

Public Assessment Report

Scientific discussion

Ivabradine DOC Generici 2.5 mg, 5 mg and 7.5 mg, film-coated tablets

(ivabradine hydrochloride)

NL/H/3623/001-003/DC

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This module reflects the scientific discussion for the approval of Ivabradine DOC Generici 2.5 mg, 5 mg and 7.5 mg, film-coated tablets. The procedure was finalised on 15 December 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
BHT	Butylhydroxytoluene
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
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 Ivabradine DOC Generici 2.5 mg, 5 mg and 7.5 mg, film-coated tablets from DOC Generici S.r.l.

The product is indicated for:

Symptomatic treatment of chronic stable angina pectoris

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

Treatment of chronic heart failure

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 ≥ 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 indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Procoralan 5 mg and 7.5 mg film-coated tablets which have been registered in the EEA by Les Laboratoires Servier since 25 October 2005 through a centralised procedure (EU/1/05/316).

The concerned member state (CMS) involved in this procedure was Italy.

The marketing authorisation has been granted pursuant to Article 10(1) (5 mg and 7.5 mg strength) and Article 10(3) of Directive 2001/83/EC. Article 10(3) concerns a hybrid application since Ivabradine DOC Generici 2.5 mg, film-coated tablets is referenced to half a dose of Procoralan 5 mg film-coated tablets.

II. QUALITY ASPECTS

II.1 Introduction

Ivabradine DOC Generici 2.5 mg is a pink coloured, round, film-coated tablet debossed with '19VB' on one side and '2.5' on the other side. One film-coated tablet contains 2.5 mg ivabradine (equivalent to 2.695 mg ivabradine hydrochloride).

Ivabradine DOC Generici 5 mg is a pink coloured, round, film-coated tablet debossed with '19VB' and a score line on one side and '5' on the other side. The tablet can be divided into equal doses. One film-coated tablet contains 5 mg ivabradine (equivalent to 5.390 mg ivabradine hydrochloride).

Ivabradine DOC Generici 7.5 mg is a pink coloured, round, film-coated tablet debossed with '19VB' on one side and '7.5' on the other side. One film-coated tablet contains 7.5 mg ivabradine (equivalent to 8.085 mg ivabradine hydrochloride).

The film-coated tablets are packed in PVC/PE/PVDC/Aluminium or Aluminium/Aluminium blisters.

The excipients are:

Tablet core – betadex, microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

Film-coating – hypromellose (HPMC 2910), lactose monohydrate, titanium dioxide (E171), macrogol 4000, red iron oxide (E172), yellow iron oxide (E172) and black iron oxide (E172)

The three strengths are dose-proportional.

II.2 Drug Substance

The active substance is ivabradine hydrochloride, an established active substance however not described in any pharmacopoeia. It is a white to almost white, hygroscopic powder, which is freely soluble in water, dimethyl sulfoxide, methanol and dichloromethane, soluble in ethanol and slightly soluble in acetone. The substance exhibits chirality (1 chiral centre is present). Ivabradine hydrochloride exists as S-isomer & R-isomer. The S-isomer is used and the R-isomer is regarded as an impurity and controlled in the drug substance. The polymorphic form manufactured is mainly Ivabradine hydrochloride delta dehydrated polymorph (i.e., polymorph having 0% water content) with a low content of Ivabradine hydrochloride non-stoichiometrically hydrated delta polymorphic form.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The choice of the starting materials and the applied specifications are considered acceptable. The synthesis is performed in at least seven steps. The manufacturing process is sufficiently described.

Quality control of drug substance

Adequate drug substance specifications have been laid down. The analytical methods have been sufficiently described and adequately validated. Batch analysis results have been submitted for six batches of drug substance with results meeting the set drug substance specification.

Stability of drug substance

Six batches of drug substance have been put on stability. For three batches 12 months data at 25°C/60% RH, 14 months data at 30°C/65% RH, and 6 months data at 40°C/75% RH are available. All intermediate and long-term stability results show that the drug substance specifications are met. At accelerated conditions, an increase in one impurity was observed. Therefore, the storage condition of not above 30°C for ivabradine hydrochloride has been established. The results support a shelf life of 18 months.

II.3 Medicinal Product

Pharmaceutical development

The MAH developed dose proportional formulations of the 2.5 mg, 5 mg and 7.5 mg strengths. Due to patent reasons the MAH chose to use crystalline ivabradine hydrochloride form delta as drug substance. Ivabradine hydrochloride is present in amorphous form in the drug product.

The subdivision of the 5 mg strength is in accordance with the Ph. Eur. requirements and good results were obtained. In addition, as part of the development, the subdivision of the tablets had been assessed during stability. Tablets after 6 months at 40°C/75%RH and 25°C/60%RH packaged in PVC/PVDC/Al and Al/Al blisters met the requirements for subdivision.

A bioequivalence study was performed by comparing the 7.5 mg strength to Procoralan 7.5 mg. Comparative dissolution studies have been performed. At 15 min both test and reference biobatches were almost completely dissolved. The justification given for waiving the bioequivalence of the 5 mg strength is considered acceptable. Dissolution profiles of the two strengths were similar at three pH values.

Overall, the pharmaceutical development is considered acceptable.

Manufacturing process

The product is manufactured by a wet granulation process. Steps include dissolving, spaying, heating, blending, compression and film coating. The process can be considered standard. The in-process controls are considered acceptable. All finished product analyses on the final film-coated tablets were

satisfactory and meeting the set requirements. Validation has been performed on three batches, for each strength.

Control of excipients

All excipients used are well-known and widely used as pharmaceutical ingredients and comply with the relevant pharmacopoeial monographs and/or directives.

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 appearance, identification, water content, assay, uniformity of dosage units, impurities and dissolution. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. As a final check the MAH determined microbial content in the stored drug product after 1 year and will perform this another time at the end of shelf-life, as final support for the absence of release and shelf-life specifications; all microbial results were satisfactory so far.

Batch analysis data from three batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Batch analysis data have been provided on three batches of each strength stored at 25°C/60% RH (18 months), 40°C/75% RH (6 months). All results met the set requirements. However, for dissolution a decreasing trend is observed, especially in the 2.5 mg batches. It can be seen that the average dissolution result may decrease with 7-10%. In line with the Guideline Evaluation of stability data – Appendix A, if there is a clear change observed in the long-term data and a statistical evaluation has not been provided, extrapolation with only 6 months can be accepted. In view of this a shelf-life of 24 months if stored in the proposed packaging without specific temperature storage condition can be granted. The photostability studies demonstrated that the drug product is not light sensitive.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies

Regarding TSE risk, for lactose monohydrate an adequate BSE/TSE statement has been provided. The lactose has been certified by the suppliers as produced from milk obtained from healthy animals in the same condition as those used to collect milk for human consumption.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ivabradine DOC Generici 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 Ivabradine DOC Generici is intended for 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 and hybrid formulation of Procoralan, 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

Ivabradine 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ivabradine DOC Generici 7.5 mg film-coated tablets (DOC Generici S.r.l. Italy) is compared with the pharmacokinetic profile of the reference product Procoralan 7.5 mg, film-coated tablets (Les Laboratoires Servier Industrie, France).

Biowaiver

The 2.5 mg, 5 mg and 7.5 mg strengths are dose-proportional and are manufactured by the same manufacturing site using the same manufacturing process. The qualitative composition of the different strengths is the same and appropriate in vitro dissolution data confirmed the adequacy of waiving additional in vivo bioequivalence testing. Both strengths dissolved for more than 85% within 15 minutes. The biowaiver for the 2.5 mg and 5 mg strengths is considered acceptable.

Bioequivalence study

Design

A single-dose, randomised, two-way cross-over, two treatment, two period bioequivalence study was carried out under fed conditions in 36 healthy subjects (34 male and 2 female), aged 20-41 years. In each period each subject received a single dose (7.5 mg) of one of the 2 ivabradine formulations. The subjects fasted for at least 10 hours prior to the start of a breakfast. At 30 minutes before the medicinal product administration, subjects received a portioned amount of food and milk that comprised a standard high-fat, high-calorie breakfast. The breakfast consisted of bread with butter, French fries, fried chicken, 2 fried eggs and a glass of milk. The wash-out period between the treatments was 7 days.

Blood samples were withdrawn prior to dosing and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 12.00 and 24.00 hours after administration of the products.

The study design and blood sampling scheme are acceptable. The washout period is adequate. As the product should be administered with food, the choice of a high fat, high caloric meal is acceptable

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 was withdrawn from the study due to non-compliance to the fed condition and one subject dropped out of the study due to personal reasons. Therefore, 34 subjects completed the study and were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ SD, $t_{\max}$ (median, range)) of ivabradine under fed conditions.

Treatment N=34	AUC _{0-t} ng.h/ml	AUC _{0-∞} ng.h/ml	C _{max} ng/ml	t _{max} h
Test	175 $\pm$ 69.8	181 $\pm$ 70.9	36.0 $\pm$ 14.2	1.6 (0.25 - 4.0)
Reference	175 $\pm$ 73.6	181 $\pm$ 74.1	37.4 $\pm$ 16.2	1.9 (0.5 - 3.5)
*Ratio (90% CI)	1.02 (0.96 – 1.08)	--	0.98 (0.90 – 1.06)	--
CV (%)	15.0	--	19.5	--
AUC_{0-∞} 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 CV coefficient of variation				

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Ivabradine DOC Generici is considered bioequivalent with Procortalan.

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 Ivabradine DOC Generici.

Summary of safety concerns	
Important identified risks	• Bradycardia • Phosphenes/Blurred vision • 2nd and 3rd degree atrioventricular blocks • Increase in blood pressure in hypertensive patients • Atrial fibrillation (AF) • ECG prolonged QT interval
Important potential risks	• Supraventricular tachyarrhythmia (SVT) other than atrial fibrillation • Immune system disorders • Severe ventricular arrhythmia • Myocardial infarction
Missing information	• Children and adolescents (< 18 years old) • Pregnant and lactating women • Severe hepatic insufficiency • Severe renal impairment • Chronic heart failure patients with intraventricular conduction defects

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 Procoralan. 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 user test of the leaflet of Procoralan which has been assessed and approved by respective authorities. Readability is further assured by applying the MAH's layout for which user friendliness has been shown in several previously performed user-tests. The bridging report has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ivabradine DOC Generici 2.5 mg, 5 mg and 7.5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms (5 mg and 7.5 mg) and hybrid (2.5 mg) of Procoralan film-coated tablets. Procoralan 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 Ivabradine DOC Generici with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 December 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse