellow and oblong (17 x 7.5 mm).
- 40 mg / 25 mg tablets are dark pink and oblong (17 x 7.5 mm).

The qualitative composition is as follows:

- Olmesartan medoxomil
- Hydrochlorothiazide

- Lactose monohydrate
- Microcrystalline cellulose
- Low substituted hydroxypropylcellulose
- Calcium stearate
- Yellow/red iron oxide
- Sepicoat white (composed of modified starch, talc, polyol, soya lecithin and titanium dioxide).

The drug product is packaged in plates formed by a polyamide/aluminium/PVC support sheet and an aluminium foil for covering, both heat-sealed.

Pharmaceutical development
The pharmaceutical development has been adequately described.
Excipients are commonly used in this dosage form. Their election and concentrations are justified, and their function in the drug product described.
The dissolution test is correctly designed and its discriminatory power has been demonstrated.

Manufacture of the product and process controls
The manufacturing process is sufficiently described and the process controls are appropriate, considering the nature of the product and the manufacturing method.
Commercial batch sizes are defined.
The dossier includes sufficient validation data to guarantee that the manufacturing process is controlled and to ensure batch to batch reproducibility and compliance with product specifications.

Excipients
Excipients used in this dosage form are of Ph. Eur. quality (with the exception of Sepicoat White). The specifications for the different excipients are justified by their official adoption in the relevant Ph. Eur. monograph or by an in-house monograph (for the non-compendial excipient). Certificates of analysis have been provided.

Product specification
The specifications proposed for the drug product are adequate. The limits proposed for the different parameters have been adequately justified.
The analytical methods have been properly described and validated.

Container closure system
Tablets are packaged in plates formed by a complex foil support consisting of polyamide/aluminium/PVC and an aluminium foil for covering, both heat-sealed. The components of the container closure system comply with the specifications established in the applicable Ph. Eur. monographs.

Stability of the product
The stability studies have been performed following the ICH guidelines. The stability data support the proposed shelf-life and storage conditions.

II-2 Non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of the active substance has been provided, which is based on up-to-date and adequate scientific literature. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology

is adequate and the Member States agreed that no further non-clinical studies are required.

Environmental Risk Assessment (ERA)

No ERA was submitted. The medicinal product has the same quantitative and qualitative composition in active substances and a similar pharmaceutical form to the reference product. The introduction on the market of this medicinal product will not mean an increased exposure to the environment, since the generic medicinal product is intended to substitute the reference medicinal product as well as other generic products in the market.
In accordance with the Guideline on the Environmental Risk Assessment for medicinal products for human use (CPMP/SWP/4447/00), the absence of this Environmental Risk Assessment is therefore justified.

II.3 Clinical aspects

Introduction

Olmesartan medoxomil and hydrochlorotiazide are well-known drugs with established efficacy and safety.

No new clinical efficacy or safety studies were conducted, which is acceptable for this abridged application. A clinical overview has been provided, which is based on scientific literature. The Member States agreed that no further clinical studies are required.

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

Biowaiver
The bioequivalence between test and reference products has been demonstrated for the 40 mg/25 mg strength (please refer to the section of results). These data can be extrapolated to the other strengths since all the requirements described in section 4.1.6 of the Bioequivalence Guideline are fulfilled.

Bioequivalence

The Applicant has submitted the bioequivalence study ITHUEC-OLM-HTZ/13-3: ña randomized, open label, two treatment, two period, two sequence, single dose, crossover bioequivalence study of Olmesartan/Hydrochlorothiazide Alter 40 mg/25 mg tablets (Laboratorios Alter, Spain) and Olmetec Plus® 40 mg/25 mg tablets (Daiichi Sankyo, S.A., Spain) in healthy human adult subjects, under fasting conditionsò to demonstrate bioequivalence with the reference product according to the requirements of the EMA Guideline on the investigation of bioequivalence.
The clinical part of the study was performed from 13/02/2014 to 12/03/2014.
The analytical part was conducted from 17/03/2014 to 25/04/2014.
The Clinical part of the study was performed at Clinical Trials Unit, Hospital Universitario de la Princesa. C/ Diego de León, nº 62, Madrid.
The analytical portion was conducted at Laboratorios KYMOS Pharma Service S.L.
The trial has been conducted in compliance with GCP requirements. Monitoring reports have been submitted. QA statement of audits assuring compliance to GCP were issued by Head-QA.

The clinical, the analytical, the pharmacokinetic and the statistical sites were inspected by Regulatory Authorities of the European Union without critical findings.

Design
An open label, two treatment, two period, two sequence, single dose, crossover bioequivalence study in healthy human adult subjects, under fasting conditions with a washout period of 7 days.

The application concerns an oral immediate release formulation (film-coated tablets) with a linear PK over the therapeutic dose for both drugs. In addition, as described in the SmPC of the reference, olmesartan/hydrochlorothiazide tablets can be administered with or without food. Therefore, a single dose bioequivalence study under fasting conditions with the 40 mg/25mg strengths is considered adequate for the application.
The wash-out period and the sampling schedule are considered acceptable for an adequate characterisation of the systemic exposure of a drug with such a half-life and Tmax.

The reference product is adequate with regards to expiry date, content and it was obtained from Spanish market.
All batches were tested before expiry date and a similar content of active substance is shown. Therefore, content correction is not necessary.

In the present study, thirty six (36) subjects (18 men and 18 women) were enrolled and randomised to a treatment sequence in the study, in accordance with the protocol. All of them completed the study and were included in the pharmacokinetic analysis.

The study population is considered acceptable with regards to demographic characteristics. The inclusion and exclusion criteria are considered to be acceptable.

Analytical methods
The analytical method has been adequately validated before the conduct of the study and during the analysis of the subject samples. Therefore, the analytical method is considered acceptable for analysis of the plasma samples.

Pharmacokinetic data analysis
Pharmacokinetic parameters were calculated using a non-compartmental method with acceptable software. AUC was calculated by the trapezoidal rule. The methods used in this study for the pharmacokinetic calculations are considered acceptable

Statistical analysis
The methods used in this study for the statistical evaluation are considered acceptable. ANOVA was performed on log-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} were considered as the primary pharmacokinetic parameters. The analysis of variance model included the following factors: sequence, subjects nested within sequence, period and treatment.
Values for the T_{max} parameter were analysed by a non-parametric approach (Wilcoxon Signed-Rank Test).

Based on the log-transformed parameters, the 90% confidence intervals of the relative mean plasma for AUC_{0-t} and C_{max} of the test to reference products should be between 80-125% to conclude bioequivalence.

Results
The 90% confidence intervals mean treatment T/R ratios are shown in the following table:

Bioequivalence evaluation of olmesartan

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln ($AUC_{0-t)}$	96.49	90.41-102.98
Ln (C_{max})	91.47	84.92-98.53
Ln ($AUC_{0-Ð}$)	96.41	90.51-102.70

Bioequivalence evaluation of hydrochlorothiazide

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln ($AUC_{0-t)}$	106.19	99.98-112.79
Ln (C_{max})	110.61	100.58-121.65
Ln ($AUC_{0-Ð}$)	106.82	100.72-113.28

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 ï 1.25 and therefore bioequivalence has been proven. No clinically significant differences were observed between the median Tmax of test and reference products.

Risk Management Plan

A risk management plan in accordance with the requirements of Directive 2001/83/EC as amended has been submitted.

No additional risk minimization activities were required beyond those included in the product information.

Discussion on the clinical aspects

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference product.

Efficacy and safety of the active substances olmesartan medoxomil and hydrochlorotiazide are well documented for the reference medicinal product. The design of the submitted bioequivalence study is adequate and the results allow us to conclude bioequivalence with the reference.

III OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Bioequivalence has been shown to be in compliance with the requirements of European Union guidance documents.

The SmPC, PIL and labelling are considered satisfactory and consistent with the information for the reference medicinal product. The user testing of the Package Information Leaflet has been tested in accordance with Article 59(3) of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The benefit/risk balance was considered to be positive.

Agreement between Member States was reached during the procedure. The decentralised procedure was finalised with a positive outcome in January 2016.