IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Ivabradine Krka 7.5 mg Film-coated Tablets
Ivabradine
PA1347/065/002

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

This product was initially authorised under procedure number HU/H/0439/001-002 with Hungary as RMS. The responsibility of RMS was transferred to Ireland on 09 March 2021 under procedure number IE/H/1177/001-002
Please note the following detail for the product in IE:
Marketing Authorisation Number: PA1347/065/001-002
Marketing Authorisation Holder: KRKA, d.d., Novo mesto

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

The Hungarian 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 marketing authorisation for **IvabradineKrka5mgand7,5mgfilm-coatedtablets**(Krka d.d., Novo mesto).

The products are indicated for the treatment of chronic stable angina pectoris.
Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in cor- onary 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.

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.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The Applicant has adequately demonstrated bioequivalence be- tween the product and reference products.

The originator products are Procoralan 5 mg film-coated tablets and Procoralan 7,5 mg film- coated tablets by Les Laboratoires Servier, France, EU, approved since 25-10-2005.

II. QUALITY ASPECTS

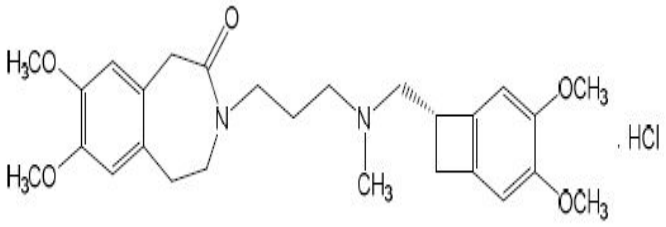
II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Ivabradine Krka 5 mg and 7.5 mg film-coated tablets via a decentralized procedure according to Article 10.1 of Directive 2001/83/EC (i.e a generic application). The products have been developed by KRKA d.d. Novo mesto.
Reference products are Procoralan 5 mg and 7.5 mg tablets (containing 5 and 7.5 mg ivabradine hydrochloride, respectively as active ingredient) which were the original products of Servier.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the applicant's submission using the Active Substance Master File (ASMF) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

International non proprietary name (rINN): Ivabradine
Chemical name: 3-[3-[[[(7S)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl]methyl]methylamino]propyl]-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one hydrochloride
Structure:



The active substance is white or almost white powder; hygroscopic; freely soluble in water, methanol and sparingly soluble in ethanol (96% V/V). The molecule contains one asymmetric carbon atom. Ivabradine has the S-configuration. It shows polymorphism, the manufacturer consistently produces the same polymorphic form.

The ASMF holder presented complete details of the manufacturing process. Description of the manufacturing process of the active pharmaceutical ingredient (API) is adequate.

Evidence of the structure has been confirmed by spectroscopy (FT-IR, 1H-NMR, 13C-NMR), mass spectrometry (MS) and elemental analysis. The discussion of the impurity profile of the API contains detailed information about genotoxic impurities, residual solvents and catalysts.

Ivabradine hydrochloride is not official in the Ph.Eur. Therefore, an in-house specification has been set for the active substance, which includes the following tests: appearance, identification by IR, chlorides identification, chiral identification, water content, sulphated ash, related sub- stances, chiral purity, residual solvents, assay and microbiological purity.

The presented specification is in accordance with the Ph.Eur. general monograph on Substances for Pharmaceutical Use and the ICH Q6A guideline. The specifications reflect all relevant qual- ity attributes of the active substance and were found to be adequate to control the quality of the drug substance. The limits set are properly justified.
Testing methods not described in details in the Pharmacopoeia are adequately drawn up and satisfactorily validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.
The substance complies with the requirements of the EMA guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

Stability studies have been performed with the drug substance. According to the presented sta- bility data the proposed re-test period is acceptable with no special storage condition.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product
The aim was to develop tablets containing ivabradine hydrochloride as drug substance in 5 and 7.5 mg doses bioequivalent and pharmaceutically equivalent to the reference medicinal product
Procoralan 5 mg and 7.5 mg film-coated tablets, the branded original products of Servier.

A satisfactory package of data on development pharmaceutics has been presented. Brief discus- sion on reasons for inclusion and quantity of excipients has been provided.
As regards dissolution and impurity profile the product is shown to be similar to the reference product.

The compositions and the pharmaceutical tests evaluated during development of the final for- mulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

5 mg film-coated tablets are pale pinkish orange, rectangular shaped, slightly biconvex with score line on one side, dimensions 8 mm x 4.5 mm. The tablet can be divided into equal doses.

7.5 mg film-coated tablets are pale pinkish orange, round, slightly biconvex film-coated tablets with bevelled edges, 7 mm in diameter.

The excipients used in the finished product are maltodextrin, lactose monohydrate, maize starch, silica, colloidal anhydrous, magnesium stearate, hypromellose 3 cP and coating mixture (hypromellose 6 cP, titanium dioxide (E171), propylene glycol, yellow iron oxide (E172), red iron oxide (E172), talc). All excipients used comply with their respective European Pharmaco- poeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia *on theProducts with the risk of TSE*has been demonstrated by the applicant.

A description and flow chart of the manufacturing method has been provided. Appropriate in- process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph.Eur. and the ICH Q6A guideline. Appropriate control strategy was se- lected. The test methods have been described and have been adequately validated, as appropri- ate. Batch data have been provided and complied with the specification. Certificates of analysis for the batches involved in the bioequivalence study are presented.

The container closure system of the product is OPA/Al/PVC//Al blister or perforated unit dose OPA/Al/PVC//Al blister and box. Specifications and quality certificates for all packaging com- ponents are enclosed.

Finished product stability studies have been conducted in accordance with the current guide- lines. Based on the results, a shelf-life of 2 years with no special storage conditions is approved. The Summary of Product Characteristics, patient Information Leaflet and label texts are phar- maceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Conclusion: The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of ivabradine are well known. As ivbradine is a widely used, well-known active substance, no further studies are required and the applicant provides none. The non-clinical overview is therefore based on a review of data available in several scientific databases or published in relation to the active ingredient, ivabradine.

III.2 Ecotoxicology/ environmnetal risk assessment (ERA)

Ivabradine Krka 5 mg and 7,5 mg film-coated tablets are 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.3 Discussionon the non-clinical aspects

Pharmacodynamics, pharmacokinetics and toxicology of ivabradine are well-known. As Ivabradine Krka is a generic product there is no need for further excessive non-clinical studies. The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of ivabradine is well known.

Except for showing bioequivalence, no specific clinical studies have been performed, as the application is submitted in accordance with Article 10(1) of Directive 2001/83/EC as amended. The application contains an adequate review of published clinical data.

IV.2 Pharmacokinetics

Absorption/distribution:

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.

Food delayed absorption by approximately 1 hour, and increased plasma exposure by 20 to 30 %. The intake of the tablet during meals is recommended in order to decrease intra-individual variability in exposure.

Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady-state is close to 100 l in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily is 22 ng/ml (CV=29%). The av- erage plasma concentration is 10 ng/ml (CV=38%) at steady-state.

Biotransformation and elimination:

Ivabradine is extensively metabolised by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. The major active metabolite is the N-desmethylated derivative (S 18982) with an exposure about 40% of that of the parent compound. The metabolism of this active metabolite also involves CYP3A4. Ivabradine has low affinity for CYP3A4, shows no clinically relevant CYP3A4 induction or inhibition and is therefore unlikely to modify CYP3A4 substrate metabolism or plasma concentrations. Inversely, potent inhibitors and inducers may substantially affect ivabradine plasma concentrations.

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 total clearance is about 400 ml/min and the renal clear- ance is about 70 ml/min. Excretion of metabolites occurs to a similar extent via faeces and urine. About 4% of an oral dose is excreted unchanged in urine.

Bioequivalence Biowaiver

The development studies focused on obtaining a product having similar characteristics to the reference product, i.e. dissolution profile and bioavailability.

For registration purpose a bioequivalence study was performed with Ivabradine 7.5 mg film- coated tablets (manufacturer: KRKA, d.d., Novo mesto, Slovenia) and the relevant strength of the innovator product, Procoralan® 7.5 mg film-coated tablets (manufacturer: Servier De- utschland GmbH, Germany).

Biowaiver

The Applicant claimed for biowaiver for the dose strength of 5 mg on the basis of general biowaiver requirements (CPMP/EWP/QWP/1401/98 Rev 1 Corr**):

a) Both strengths i.e. 5 and 7.5 mg of proposed pharmaceutical products are manufactured by the same manufacturer and using the same manufacturing process.
b) The qualitative composition of the different strengths is the same.
c) The composition of the claimed two strengths (5 and 7.5 mg) is proportionally similar.
d) The in-vitro dissolution data confirm the in-vivo similarity between the claimed two strengths.
e) Ivabradine exhibits linear pharmacokinetics in the claimed therapeutic range.

Biowaiver claim for the 5 mg dose-strengths is justified as general requirements for biowaiver are completely fulfilled.

Bioequivalence study

The applicant has submitted a bioequivalence study comparing the bioavailability between Ap- plicant's Ivabradine 7.5 mg film-coated tablets (manufacturer: KRKA, d.d., Novo mesto, Slo- venia) and the reference product Procoralan® 7.5 mg film-coated tablets (manufacturer: Servier Deutschland GmbH, Germany) in healthy subjects.

This was a comparative, randomised, single dose, 2-way cross over bioavailability study of two Ivabradine 7.5 mg tablet formulations with a 7-day washout period between the two periods, in healthy adult volunteers under fed conditions.

62 subjects were dosed in this period and 60 completed the study. 2 subjects were withdrawn from the study (reasons were intercurrent illness and personal reasons).

Subjects were administered the Test- and Reference medication (as per the randomisation scheme) as a single oral dose of 1 film-coated tablet containing 7.5 mg of ivabradine with 240 mL of room temperature water 30 minutes after the high fat breakfast had been started, during each study period.

A total of 22 blood samples (3 mL each) were taken at per period

. Results:

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0-t)}$	100.62%	94.97% - 106.60%	19.1%
Cmax	104.21%	94.90% - 114.44%	31.4%

[1]Estimated from the Residual Mean Squares.

Both formulations were well tolerated, with no major side effects and no relevant differences in safety profiles were observed between the preparations.

Conclusion on bioequivalence studies:
Results derived from analysis of log-transformed primary efficacy parameters (Cmax, AUC(0-t)) for ivabradine showed that the Test/Reference ratios of LS (least-squares) mean val- ues and their 90% confidence intervals also were entirely included within the acceptance range of 80% - 125%.
Based on the submitted bioequivalence study the Ivabradine 7.5 mg film-coated tablets (KRKA, d.d., Novo mesto, Slovenia) (Test) is considered to be bioequivalent with the Procoralan® 7.5 mg film-coated tablets (Servier Deutschland GmbH Germany, EU) (Reference).

The results of the study with 7,5 mg formulation can be extrapolated to 5 mg strength, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*.

IV.3 Pharmacodynamics

Clinical pharmacology studies to evaluate the pharmacodynamics of Ivabradine Krka 5 mg and 7.5 mg tablets were not performed.

IV.4 Clinical efficacy

No new efficacy data have been submitted and none are required. The applicant has provided an adequate review of clinical trials published in the literature, describing the efficacy and safety profile of ivabradine.

IV.5 Clinical safety

With the exception of the data generated during the bioequivalence studies, no new safety data were submitted and none were required for this application. No new or unexpected safety issues were raised by the bioequivalence data.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance System

The Applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant GVP module, the Summary is considered acceptable.

Summary of safety concerns	
Important identified risks	• Bradycardia • Phosphenes/blurred vision • 2nd and 3rd degree atrioventricular blocks (AVB II and III) • Increase in blood pressure in hypertensive patients • Atrial fibrillation (AF) • ECG prolonged QT interval
Important potential risks	• Supra-ventricular tachyarrhythmia(SVT) other than atrial fibrillation • Immune disorders • Severe ventricular arrhythmia

	• Myocardial infarction
Missing information	• Use in children under 18 years old • Use in pregnancy and breastfeeding women • Use in patients with severe hepatic insufficiency • Use in patients with severe renal impairment • Use in chronic heart failure patients with intra-ventricular conduction defects

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety con- cerns connected to Ivabradine Krka 1g and 2 g powder for solution for injection/infusion.
No additional activities are proposed.

Risk Minimisation Measures

Routine risk minimisation measures (i.e. wording in SmPC, PL and classification as a prescription only medicine) are considered sufficient to manage all of the safety concerns con- nected to Ivabradine Krka 1g and 2 g powder for solution for injection/infusion.
No additional activities are proposed. For any further information on risk minimisation, please refer to the product information.

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for these medicinal products are set out in the list of Union reference dates (EURD list) provided for un-der Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

IV.7 Discussion on the clinical aspects

The application concerns a generic product.

The indications are the 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 be- tablocker 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 ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

To support the application the Applicant has adequately demonstrated bioequivalence between Ivabradine Krka 5 mg and 7,5 mg film-coated tablets and the reference product Procoralan 5 mg and 7,5 mg film-coated tablets.
There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSIONS

V.1 Summary
The bioequivalence study has shown that the applicant's product is bioequivalent to the refer- ence product. The benefit risk assessment is considered positive and approval is recommended from a clinical point of view.

Based on the review of the data on safety and efficacy, the RMS considers that the application for Ivabradine Krka 5 mg and 7,5 mg film-coated tablets, **is approvable.**

V.2 Classification

Prescription-only medicine.

VI. REVISION DATE

25 April 2024

VII. UPDATES

SCOPE	PROCEDURE NUMBER	PRODUCT INFORMATION AFFECTED	DATE OF START OF PROCEDURE	DATE OF END OF PROCEDURE
RMS transfer	From HU/H/0439/001-002 to IE/H/1177/001-002	N/A	09 March 2021	N/A