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Public Assessment Report

Name of the Product:

Ivabradine Krka

5 mg and 7,5 mg

film-coated tablets

(Ivabradine hydrochloride)

Procedure number: HU/H/0439/001-002/DC

Marketing authorisation holder: KRKA, d.d., Novo mesto

Date: 17th March 2021

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Ivabradine Krka 5 mg and 7,5 mg film-coated tablets. The holder of the marketing authorisation is KRKA, d.d., Novo mesto.

The active substance is ivabradine.

Ivabradine Krka 5 mg film-coated tablets:
Each film-coated tablet contains 5 mg ivabradine (as ivabradine hydrochloride).

Ivabradine Krka 7.5 mg film-coated tablets:
Each film-coated tablet contains 7.5 mg ivabradine (as ivabradine hydrochloride).

The other ingredients (excipients) are maltodextrin, lactose monohydrate, maize starch, colloidal anhydrous silica, magnesium stearate (E470b) and hypromellose 3 cP in the tablet core and hypromellose 6 cP, titanium dioxide (E171), talc, propylene glycol, yellow iron oxide (E172) and red iron oxide (E172) in the film coating. See section 2 "Ivabradine Krka contains lactose".

The appearance of the film-coated tablets:

Ivabradine Krka 5 mg and 7,5 mg film-coated tablets are supplied in the following pack sizes:
Ivabradine Krka 5 mg film-coated tablets:
Film-coated tablets (tablets) are pale pinkish orange, rectangular, slightly biconvex, with a score line on one side, dimensions 8 mm x 4.5 mm. The tablet can be divided into equal doses.

Ivabradine Krka 7.5 mg film-coated tablets:
Film-coated tablets (tablets) are pale pinkish orange, round, slightly biconvex, with bevelled edges, 7 mm in diameter.

Not all pack sizes may be marketed.

What Ivabradine Krka is and what it is used for

Ivabradine Krka (ivabradine) is a heart medicine used to treat:
- Symptomatic stable angina pectoris (which causes chest pain) in adult patients whose heart rate is over or equal to 70 beats per minute. It is used in adult patients who do not tolerate or cannot take heart medicines called beta-blockers. It is also used in combination with beta-blockers in adult patients whose condition is not fully controlled with a beta-blocker.
- Chronic heart failure in adult patients whose heart rate is over or equal to 75 beats per minute. It is used in combination with standard therapy, including beta-blocker therapy or when beta-blockers are contraindicated or not tolerated.

About stable angina pectoris (usually referred to as “angina”):
Stable angina is a heart disease which happens when the heart does not receive enough oxygen. It usually appears between 40 and 50 years of age. The most common symptom of angina is

chest pain or discomfort. Angina is more likely to happen when the heart beats faster in situations such as exercise, emotion, exposure to the cold or after eating. This increase in heart rate can cause the chest pain in people who suffer from angina.

About chronic heart failure:
Chronic heart failure is a heart disease which happens when patient's heart cannot pump enough blood to the rest of his/her body. The most common symptoms of heart failure are breathlessness, fatigue, tiredness and ankle swelling.

How does Ivabradine Krka work?
Ivabradine Krka mainly works by reducing the heart rate by a few beats per minute. This lowers the heart's need for oxygen especially in the situations when an angina attack is more likely to happen. In this way Ivabradine Krka helps to control and reduce the number of angina attacks.

Furthermore as elevated heart rate adversely affects the heart functioning and vital prognosis in patients with chronic heart failure, the specific heart rate lowering action of ivabradine helps to improve the heart functioning and vital prognosis in these patients.

What patients need to know before using Ivabradine Krka

Ivabradine Krka must not be given:
- if the patient is allergic to ivabradine or any of the other ingredients of this medicine (listed in section 6);
- if the patient's resting heart rate before treatment is too slow (below 70 beats per minute);
- if the patient is suffering from cardiogenic shock (a heart condition treated in hospital);
- if the patient suffers from a heart rhythm disorder;
- if the patient is having a heart attack;
- if the patient suffers from very low blood pressure;
- if the patient suffers from unstable angina (a severe form in which chest pain occurs very frequently and with or without exertion);
- if the patient has heart failure which has recently become worse;
- if the patient's heart beat is exclusively imposed by his/her pacemaker;
- if the patient suffer from severe liver problems;
- if the patient is already taking medicines for the treatment of fungal infections (such as ketoconazole, itraconazole), macrolide antibiotics (such as josamycin, clarithromycin, telithromycin or erythromycin given orally), medicines to treat HIV infections (such as nelfinavir, ritonavir) or nefazodone (medicine to treat depression) or diltiazem, verapamil (used for high blood pressure or angina pectoris);
- if the patient is a woman able to have children and not using reliable contraception;
- if the patient is pregnant or trying to become pregnant;
- if the patient is breast-feeding.

Warnings and precautions

Patients should talk to their doctor, pharmacist before they take Ivabradine Krka:

- if the patient suffers from heart rhythm disorders (such as irregular heartbeat, palpitation, increase in chest pain) or sustained atrial fibrillation (a type of irregular heartbeat), or an

abnormality of electrocardiogram (ECG) called 'long QT syndrome';
- if the patient has symptoms such as tiredness, dizziness or shortness of breath (this could mean that his/her heart is slowing down too much);
- if the patient suffers from symptoms of atrial fibrillation (pulse rate at rest unusually high (over 110 beats per minute) or irregular, without any apparent reason, making it difficult to measure);
- if the patient has had a recent stroke (cerebral attack);
- if the patient suffers from mild to moderate low blood pressure;
- if the patient suffers from uncontrolled blood pressure, especially after a change in his/her antihypertensive treatment;
- if the patient suffers from severe heart failure or heart failure with abnormality of ECG called 'bundle branch block';
- if the patient suffers from chronic eye retinal disease;
- if the patient suffers from moderate liver problems;
- if the patient suffers from severe renal problems.

If any of the above applies to the patient, he/she should talk straight away to his/her doctor before or while taking Ivabradine Krka.

Children and adolescents

Ivabradine Krka is not intended for use in children and adolescents younger than 18 years.

Other medicines and Ivabradine Krka

Patients should tell their doctor or pharmacist if they are taking, have recently taken or might take any other medicines.

Patients should make sure to tell his/her doctor if they are taking any of the following medicines, as a dose adjustment of Ivabradine Krka or monitoring should be required:
- fluconazole (an antifungal medicine)
- rifampicin (an antibiotic)
- barbiturates (for difficult sleeping or epilepsy)
- phenytoin (for epilepsy)
- *Hypericum perforatum* or St John's Wort (herbal treatment for depression)
- QT prolonging medicines to treat either heart rhythm disorders or other conditions:
  - quinidine, disopyramide, ibutilide, sotalol, amiodarone (to treat heart rhythm disorders)
  - bepridil (to treat angina pectoris)
  - certain types of medicines to treat anxiety, schizophrenia or other psychoses (such as pimozide, ziprasidone, sertindole)
  - anti-malarial medicines (such as mefloquine or halofantrine)
  - intravenous erythromycin (an antibiotic)
  - pentamidine (an antiparasitic medicine)
  - cisapride (against the gastro-oesophageal reflux)
- Some types of diuretics which may cause decrease in blood potassium level, such as furosemide, hydrochlorothiazide, indapamide (used to treat oedema, high blood pressure).

Ivabradine Krka with food and drink

Patients should avoid grapefruit juice during treatment with Ivabradine Krka.

Pregnancy, breast-feeding and fertility

Patients should not take Ivabradine Krka if they are pregnant or are planning to have a baby (see "Do not take Ivabradine Krka").
If the patients is pregnant and have taken Ivabradine Krka, she should talk to her doctor.
Patients should not take Ivabradine Krka if they are able to become pregnant unless they use reliable contraceptive measures (see "Do not take Ivabradine Krka").
Patients should not take Ivabradine Krka if they are breast-feeding (see "Do not take Ivabradine Krka"). Patients should talk to their doctor if they are breast-feeding or intending to breast-feed as breastfeeding should be discontinued if they take Ivabradine Krka.
If the patient is pregnant or breast-feeding, think she may be pregnant or is planning to have a baby, she should ask her doctor or pharmacist for advice before taking this medicine.

Driving and using machines

Ivabradine Krka may cause temporary luminous visual phenomena (a temporary brightness in the field of vision, see "Possible side effects"). If this happens to the patient, he/she should be careful when driving or using machines at times when there could be sudden changes in light intensity, especially when driving at night.

Ivabradine Krka contains lactose

If the patient have been told by his/her doctor that he/she have an intolerance to some sugars, he/she should contact his/her doctor before taking this medicinal product.

How to use Ivabradine Krka?

Patients should always take this medicine exactly as their doctor or pharmacist has told them.
Patients should check with their doctor or pharmacist if they are not sure.
Ivabradine Krka should be taken during meals.

<u>If the patient is being treated for stable angina pectoris</u>
The starting dose should not exceed one tablet of Ivabradine Krka 5 mg twice daily. If the patient still have angina symptoms and if he/she has tolerated the 5 mg twice daily dose well, the dose may be increased. The maintenance dose should not exceed 7.5 mg twice daily. The doctor will prescribe the right dose for the patients. The usual dose is one tablet in the morning and one tablet in the evening. In some cases (e.g. if the patients are elderly), the doctor may prescribe half the dose i.e., one half 5 mg tablet of Ivabradine Krka 5 mg (corresponding to 2.5 mg ivabradine) in the morning and one half 5 mg tablet in the evening.

<u>If the patient is being treated for chronic heart failure</u>
The usual recommended starting dose is one tablet of Ivabradine Krka 5 mg twice daily increasing if necessary to one tablet of Ivabradine Krka 7.5 mg twice daily. The doctor will decide the right dose for the patients. The usual dose is one tablet in the morning and one tablet in the evening. In some cases (e.g. if the patients are elderly), the doctor may prescribe half the dose i.e., one half 5 mg tablet of Ivabradine Krka 5 mg (corresponding to 2.5 mg ivabradine) in

the morning and one half 5 mg tablet in the evening.

What to do if more Ivabradine Krka was taken that it should have been?

A large dose of Ivabradine Krka could make the patient feel breathless or tired because his/her heart slows down too much. If this happens, patients should contact their doctor immediately.

What to do if taking Ivabradine Krka was forgotten?

If the patient forgets to take a dose of Ivabradine Krka, take the next dose at the usual time. Do not take a double dose to make up for a forgotten tablet.

If the patient stops using Ivabradine Krka

As the treatment for angina or chronic heart failure is usually life-long, the patient should discuss with his/her doctor before stopping this medicinal product.
If the patient thinks that the effect of Ivabradine Krka is too strong or too weak, talk to his/her doctor or pharmacist.
If patients have any further questions on the use of this medicine, they should ask their doctor or nurse.

Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most common adverse reactions with this medicine are dose dependent and related to its mode of action:

Very common (may affect more than 1 in 10 people)*:*
Luminous visual phenomena (brief moments of increased brightness, most often caused by sudden changes in light intensity). They can also be described as a halo, coloured flashes, image decomposition or multiple images. They generally occur within the first two months of treatment after which they may occur repeatedly and resolve during or after treatment.

Common (may affect up to 1 in 10 people):
Modification in the heart functioning (the symptoms are a slowing down of the heart rate). They particularly occur within the first 2 to 3 months of treatment initiation.

Other side effects have also been reported:

Common (may affect up to 1 in 10 people):
Irregular rapid contraction of the heart, abnormal perception of heartbeat, uncontrolled blood pressure, headache, dizziness and blurred vision (cloudy vision).

Uncommon (may affect up to 1 in 100 people):
Palpitations and cardiac extra beats, feeling sick (nausea), constipation, diarrhoea, abdominal pain, spinning sensation (vertigo), difficulty breathing (dyspnoea), muscle cramps, changes in laboratory parameters : high blood levels of uric acid, an excess of eosinophils (a type of white blood cell) and elevated creatinine in blood (a breakdown product of muscle), skin rash,

angioedema (such as swollen face, tongue or throat, difficulty in breathing or swallowing), low blood pressure, fainting, feeling of tiredness, feeling of weakness, abnormal ECG heart tracing, double vision, impaired vision.

Rare (may affect up to 1 in 1,000 people):
Urticaria, itching, skin reddening, feeling unwell.

Very rare (may affect up to 1 in 10,000 people):
Irregular heart beats.

Reporting of side effects

If the patients get any side effects, they should talk to their doctor, pharmacist. This includes any possible side effects not listed in this leaflet. Patients can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects patients can help provide more information on the safety of this medicine.

How to store Ivabradine Krka?

This medicine should be kept out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or blister after EXP. The expiry date refers to the last day of that month.
This medicinal product does not require any special temperature storage conditions.

Patients should not throw away any medicines via wastewater or household waste. Their pharmacist should be asked how to throw away medicines they no longer use. These measures will help protect the environment.

SCIENTIFIC DISCUSSION

This module reflects the scientific discussion for the approval of Ivabradine Krka 5 mg and 7,5 mg film-coated tablets. The procedure was finalised on 20-10-2020. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for **Ivabradine Krka 5 mg and 7,5 mg film-coated tablets** (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 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.

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 between 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

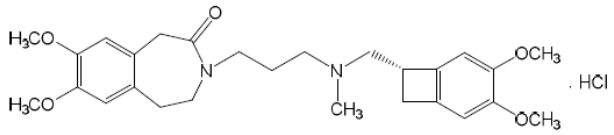
II.1 Introduction

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, ^{1}H-NMR, ^{13}C-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 substances, 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 quality 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 stability 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 discussion 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 formulation 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 Pharmacopoeia monograph. Compliance of the product with the general monograph of the European Pharmacopoeia *on the Products 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 selected. The test methods have been described and have been adequately validated, as appropriate. 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 components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. 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 pharmaceutically 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 Discussion on 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 average 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 clearance 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 Deutschland 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 Applicant's Ivabradine 7.5 mg film-coated tablets (manufacturer: KRKA, d.d., Novo mesto, Slovenia) 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.

Safety:
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 values 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.

IV.6.2 Risk Management Plan

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 intraventricular conduction defects

Pharmacovigilance plan

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns 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 connected 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 CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The bioequivalence study has shown that the applicant's product is bioequivalent to the reference 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.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.
The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of the initial pilot study and then two phases of testing with ten subjects'. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. UPGRADE: STEPS TAKEN AFTER THE INITIAL PROCEDURE WITH AN INFLUENCE ON THE PUBLIC ASSESSMENT REPORT

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval
B.I.a).1. a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	HU/H/0439/001/IA/001	No	2017.01.24	2017.02.21	Positive
B.I.a).1. a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	HU/H/0439/002/IA/001	No	2017.01.24	2017.02.21	Positive
B.I.a).1. a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a).3. a) Up to 10-fold increase compared to the originally approved batch size	HU/H/0439/001/IB/002/G	No	2017.03.10	2017.04.10	Approved
B.I.a).1. a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a).3. a) Up to 10-fold increase compared to the originally approved batch size	HU/H/0439/002/IB/002/G	No	2017.03.10	2017.04.10	Approved
C.I.2. a) Implementation of change(s) for which no new additional data is required to be submitted by	HU/H/0439/001/IB/003	Yes	2018.04.11	2018.05.11	Approved

the MAH Harmonization of documents for ivabradin tablets with changes that originator made in April 2016.					
C.I.2. a) Implementation of change(s) for which no new additional data is required to be submitted by the MAH Harmonization of documents for ivabradin tablets with changes that originator made in April 2016.	HU/H/0439/002/IB/003	Yes	2018.04.11	2018.05.11	Approved
B.I.d).1.b). 1 Change to more restrictive storage conditions of the active substance	HU/H/0439/001/IB/004	No	2018.08.06	2018.10.30	Approved
B.I.d).1.b). 1 Change to more restrictive storage conditions of the active substance	HU/H/0439/002/IB/004	No	2018.08.06	2018.10.30	Approved
B.II.f).1.b). 1 As packaged for sale (supported by real time data)	HU/H/0439/001/IB/005	Yes	2018.09.18	2018.10.18	Approved
B.II.f).1.b). 1 As packaged for sale (supported by real time data)	HU/H/0439/002/IB/005	Yes	2018.09.18	2018.10.18	Approved
A.7. Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)* B.II.b).3. a) Minor change in the manufacturing process	HU/H/0439/001/IA/006/G	No	2018.10.30	2018.11.29	Positive
A.7. Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)* B.II.b).3. a) Minor change in the manufacturing process	HU/H/0439/002/IA/006/G	No	2018.10.30	2018.11.29	Positive
B.I.a).1. z) Other variation B.I.a).2. e) Minor change to the restricted part of an Active Substance	HU/H/0439/001/IB/007/G	No	2019.04.01	2019.06.21	Approved

Master File B.I.b).2. e) Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate					
B.I.a).1. z) Other variation B.I.a).2. e) Minor change to the restricted part of an Active Substance Master File B.I.b).2. e) Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	HU/H/0439/002/IB/007/G	No	2019.04.01	2019.06.21	Approved
A.4. Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites) B.I.b).2. a) Minor changes to an approved test procedure	HU/H/0439/001/IA/008/G	No	2020.07.10	2020.08.09	Positive
A.4. Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites) B.I.b).2. a) Minor changes to an approved test procedure	HU/H/0439/002/IA/008/G	No	2020.07.10	2020.08.09	Positive

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)