IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ivabradine 7.5 mg film-coated tablets
Ivabradine
PA0343/012/002

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Ivabradine 5 mg & 7.5 mg film coated tablets, from Key Pharmaceuticals Ltd on 17th July 2020 for the following indications:
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 beats per minute beats per minute (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 section 5.1)

This application for a marketing authorisation was submitted under Article 10(1) of Directive 2001/83/EC as amended and via the decentralised procedure whereby Ireland (IE) was the Reference Member State and the United Kingdom is the sole the Concerned Member States.

This application concerns a generic application with Procoralan 7.5 mg film-coated tablets (Marketing authorisation holder: Les Laboratoires Servier) as the medicinal reference product.
Procoralan has been registered since 2005, having been approved by Centralised Procedure.

The applicant's product Ivabradine 5 mg & 7.5 mg film coated tablets are of the same indication, strength and route of administration as that of the reference medicinal product Procoralan 5mg and 7.5 mg film-coated tablets.

Ivabradine 5 mg & 7.5 mg film coated tablets are subject to prescription which may be renewed.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Ivabradine 7.5 mg film-coated tablets
Name(s) of the active substance(s) (INN)	Ivabradine
Pharmacotherapeutic classification (ATC Code)	C01EB17
Pharmaceutical form and strength(s)	7.5 mg, Film-coated tablet
Marketing Authorisation Number(s) in Ireland (PA)	PA0343/012/002
Marketing Authorisation Holder	Key Pharmaceuticals Ltd Galen House 83 High Street, Somersham Cambridgeshire PE28 3JB United Kingdom
MRP/DCP No.	IE/H/1092/002/DC
Reference Member State	Ireland
Concerned Member State(s)	UK

II. QUALITY ASPECTS

II.1. Introduction

This application is for Ivabradine 5 mg and 7.5 mg film-coated tablets.

II.2 Drug substance

The active substance is ivabradine hydrochloride, an established active substance not described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at a suitably qualified manufacturing site.

The manufacturing process has been validated according to relevant European guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for tablets, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site have been provided, and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.7 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with EU legislation for use with foodstuffs requirements.

P.8 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical and Pharmaceutical Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Ivabradine 5 mg and 7.5 mg film-coated tablets.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This active substance is a generic formulation of Procoralan on the European market. No new preclinical data have been submitted. This is acceptable for this type of application. Pharmacodynamic, pharmacokinetic and toxicological properties of ivabradine are well known. As ivabradine is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate from this type of application.

III.2 Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment has not been performed as this product is intended for generic substitution and therefore will not result in an increase of risk to the environment during use, storage and disposal.

III.3 Discussion on the non-clinical aspects

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate. Non-clinical findings are adequately mentioned in the appropriate sections of the SmPC. It should be noted that section 5.3 of the reference SmPC states that an ERA of ivabradine has been conducted and showed that ivabradine does not pose a threat to the environment.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a generic application submitted under article 10(1) of Directive 2001/83/EC.

Ivabradine is a well-known active substance with established efficacy and tolerability.

To support the application, the applicant has submitted the report of a bioequivalence study with the 7.5mg strength and a justification for waiver of a bioequivalence study with the 5mg strength.

Bioequivalence study: 7.5mg strength

An open label, laboratory-blind, balanced, randomized, 2-treatment, 2-sequence,2-period, single oral dose, crossover bioequivalence study in normal, healthy, adult, human male subjects under fed conditions was carried out.

Based on the pharmacokinetic parameters of active substance ivabradine, the reference tablet Procoralan 7.5mg film-coated tablets marketed by Les Laboratoires Servier and test tablet Ivabradine 7.5mg film coated tablet are bioequivalent with extent to the rate and extent of absorption and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

All criteria for a biowaiver are fulfilled for the 5 mg tablets. A biowaiver can therefore be granted based on bioequivalence of the 7.5 mg tablets with the reference product

The HPRA has been assured that GCP standards were followed in an appropriate manner in the studies conducted.

The content of the SmPCs approved during the decentralised procedure is in accordance with that accepted for the reference product Procoralan 5mg and 7.5mg film-coated tablets marketed by Les Laboratoires Servier.

IV.2 Pharmacokinetics

Ivabradine is rapidly and almost completely absorbed after oral administration with a peak plasma level reached in about 1 hour under fasting condition. The absolute bioavailability of the film-coated tablets is around 40%, due to first-pass effect in the gut and liver. Ivabradine is extensively metabolised by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. Ivabradine is eliminated with a main half-life of 2 hours (70-75% of the AUC) in plasma and an effective half-life of 11 hours. The kinetics of ivabradine is linear over an oral dose range of 0.5 – 24 mg.

IV.3 Pharmacodynamics

Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker If current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.

IV.4 Clinical Efficacy

The efficacy of ivabradine in the proposed indications is established in clinical use. No new clinical efficacy studies are provided and none are required.

IV.5 Clinical Safety

The overall safety profile of ivabradine is established and generally known. No new safety studies are provided and none are required.

The safety information in the SmPC and Package Leaflet are in line with those of the reference product.

IV.6 Discussion on the clinical aspects

As this is a generic application under Article 10(1) of Directive 2001/83/EC, additional non-clinical and clinical studies to demonstrate efficacy and safety are not required.
The applicant has submitted the results of a suitable bioequivalence study, which has demonstrated the similarity of the test product Ivabradine 7.5mg film-coated tablets P, in accordance with the relevant guidance. A justification for waiver of a study with the 5 mg strength has been provided. No additional tests are required for this application.

IV.7 Pharmacovigilance System

IV.8 Risk Management Plan (RMP)
The MAH 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 5mg and 7.5 mg film-coated tablets.
The submitted Risk Management Plan, version 3, signed 28 April 2020 is considered acceptable. Routine pharmacovigilance and routine risk minimisation are considered sufficient. The MAH is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary table of safety concerns as approved in RMP:

Important identified risks	Bradycardia Phosphenes and blurred vision 2nd and 3rd degree atrioventricular blocks ECG prolonged QT interval Increase in blood pressure in hypertensive patients Atrial fibrillation
Important potential risks	Supra-ventricular tachyarrhythmia other than atrial fibrillation Immune disorders Severe ventricular arrhythmias* Myocardial infarction
Missing information	Children and adolescent (< 18 years old) Pregnant and lactating women Severe hepatic insufficiency Severe renal insufficiency Chronic heart failure patients with intraventricular conduction defects

**Including Torsades des pointes, ventricular fibrillation/flutter/tachycardia/arrhythmia*

IV.9 Periodic Safety Update Report (PSUR)
With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines

web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.

- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

V. OVERALL CONCLUSIONS

Ivabradine 5 mg and 7.5 mg film-coated tablets is a generic form of Procoralan 5 mg and 7.5 mg film-coated tablets. Procoralan 5 mg and 7.5 mg film-coated tablets is a well-known medicinal product with a proven chemical-pharmaceutical quality and an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the CHMP guidance documents. The SmPC is consistent with that of the reference product.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The HPRA, on the basis of the data submitted considered that Ivabradine 5 mg and 7.5 mg film-coated tablets demonstrated bioequivalence with the reference product as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

VI. REVISION DATE

May 2021

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
MAH transfer	CRN00C5H6	SmPC section 7, 8, 10 Package Leaflet New MA Holder: Lexon Pharmaceuticals (Ireland) Limited New PA number: PA23176/008/002	N/A	21/05/2021