

Public Assessment Report

Scientific discussion

**Bisoprolol Pensa 1.25 2.5, 3,75, 5, 7.5 y 10 mg
Tablets**

Bisoprolol fumarato

Registration number in Spain:xxx

ES/H/0359/001-003/DC

ES/H/0360/001-003/DC

Applicant: Pensa Pharma, S.A.

This module reflects the scientific discussion for the approval of **Bisoprolol Pensa 1.25 2.5, 3,75, 5, 7.5 y 10 mg 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 Emcor[®] tablets (Merck Ltd. UK). Emcor[®] tablets have been registered in the UK since February 1988.

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

The Concerned Member State involved in this procedure is IT.

The efficacy and security of bisoprolol fumarate has been demonstrated in several studies conducted with the reference product as well as with its use experience after placed in the market. Bisoprolol Pensa 1.25 2.5, 3.75, 5, 7.5 y 10 mg tablets are submitted under an abridged application and no studies regarding pharmacology, pharmacokinetic, security and efficacy has been carried out besides the bioequivalence studies against the reference product.

The product is indicated for:

- Treatment of the hypertension,
- Treatment of the chronic stable angina pectoris,
- Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

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 Bisoprolol Pensa 1.25 2.5, 3.75, 5, 7.5 y 10 mg tablets for Pensa Pharma, S.A.,.

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

DRUG SUBSTANCE

Bisoprolol a known active substance described in Ph.Eur. A Ph. Eur. The supplier of active substance has been submitted a Certificate of Suitability to support the quality of the active ingredient.

No retest period has been granted on the CEP, but stability studies have been supplied. The proposed retest period of 5 years when stored in double PE bags inside drums or containers can be granted.

DRUG PRODUCT

Description of the product

The finished product is formulated as tablets containing 1.25, 2.5, 3.75, 5, 7.5 and 10 mg of bisoprolol fumarate. All tablets are white to off white, round, plain biconvex tablets with or without breakline on one side. The difference between tablets strengths is the diameter ranging from 5 mm to 10.5mm and the different strengths are debossed to state the strength on the tablet.



The qualitative composition of the tablets is as follows:

- Bisoprolol fumarate
- Microcrystalline Cellulose
- Silica colloidal anhydrous
- Croscarmellose sodium
- Sodium Starch glycolate (Type A)
- Magnesium Stearate

The product is packed in blister of PVC/PVDC or PVC/PCTFE sealed with Aluminium foil.

Pharmaceutical development

The pharmaceutical development has been properly described.

The function of the excipients has been discussed. Selection of the dissolution method has been justified and the discriminatory power of dissolution method has been demonstrated.

Manufacture of the product and process controls

The manufacturing process is described in detail. The manufacture involves sequential blending of the components followed by direct compression. Acceptable validation data have been presented for 2 pilot scale batches of each tablet strength manufactured and acceptable validation protocol have been supplied to support upscaling of the blend and compression batches to the maximum size proposed in the file.

Excipients

The information provided is adequate. The analytical procedures used to control the excipients are performed according to the European Pharmacopoeia monographs.

Product specification

Specifications proposed are adequate. The limits proposed for the different parameters have been adequately justified.

All analytical methods have been correctly validated following the ICH Q2 (R1) Guideline.

Container closure system

Bisoprolol tablets are packed in:

Blisters PVC/PVDC sealed with Aluminium foil.

Bliesters PVC/PCTFE sealed with Aluminium foil

The components of the container closure system comply with the requirements of Commission Regulation (EU) No 10/2011.

Stability

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 submitted application concerns tablets with the active substance in the same form as the reference product.

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. This was justified by the Applicant, since the applications of Bisoprolol Fumarate 1.25, 2.5, 3.75, 5, 7.5 and 10 mg tablets are applied according to Article 10 (1) 2001/83/EC (as amended) "generic application". The brand leader Emcor[®] has been authorised in the Community for approximately 30 years. This marketing authorisation application is for a drug product which will not be administered at a higher dosage level, for a longer duration or for different indications than were previously in effect. There is no increased environmental risk associated with the introduction of this generic product.

II.3 Clinical aspects

Introduction

Bisoprolol fumarate is 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 10 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 BIS-CHA-T1008/654 òa single centre, open-label, randomised, single-dose study with two-way crossover design to compare the bioequivalence of Bisoprolol 10 mg tablet Chanelle Medical, Ireland and Cardicor[®] 10 mg tablet Merck Pharmaceuticals, after oral administration in healthy adults under fasting conditions.

The clinical part was performed from November 17th, 2008 to December 04th, 2008

The analytical portion was conducted from April 06th, 2009 to April 26th, 2009

The clinical, bioanalytical, pharmacokinetics and biostatistics research was performed at International Pharmaceutical. Research Center (IPRC)-Sport City Circle, Amman-Jordan and the principal investigator was Dr. Usarna Harb.

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

This was an open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover, oral bioequivalence study in healthy, adult, male subjects under fasting conditions with a washout period of 7 days.

The application concerns an immediate release film-coated tablet and according to the reference product SmPC, the administration is irrespective of food intake; therefore a single dose study under fasting conditions is considered acceptable to demonstrate bioequivalence with the reference product under the assumption that the reference product does not employ special manufacturing technology that may alter the food effect.

According to the Guideline on investigation of bioequivalence, the use of the highest strength is acceptable (i.e. 10 mg) since bisoprolol pharmacokinetics is dose-proportional after oral administration in the therapeutic range.

The wash-out period of 7 days (more than five times the half-life) is considered adequate since the drug has a half-life of approximately 10-12 hours and no pre-dose level was detected.

Test product: Bisoprolol 10 mg tablets manufactured by Chanelle Medical, Ireland. Batch number: 15234I. Batch size: 137,500 tablets. Expiry date: August 2011. Assay (content): 101.8% of label claim (please refer to module 3.2.P.5.4 öBatch Analysisö).

Reference product: Cardicor[®] 10 mg tablets manufactured by Merck Pharmaceuticals, UK from the UK market. Batch number: 5301220. Expiry date: May 2012. Assay (content): 101.3% of label claim.

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, twenty-eight (28) subjects 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 and statistical 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} , AUC_{0-t} and $AUC_{0-\infty}$ were considered as the primary pharmacokinetic parameters.

The statistical method employed by the Applicant is Kinetica[™] 2000 is known to provide incorrect results when the studies are imbalanced, but the present study is balanced and the results are correct. The ANOVA model was performed adequately and sequence, subject (sequence), period and formulation were included as fixed effects.



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:

Parameter	Ratio (Test/Reference)	90% Confidence Interval
Ln (AUC_{0-t})	104.96	100.63-109.47
Ln (C_{max})	108.81	103.21-114.70
Ln ($AUC_{0-\infty}$)	105.44	101.17-109.90

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 to 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 substance bisoprolol fumarate is 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 September 2016.