Public Assessment Report
Scientific discussion

Ivabradine Urquima 5 mg and 7.5 mg and film-coated tablets

Ivabradine hydrochloride

ES/H/0383/001-002/DC

Registration number in Spain:
81476, 81477

This module reflects the scientific discussion for the approval of **Ivabradina Urquima 5 mg and 7.5 mg film-coated tablets.** The procedure was finalised on October 2016. For information on changes after this date please refer to the module ôUpdateô.

INTRODUCTION

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Procoralan film-coated tablets by Les Laboratories Servier. Procoralan film-coated tablets have been registered since October 25th, 2005 through the centralised procedure.

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

The Concerned Member State involved in this procedure is:

- ES/H/0383/001-002/DC: DE

The efficacy and security of ivabradine hydrochloride have been demonstrated in several studies conducted with the reference product as well as with its use experience after placed in the market. Ivabradine Urquima 5 mg and 7.5 mg film-coated tablets are submitted under an abridged application and no studies regarding pharmacology, pharmacokinetic, security and efficacy have been carried out besides the bioequivalence studies against the reference product.

Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate Ó 70 bpm. Ivabradine is indicated:

- in adults unable to tolerate or with a contra-indication to the use of beta-blockers
- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is Ó 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

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 **Ivabradine Urquima 5 mg and 7.5 mg film-coated tablets** for J. Uriach y Compañía, S.A..

I. SCIENTIFIC OVERVIEW AND DISCUSSION

II-1 Quality aspects

Drug substance

General Information

The active substance master file procedure is used for Ivabradine hydrochloride. The corresponding letter of access has been provided. The ASMF-holder commits to ensure batch-to-batch consistency and to inform J. Uriach y Compañía, S.A. and the Health Authorities of any change in the ASMF.

Manufacture, characterisation and process controls
The manufacturing process is adequately described in the restricted part of the ASMF.

Specification
Ivabradine hydrochloride is not described in Ph. Eur., the ASMF-holder has justified the specification and limits based on ICH guidelines and Ph. Eur. general monographs. The proposed limits for assay are acceptable based on batch results and stability data. Considering the maximum daily dose of Ivabradine hydrochloride, the proposed limits for related substances are in compliance with ICH guidelines.

Stability
Stability studies have been performed with the drug substance. The stability studies indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container

Drug Product

Manufacture, characterisation and process controls
The physicochemical properties of the active substance have been described. The choice of excipients is justified and their functions explained. The development of the drug product has been described.
The proposed manufacturing process, a standard process, has been described. In-process controls have been set. A holding time for the bulk product has been proposed and justified. Validation data have been presented.

Specification
The product specifications cover appropriate parameters for this dosage form. Validation of the analytical methods has been presented. Batch analysis has been performed on three batches of each strength. Batch analysis results show that the finished products meet the specifications proposed.

Stability
Aluminium/aluminium blister has been proposed as primary container. Compliance with the food contact requirements of *Commission regulation (EU) No 10/2011* is fulfilled.
The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up.
The proposed shelf-life of 36 months with no special storage conditions to be specified for the drug product is considered acceptable.

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 film coated tablets with the active substances 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. 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

Ivabradine hydrochloride is a 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 7.5 mg strength (please refer to the section of results). These data can be extrapolated to the other strength (i.e., 5 mg) since all the requirements described in section 4.1.6 of the Bioequivalence Guideline are fulfilled.

Bioequivalence

The Applicant has submitted the bioequivalence study GE/14/IVA/I/14 ña pivotal, single-dose, randomized, open-label, four-period, two-sequence, two-treatment, single-centre, replicate, comparative bioavailability study of Ivabradine 7.5 mg film-coated tablets (J. Uriach y Compañía S.A., Spain) and Procoralan® 7.5 mg film-coated tablets (Servier Laboratories Limited). The products were studied using a replicate design with 36 healthy male and female non-smoking volunteers being administered an oral dose of 1 × 7.5 mg film-coated tablets under fed conditionsò.

The clinical part was performed from June 28th, 2014 to July 20th, 2014 at BioPharma Services Inc. 4000 Weston Road Toronto, Ontario, Canada.

The analytical portion was conducted from July 23rd, 2014 to September 04th, 2014 at Anapharm Europe, S.L.U. Encuny 22, 2º 08038 Barcelona Spain.

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

A Single-Dose, Randomized, Open-Label, Fully Replicate, Pivotal, Comparative Bioavailability Study of Ivabradine 7.5 mg tablets (J. Uriach y Compañía S.A.) and Procoralan 7.5 mg tablets (Servier Laboratories Limited) in Healthy Male and Female Volunteers under Fed Conditions with a washout period of 7 days.

This approach is acceptable as the application concerns an oral immediate release formulation (film-coated tablets) and according to the SmPC ñtablets must be taken orally twice daily, i.e. once in the morning and once in the evening during mealsò; therefore a single dose study under fed conditions is considered acceptable to demonstrate bioequivalence with the reference product.

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 2 hours and no pre-dose level was detected.

Considering the expected time to peak concentration (1 hours in fasting and food delayed absorption by approximately 1 hour) and the elimination half-life, the sampling schedule and the sampling time period of 12 hours seems long enough to estimate PK parameters.

Test product: Ivabradine 7.5 mg film-coated tablets manufactured by J. Uriach y Compañia S.A. Batch number: 1003. Batch size: 100,000 tablets. Expiry date: April 2015. Assay (content): 97.79% of label claim.

Reference product: Procoralan 7.5 mg film-coated tablets manufactured by Servier Laboratories Ltd. (from the Spanish market). Batch number: M-001. Expiry date: September 2016. Assay (content): 97.5 % of label claim.

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.

Thirty-six (36) healthy volunteers were included. Out of 36 subjects, 33 subjects completed all periods and 35 (17 male and 18 female) were included in the pharmacokinetics and statistical analysis.

A TRTR/RTRT replicate cross-over design was used. The design is considered acceptable to justify a widening of the limits for C_{max}.

Subject number 21 and 31 withdrew from the study for personal reason in the 4 and 2 period, respectively. Subject 01 dismissed due to vomiting after dosing in period 4.

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 average bioequivalence analysis was performed using PROC GLM in SAS®, with sequence, subject (sequence), period, and treatment as the independent variables. All main effects were tested against the mean square error term except where sequence effect was tested

against the error term of subject (sequence). Least square means (LSMEANS) and the standard errors (ESTIMATE) for the treatment and the differences between treatment means and the standard errors associated with these differences were calculated.

The 90% confidence intervals of the Test/Reference ratios for AUC_{0-t}, $AUC_{0-Đ}$ and C_{max} were calculated. The confidence intervals are presented for the Test/Reference ratios for the geometric means (obtained from data transformed to their natural logarithms). Power for treatment comparisons for the pharmacokinetic parameters was calculated as the probability (type I error fixed at the 5% level) of detecting a difference at least equal to 20% of the reference treatment mean.

To establish bioequivalence, the calculated 90% confidence interval for the ratio of geometric means for AUC_{0-t} and C_{max} must fall within 80.00% to 125.00% unless the observed intra-subject variability of the reference product is greater than 30%, in which case the acceptance range would be widened.

Results

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

Pharmacokinetic parameter	Geometric Ratio	90% Confidence Intervals	Intra-subject (CV%)	Reference Intra-subject (CV%)
AUC_{0-t}	100.64%	96.62%-104.94%	14.49%	-
$AUC_{0-Đ}$	100.41%	96.41%-104.59%	14.44%	-
C_{max}	101.41%	93.69%-109.78%	29.52%	35.04%

Based on the statistical analysis submitted by the Applicant the test product is equivalent to the reference with respect to the extent and rate of absorption/exposure as the 90% confidence intervals for the ln-transformed AUC_{0-t} amd $AUC_{0-Đ}$ are within the acceptance range of 80-125% and in accordance with Guideline on the investigation of bioequivalence, section 4.1.10 as the within reference intra-subject CV% of ln-transformed was 35.04% larger than 30%, the acceptance criteria for C_{max} was widened to the acceptance range of 77.21-129.51%. This new acceptance interval is acceptable and the C_{max} results were within of conventional accpetance range (93.69-109.78%).

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 ivabradine hydrochloride 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 October 2016.