IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ivabradine Rowex 5 mg Film-coated Tablets
Ivabradine
PA0711/265/001

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

This product was initially authorised under procedure number NL/H/3640/001-002 with the Netherlands (NL) as RMS. The responsibility of RMS was transferred to Ireland on 21 December 2022 under procedure number IE/H/1271/001-002
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA0711/265/001-002
Marketing Authorisation Holder: Rowex Ltd

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

The NL public assessment report published at the time of the initial marketing authorisation is provided herein

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Ivabradine Sandoz 5 mg and 7.5 mg film-coated tablets from Sandoz B.V.

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 states (CMS) involved in this procedure were Austria, Belgium, Cyprus, Czech Republic, France, Germany, Greece, Hungary, Ireland, Luxembourg, Poland, Portugal, Romania, Slovakia and Spain.

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

II. QUALITY ASPECTS

II.1 Introduction

Ivabradine Sandoz 5 mg is a yellow coloured, round, film-coated tablet debossed with ´5´ on one side and scored on other side. The tablet can be divided into equal doses. One film-coated tablet contains
5 mg ivabradine (equivalent to 5.961 mg ivabradine as oxalate).

Ivabradine Sandoz 7.5 mg is an orange-yellow coloured, round, biconvex, film-coated tablet debossed with ´7.5´ on one side. One film-coated tablet contains 7.5 mg ivabradine (equivalent to 8.941 mg ivabradine as oxalate).

The film-coated tablets are packed in OPA/Aluminium/PVC-Aluminium blisters, PVC/PE/PVdC - Aluminium blisters and HDPE tablet container with PP child resistant screw cap containing desiccant (silica gel).

The excipients are:
Core-lactose anhydrous, colloidal anhydrous silica, croscarmellose sodium (E468), butylhydroxy- toluene (E321), magnesium stearate (E470b)

Film-coating-hypromellose (E 464), titanium dioxide (E171), macrogol 6000, magnesium stearate (E470b), iron oxide yellow (E172), glycerol (E 422), iron oxide red (E172)

The two strengths are dose-proportional.

II.2 Drug Substance

The active substance is ivabradine oxalate, an established active substance however not described in any pharmacopoeia. It is a white to off white, hygroscopic powder, which is soluble in chloroform and sparingly soluble in methylene chloride. The substance exhibits chirality (1 chiral centre is present). Ivabradine oxalate 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. Ivabradine oxalate can exist in various polymorphic forms. The crystalline form is manufactured.

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 starting materials are non-complex substances. The choice of the starting materials and the applied specifications are considered acceptable. 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 2 batches of drug substance with results meeting the set drug substance specification.

Stability of drug substance
Three batches of drug substance have been put on stability for 18 months at 25°C/60% RH and 6 months data at 40°C/75% RH. In addition data are available from batches produced by a different manufacturing process, a recrystallized drug substance batch and batches using an intermediate
stage.

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 ivabradine oxalate has been established as "Store in a well closed container at a temperature not exceeding 25°C". The results support the claimed shelf life of 36 months.

II.3 Medicinal Product

Pharmaceutical development
The MAH developed dose proportional formulations of the 5 mg and 7.5 mg strengths. Due to patent reasons the MAH chose to use ivabradine oxalate in stead of ivabradine hydrochloride, which is present in the innovator product. Although solubility of the oxalate is similar than the hydrochloride salt, the oxalate salt is more prone to oxidative degradation. For this reason very low quantities of butylhydroxytoluene (BHT) have been included in the formulation.

A bioequivalence study was performed by comparing the 7.5 mg test product to Procoralan 7.5 mg. Comparative dissolution studies have been performed. At 15 min both test and reference biobatches were almost completely dissolved. Dissolution

profiles of the two strengths were similar at three pH values. The justification given for waiving the bioequivalence of the 5 mg strength is considered acceptable. The subdivision of the 5 mg strength is in accordance with the Ph. Eur. requirements.

Manufacturing process
The product is manufactured by a dry granulation process. Steps include sifting, blending, roll compaction, milling, lubrication, compression and film coating. Based on validation results for three batches of 5 mg it was demonstrated that the inclusion of the low-level BHT is well under control. Content uniformity of BHT has been determined as well for various manufacturing stages. It was demonstrated that the low dosed antioxidant is adequately and uniformly distributed at all manufacturing stages of the drug product, and that acceptable level of antioxidant remain in the final drug product for protecting the product.

Controlof excipients
The excipients lactose anhydrous, croscarmellose sodium, colloidal anhydrous silica, butylhydroxy- toluene, magnesium stearate and purified water included in Ph. Eur. are tested according to the requirements described in the respective monograph.

The Opadry coating ingredients used in the coating of 5 mg and 7.5 mg comply with in-house testing procedures. These specifications are acceptable.

Qualitycontrolof drug product
Drug product specifications are applied for description, identification, water content, assay, uniformity of dosage units, subdivision of tablets (5 mg tablet), related substances, dissolution and microbiological quality. All analytical procedures have been described and adequately validated.

Batch analysis results are provided for 3 batches of each strength. All results met the set requirements.

Three 5 mg validation batches will be put on stability. The shelf-life specification on BHT will be reconsidered if necessary.

Stability of drug product
Batch analysis data have been provided on three batches of each strength stored at 25°C/60% RH,
30°C/65% RH and 40°C/75% RH. 18 months stability data for two batches packed in HDPE containers and blisters are available.
Photostability studies demonstrated that the drug product is not light sensitive.
Based on the available stability data for the two blister products the shelf-life claim of 24 months without specific storage condition can be accepted.
Based on the real time results for the HDPE container product the shelf-life claim of 18 months without specific storage condition can be accepted. The in-use stability shelf-life is restricted to 6 months
based on acceptable stability data up to 6 months. New in-use stability studies will be based on the three 5 mg validation batches.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
Regarding TSE risk, for lactose anhydrous an adequate BSE/TSE statement has been provided, and for magnesium stearate the stearic acid used is of vegetable origin.

II.4 Discussion on chemical,pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ivabradine Sandoz 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 riska ssessment (ERA)
Since Ivabradine Sandoz 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 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 as reports 2 bioequivalence studies: a pilot study to estimate the variability in the pharmacokinetic variables and a pivotal replicate design bioequivalence study with the highest dose under fed conditions.

IV.2 Pharmacokinetics

In the pilot study the test product was tested against the reference product under fed conditions in 14 subjects. The study showed that the intra-individual variability in Cmax was more than 30%. Only the pivotal study is further described below. The pilot study did not show contradictory data compared with the pivotal study.

In the pivotal bioequivalence study the pharmacokinetic profile of the test product Ivabradine Sandoz 7.5 mg (Sandoz B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product Procoralan 7.5 mg film-coated tablets (Les Laboratoires Servier, France).

The choice of the reference product in the bioequivalence study is justified as Procoralan has been registered through a centralised procedure. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver

The 5 mg and 7.5 mg strengths are dose-proportional and are manufactured by the same manufacturing site using the same manufacturing process. The pharmacokinetics of ivabradine are linear. Dissolution tests at pH 1.2, 4.5 and 6.8 showed comparable dissolution, i.e. more than 85% within 15 minutes. The biowaiver for the 5 mg tablet is considered acceptable.

Bioequivalencestudy

Design

A single-dose, randomised, two-way cross-over, four treatment, four period replicate design bioequivalence study was carried out under fed conditions in 40 healthy subjects (9 male/31 female),
aged 18-53 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 precisely 20 minutes before the medicinal product administration, subjects received a portioned amount of food and milk that comprised approximately 2/3 (two thirds) of a standard high-fat, high- calories breakfast. Content: - 1/2 slice of bread with 5 g of spread butter - 1 boiled egg - 125 g of French fries and - 150 ml whole milk. The tablet was orally administered with 200 ml water.

After dosing the subjects continued to eat the breakfast, and the remaining one third (1/3) of it's content was consumed within 10 minutes. Content: - 1/2 slice of bread with 5 g of spread butter - 1 boiled egg - 1 slice of bacon (25 g) and - 100 ml whole milk. The washout period between the treatments was 10 days.

Blood samples were withdrawn prior to dosing and at 0.333, 0.67, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.3, 3.6, 4, 4.5, 5, 5.5, 6, 6.5, 7, 8, 12 and 24 hours after administration of the products.

The study design and blood sampling scheme are acceptable. The washout period is long enough regarding the half life of 11 hours. 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. Due to

expected high intra-subject variability for the reference Cmax, the method of scaling the confidence acceptance limits was used. The within-subject coefficient of variation of the reference product was 32.33% and consequently, the acceptance limit for the 90% confidence interval of the geometric mean ratio for Cmax was widened to 78.69-127.08% (scaled bioequivalence criteria).

Results
All 40 subjects received both the test product and the reference product and completed the study

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

Treatment **N=40**	**AUC0-t** **ng.h/ml**	**AUC0-∞** **ng.h/ml**	**Cmax** **ng/ml**	**tmax h**	**t1/2 h**
Test	101.1 ±49.0	103.8 ±49.8	31.4 ±15.8	1.0 0.33 - 5.0	--
Reference	103.6 ±49.8	106.2 ±50.3	33.3 ±18.7	0.67 0.33 - 5.0	--
***Ratio (90% CI)**	0.98 (0.93 - 1.03)	--	0.97 (0.89 - 1.05)	--	--
CV(%)	19.8	--	32.4	--	--

AUC0-∞ area under the plasma concentration-time curve from time zero to infinity **AUC0-t** area under the plasma concentration-time curve from time zero to t hours **Cmax** maximum plasmaconcentration
tmax time for maximum concentration
t1/2 half-life
CV coefficient of variation

Conclusion on bioequivalencestudy
The results of the bioequivalence study show that the 90% confidence intervals calculated for AUC0-t and Cmax are within the standard bioequivalence acceptance range of 0.80 – 1.25. The predefined widened acceptance criteria for Cmax did not need to be applied. Ivabradine Sandoz 7.5 mg is considered bioequivalent with Procoralan 7.5 mg film-coated tablets.

The differences between AUC0-t and AUC0-∞ were all within 20%. In 14 subjects receiving the reference and 6 subjects receiving the test product Cmax was found on the first sampling point. This phenomenon was observed in all periods. The statistical analysis of Cmax with partial exclusion of data coming from subjects with Cmax as the first point of the PK curve was performed The MAH has shown that the consequences of deleting subjects having Cmax at the first sampling point did not jeopardise the conclusion of the study.

Safety
Nine (9) adverse events occurred during the present study, out of which the investigator deemed one (1) as being mild in severity and transient; the other eight (8) adverse events reported were related to clinical laboratory parameters found outside range at the follow-up examination in subjects who
declined to return for additional measurements of these parameters. Lacking further information, the
clinical significance of these values could not be assessed and also, the outcome and the duration were classified as "Unknown". Adverse events occurred in four out of forty subjects in the present study. The study medications were well tolerated by the healthy volunteers that participated in this study.

The MEB has been assured that the bioequivalence studies have 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 Sandoz.

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. OVERALL CONCLUSIONS

Ivabradine Sandoz 5 mg and 7.5 mg film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms 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 5 October 2017, the application was discussed. The Board concluded that the presence of the antioxidant BHT in the formulation, in order to maintain sufficient stability, has been properly justified. The MAH has demonstrated content uniformity during all manufacturing stages of the finished product.

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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 October 2016.

VI. REVISION DATE

24 April 2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From NL/H/3640/001-002 to IE/h?1271/001-002	N/A	21 December 2022	N/A