CBG MEB

Public Assessment Report

Scientific discussion

Ivabradine Xiromed 5 mg and 7.5 mg film-coated tablets

(ivabradine hydrochloride)

NL/H/3661/001-002/DC

Date: 6 June 2018

This module reflects the scientific discussion for the approval of Ivabradine Xiromed 5 mg and 7.5 mg film-coated tablets. The procedure was finalised on 14 May 2017. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

AF	Atrial fibrillation
ASMF	Active Substance Master File
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 Xiromed 5 mg and 7.5 mg film-coated tablets from Medical Valley Invest AB.

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 (see SmPC section 5.1).

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 which has been registered through centralised procedure EU/1/05/316/001-007 in the EU by Les Laboratoires Servier since 25 October 2005.

The concerned member states (CMS) involved in this procedure were the Czech Republic, Denmark, Greece, Romania, Sweden, Slovakia and the United Kingdom.

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

II. QUALITY ASPECTS

II.1 Introduction

Ivabradine Xiromed is a film-coated tablet:

- The 5 mg strength is a pale orange, capsule shape, biconvex, scored in one side, film coated tablet.
- The 7.5 mg strength is a pale orange, round, biconvex, film coated tablet.

The product contains as active substance 5 mg or 7.5 mg of ivabradine, as 5.390 mg or 8.085 mg of ivabradine hydrochloride.

The film-coated tablets are packed in blister polyamide-aluminium-PVC/aluminium.

The excipients are:
Tablet core - magnesium stearate (E 470 B), maize starch, maltodextrin, colloidal anhydrous silica (E551) and lactose monohydrate.
Film-coating - lactose monohydrate, titanium dioxide (E171), hipromellose, macrogol (E1521), iron oxide yellow (E172) and iron oxide red (E172).

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is ivabradine hydrochloride, an established active substance that is not described in the any Pharmacopoeia. The active substance is freely soluble in water. The molecule contains one asymmetric centre. The active substance is produced as a single enantiomer (S-configuration) and polymorphic form epsilon/IV (hemihydrate).

Both manufacturers used the Active Substance Master File (ASMF) procedure 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 manufacturing process consists of three chemical steps (manufacturer-I) or four steps (manufacturer-II). This is considered acceptable. The active substance has been characterised and acceptable specifications have been adopted for the starting materials, the solvents and the reagents used in the process. An adequate discussion on impurities is provided.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three batches of each manufacturer.

Stability of drug substance
Stability data on the active substance from manufacturer-I have been provided for three batches stored at 30°C/75% RH (6 months) and 40°C/75% RH (6 months). The retest period of 12 months and storage condition 'store below 30°C' can be granted.

Stability data on the active substance from manufacturer-II have been provided for five production batches stored at 30°C/65% RH (12-24 months) and 40°C/75% RH (6 months). The retest period of 36 months and storage condition 'store below 25°C' can be granted.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The 5 mg tablet can be divided into equal doses. The development of the dissolution method has been adequately described.

A bioequivalence study has been performed with the reference product Procoralan 7.5 mg tablets obtained from Spain. The test batch used in the bioequivalence study was of appropriate size and the commercial formulation and production process.

A biowaiver is requested and considered acceptable for the 5 mg tablet. Dissolution profiles of the test and reference batches of both strengths have been provided in three media with HCl 0.1N, pH 4.5 and pH 6.8. The batches showed >85% dissolution in 15 minutes in the three media and are therefore considered similar. The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is a straightforward process consisting of several pre-mix steps to obtain the common blend and direct compression prior to packaging. The description of the manufacturing process is sufficiently detailed. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with Ph.Eur. requirements except the coating mixture for which an adequate in-house specification is provided. These specifications are acceptable.

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, uniformity of mass, subdivision of tablets (5 mg tablets), dissolution, water, uniformity of dosage units, identification of colourant, identification of active substance, assay, related substances and microbial examination. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three full scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on 17 batches from both manufacturers and for both strengths, stored at 25°C/60% RH (12-24 months) and 40°C/75% RH (3-6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. Results remain well within specification. On the basis of the data submitted, a shelf-life of 24 months without specific storage restrictions was granted. The photostability results do not indicate any sensitivity to light.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Lactose monohydrate used in the manufacture of the tablets is of animal origin. Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ivabradine Xiromed has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Ivabradine Xiromed 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 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 hydrochloride 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

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Ivabradine Xiromed 7.5 mg film-coated tablets (Medical Valley Invest AB, Sweden) is compared with the pharmacokinetic profile of the reference product Procoralan 7.5 mg film-coated tablets (Servier Laboratories Limited, France).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
According to section 4.1.6 of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**) it is sufficient to establish bioequivalence at only one strength. A biowaiver for the additional strength is accepted as the following requirements are met:

- The pharmaceutical products are manufactured by the same manufacturing process.
- The qualitative composition of the different strengths is the same.
- The composition of the strengths is quantitatively proportional.
- The pharmacokinetics of ivabradine are linear and the composition of the two tablet formulations is dose proportional.
- Appropriate *in vitro* dissolution data should confirm the adequacy of waiving additional *in vivo* bioequivalence testing. Dissolution data using paddle apparatus, at 50 rpm and 900 ml media (pH 1.2, 4.5 and 6.8) showed comparable dissolution (more than 85% within 15 minutes).

Design
A single-dose, randomised, four-period, two-sequence, two-treatment, replicate bioequivalence study was carried out under fed conditions in 36 healthy subjects (18 male/18 female), aged 22-73 years. In each period subjects received a single dose (7.5 mg) of one of the two ivabradine hydrochloride formulations. Subjects were randomly assigned to one of the two dosing sequences (test-reference-test-reference or reference-test-reference-test). They consumed a breakfast starting 30 minutes prior to drug administration. The tablet was orally administered. The subjects fasted for at least 10 hours prior to the start of the breakfast. The breakfast consisted of two eggs, two slices of bacon, two slices of toast, 120 g of hash brown potatoes, 250 ml of whole milk and two teaspoons of butter. Total caloric content was about 900 kcal. There were four dosing periods, separated by a washout period of seven days.

Blood samples were collected prior to dosing and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 7, 8, 9, 10 and 12 hours after administration of the products.

The design of the study is acceptable. The replicate design was chosen to estimate the intra individual variability in C_{max}. The blood sampling scheme is acceptable, the wash-out period long enough regarding the half life of 11 hours. Ivabradine should be taken during meals in order to decrease the intra-individual variability in exposure. 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
Thirty three subjects completed all treatments. One subject was dismissed due to vomiting after dosing with the test product in period 4 and one subject withdrew before period 4. Both subjects were previously dosed with both products before they withdrew or were dismissed. These subjects were included in the pharmacokinetic and statistical analysis. One subject withdrew before period 2 and was only dosed with the reference product in period 1.
Therefore, 35 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=35	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	115 ± 37	119 ± 39	33.9 ± 13.0	1.67 (0.25 - 5.0)
Reference	116 ± 42	121 ± 45	34.0 ± 14.7	1.67 (0.5 - 6.0)
***Ratio (90% CI)**	1.01 (0.97 - 1.05)	--	1.01 (0.94 - 1.10)	--
CV (%)	14.5	--	35.0	--

$AUC_{0-\infty}$ 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
CV coefficient of variation

**ln-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 Xiromed 7.5 mg film-coated tablets is considered bioequivalent with Procoralan 7.5 mg film-coated tablets.

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 Xiromed.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Bradycardia • Phosphenes/Blurred vision • Atrioventricular block 2nd and 3rd degree • Increased in blood pressure in hypertensive patients • Atrial fibrillation (AF) • Prolonged QT interval on ECG
Important potential risks	• Supraventricular tachyarrhythmia (SVT) other than AF

	• Immune disorders • Myocardial infarction • Severe ventricular arrhythmia
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 7.5 mg film-coated 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Procoralan. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Ivabradine Xiromed 5 mg and 7.5 mg film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Procoralan 5 mg and 7.5 mg 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.

In the Board meeting of 10 May 2017, the following was discussed: The methodology of one manufacturer using the ASMF procedure appeared not to be according to ICH guidelines. Sufficient data has been provided subsequently, resolving the issue.

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 Xiromed 5 mg and 7.5 mg film-coated tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 May 2017.

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
NL/H/3661/001-002/IB/001	Change in name of the Medicinal Product in United Kingdom from “Ivabradine Liconsa 5 mg film-coated tablets” to “Ivabradine 5 mg film-coated tablets” and from “Ivabradine Liconsa 7.5 mg film-coated tablets” to “Ivabradine 7.5 mg film-coated tablets”.	6-11-2017	22-3-2018	Non-approval	--