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Public Assessment Report

Name of the Product:

Bravadin

5 mg, 7.5 mg film-coated tablets

(ivabradine hydrochloride)

Procedure number: HU/H/0441/001-002/DC

Marketing authorisation holder: Krka d.d.

Date: 25 May 2016

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the reference member state has granted the marketing authorisation of the Bravadin 5 mg and 7.5 mg film-coated tablets. The holder of the marketing authorisation is Krka d.d.

The active substance is ivabradine (as ivabradine hydrochloride).

The other ingredients (excipients) are:
- tablet core: maltodextrin, lactose monohydrate, maize starch, colloidal anhydrous silica, magnesium stearate (E470b) and hypromellose;
- film coating: hypromellose, titanium dioxide (E171), talc, propylene glycol, yellow iron oxide (E172) and red iron oxide (E172).

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

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

The film-coated tablets are available in OPA/Al/PVC//Al blisters or perforated unit dose OPA/Al/PVC//Al blisters in boxes.

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 your heart cannot pump enough blood to the rest of your body. The most common symptoms of heart failure are breathlessness, fatigue, tiredness and ankle swelling.

Ivabradine 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 Bravadin 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 taking Bravadin

Those who:
- are allergic to ivabradine or any of the other ingredients of this medicine;
- have a resting heart rate before treatment what is too slow (below 70 beats per minute);
- are suffering from cardiogenic shock (a heart condition treated in hospital);
- suffer from a heart rhythm disorder;
- are having a heart attack;
- suffer from very low blood pressure;
- suffer from unstable angina (a severe form in which chest pain occurs very frequently and with or without exertion);
- have heart failure which has recently become worse;
- have a heart beat what is exclusively imposed by the pacemaker;
- suffer from severe liver problems;
- you are 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);
- are a woman able to have children and not using reliable contraception;
- are pregnant or trying to become pregnant;
- are breast-feeding.

should not take Bravadin.

Warnings and precautions

Before taking Bravadin, patient who:
- suffer 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';
- have symptoms such as tiredness, dizziness or shortness of breath (this could mean that the heart is slowing down too much);

- suffer 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);
- have had a recent stroke (cerebral attack);
- suffer from mild to moderate low blood pressure;
- suffer from uncontrolled blood pressure, especially after a change in the antihypertensive treatment;
- suffer from severe heart failure or heart failure with abnormality of ECG called 'bundle branch block';
- suffer from chronic eye retinal disease;
- suffer from moderate liver problems;
- suffer from severe renal problems

should consult their doctor. If any of the above applies, they should talk straight away to the doctor before or while taking Bravadin.

Children and adolescents

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

Other medicines and Bravadin

Patients who are taking, have recently taken or might take any other medicines should consult their doctor.

In case of taking the following medicines, a dose adjustment of Bravadin 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 preparations (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).

Bravadin with food and drink

Avoid grapefruit juice during treatment with Bravadin.

Pregnancy and breast-feeding

Those who are pregnant or are planning to have a baby should not take Bravadin. They should contact their doctor.

Those who are able to become pregnant should not take Bravadin unless they use reliable contraceptive measures.

Those who are breast-feeding should not take Bravadin. They, and also who are intending to breast-feed should consult their doctor for breastfeeding should be discontinued when taking Bravadin.

Driving and using machines

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

Bravadin contains lactose

Those who been told by their doctor that they have an intolerance to some sugars, contact their doctor before taking this medicinal product.

How to take Bravadin?

Bravadin should be taken during meals.

Patients who are being treated for stable angina pectoris

The starting dose should not exceed one tablet of Bravadin 5 mg twice daily. If the patient still has angina symptoms and if the pateint 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. The usual dose is one tablet in the morning and one tablet in the evening. In some cases (e.g. for the elderly), the doctor may prescribe half the dose i.e., one half 5 mg tablet of Bravadin 5 mg (corresponding to 2.5 mg ivabradine) in the morning and one half 5 mg tablet in the evening.

Patients who are being treated for chronic heart failure

The usual recommended starting dose is one tablet of Bravadin 5 mg twice daily increasing if necessary to one tablet of Bravadin 7.5 mg twice daily. The doctor will decide the right dose.

The usual dose is one tablet in the morning and one tablet in the evening. In some cases (e.g. for the elderly), the doctor may prescribe half the dose i.e., one half 5 mg tablet of Bravadin 5 mg (corresponding to 2.5 mg ivabradine) in the morning and one half 5 mg tablet in the evening.

What happens if more Bravadin has been taken than it should have been
A large dose of could make the patient tofeel breathless or tired because the heart slows down too much. If this happens, the doctor should be contacted immediately.

What to do if taking Bravadin has been forgotten?

If the patient forgets to take a dose of Bravadin, he/she should take the next dose at the usual time. Do not take a double dose to make up for a forgotten tablet.

May taking Bravadin be stopped?

As the treatment for angina or chronic heart failure is usually life-long, the patient should discuss with the doctor before stopping this medicinal product.

Patients who think that the effect of Bravadin is too strong or too weak, consult their doctor.

Possible side effects

Like all medicines, Bravadin film-coated tablets can cause side effects, although not everybody experiences 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: 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.

How to store Bravadin

This medicine does not require any special storage conditions but it must be kept out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Bravadin 5 mg and 7.5 mg film-coated tablets. The procedure was finalised at 25 March 2016. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the member States concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, no concerned member state remained at the end of the procedure concerned the generic version of ivabradine 5 mg tablets and 7.5 mg film-coated tablets (Bravadin tablets).

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 products and the reference products.

The originator (reference) products were Procoralan 5 mg and 7.5 mg film-coated tablets by Les Laboratoires Servier, France, approved since 2005.

Based on the review of the quality, safety and efficacy data, the reference member state has granted marketing authorisation for Bravadin 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.

> Bravadine film-coated tablets are 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.
>
> Bravadine film-coated tablets are also 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 Summary of Product Characteristics (SmPC).

II. QUALITY ASPECTS

II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Bravadin 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. The reference products were 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.

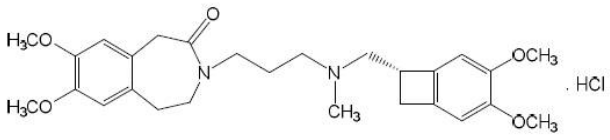
II.2 Drug substance

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 drug substance contains detailed information about genotoxic impurities, residual solvents and catalysts.

Ivabradine hydrochloride is not official in the European Pharmacopoeia (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 International Council of Harmonisation (ICH) Q6A guideline. The specification reflects 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 drug substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The drug substance complies with the requirements of the European Medicines Agency (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 drug substance 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 pharmaceutically equivalent and bioequivalent 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 has been 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.

The 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 tablets can be divided into equal doses.

The 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) and talc). All excipients used comply with their respective Ph. Eur. monographs. Compliance of the product with the general monograph of the Ph. Eur. 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 required in the relevant dosage form monograph of the Ph. Eur. as well as 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 SmPC, the package leaflet and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to meet the current regulatory requirements with regards to their 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.

From quality aspects the products are approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of ivabradine are well known. As ivabradine is a widely used, well-known active substance, no further studies were required and the applicant provided 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.

For a generic application this is acceptable.

III.2 Pharmacology

The drug product Bravadin contains as active substance ivabradine. It is oral anti-anginal drug. It belongs to the class of *If* channel inhibitors also including cilobradine and zatebradine. The If current is an ionic current that determines the slope of the diastolic depolarisation, which in turn controls the heart beating rate. Ivabradine specifically blocks cardiac pacemaker cell f-channels by entering and binding to a site in the channel pore from the intracellular side. Ivabradine is selective for the If current and exerts significant inhibition of this current and heart rate reduction at concentrations that do not affect other cardiac ionic currents. It is the first specific heart rate-lowering agent to have completed clinical development for stable angina pectoris.

The active substance is a well-known compound. No further information was provided regarding the experimental pharmacology of ivabradine.

III.3 Pharmacokinetics

No new non-clinical pharmacokinetic studies were conducted by the applicant.

III.4 Toxicology

Published information on toxicological studies with ivabradine was the basis for the evaluation.
No new toxicity studies were submitted by the applicant for the product, which is acceptable for this type of application.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Bravadin 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.6 Discussion on the non-clinical aspects

Abridged applications avoid the need for repetitive tests on animals.

Pharmacodynamics, pharmacokinetics and toxicology of ivabradine are well-known. As Bravadin is a generic product, there has been 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 demonstrating 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

IV.2.1 Literature data

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.

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 simi-

lar extent via faeces and urine. About 4% of an oral dose is excreted unchanged in urine.

IV.2.2 Bioequivalence study

Introduction

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

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

Similarities of in-vitro dissolution profiles were also justified. Dissolution study was performed for the 5 mg dose strengths.

Biowaiver

The applicant claimed for biowaiver for the dose strength of 5 mg stating that all requirements of the *Note for Guidance on Investigation of bioavailability and Bioequivalence* (CPMP/EWP/QWP/1401/98) concerning biowaiver were met.

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 (0.5 - 24 mg).

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

The study

Its main objective was to compare the rate and extent of absorption of ivabradine from Ivabradine 7.5 mg film-coated tablets (KRKA, Test) versus Procoralan® 7.5 mg film-coated tablets (Les Laboratoires Servier, Reference) administered to healthy volunteers.

This was a pivotal, single-centrum, single-dose, randomized, open-label, laboratory blind, crossover, two-period, two-treatment, two-sequence, bioequivalence study of ivabradine with a suitable washout period between the two periods, in healthy adult subjects under fed condition.

Determination of ivabradine in plasma samples was performed using a validated LC/MS/MS method.
The bioanalytical method has been successfully validated. The validation procedure and the analysis of the samples were in line with the guideline EMEA/CHMP/EWP/192217/2009.
Incurred sample reanalysis was performed and met the requirements.

All assay runs were performed within the verified plasma stability period and the acceptance criteria of the bioanalytical runs met the international standard.

The mean, standard deviation (SD), coefficient of variation (CV (%)) and range were calculated for plasma concentrations of ivabradine for each sampling time and treatment. Arithmetic means, standard deviations and coefficients of variation and range were calculated for AUC_{0-t}, C_{max} and T_{max}. Additionally, geometric means were calculated for AUC_{0-t} and C_{max}.

The calculation of pharmacokinetic parameters was performed according to the standard non-compartmental method recommended by CPMP/EWP/QWP/1401/98 Rev.1/Corr**. The pharmacokinetic results are reliable and valid.

The applicant stated that the bioequivalence studies were undertaken according to GCP guidelines. No issues regarding GLP or GCP aspects have been identified during the review of this dossier.

The results are shown in the next Table.

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.

As for 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 the bioequivalence study

The results derived from analysis of log-transformed primary efficacy parameters (C_{max}, $AUC_{(0-t)}$) 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) are considered to be bioequivalent with the Procoralan® 7.5 mg film-coated tablets (Servier Deutschland GmbH Germany).

The results with the 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 Bravadin 5 mg and 7.5 mg tablets were not performed.

IV.4 Clinical efficacy

No new efficacy or safety 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 Good Vigilance Practice (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 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 concerns connected to Bravadin 5 mg and 7.5 mg film-coated tablets. No additional activities are proposed.

Risk minimisation measures: routine measures (i.e. wording in SmPC, package leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Bravadin 5 mg and 7.5 mg film-coated tablets. No additional activities are proposed. For any further information on risk minimisation, refer to the product information.

IV.6.3 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 under 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. Abridged applications avoid the need for repetitive tests on humans. For these application the bioequivalence studies described in section IV.2 are pivotal.

The applicant has adequately demonstrated bioequivalence between Bravadin 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 present application concerns Bravadin 5 mg and 7.5 mg film-coated tablets, generic versions of ivabradine hydrochloride. The applicant and the future holder of authorisation is Krka d.d., Novo mesto.

The indications are the treatment of chronic stable angina pectoris.

Bravadine film-coated tablets are 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.

Bravadine film-coated tablets are also 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.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference products were Procoralan 5 mg and 7.5 mg film-coated tablets (Servier).

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the reference member state has granted marketing authorisation for Bravadin 5 mg and 7.5 mg film-coated tablets.

V.2 Classification

Prescription-only medicine.

In the reference member state Bravadin is a medicinal product on restricted medical prescription. It must be diagnosed by a specialist or in hospital environment, although administration and follow-up may be carried out elsewhere.

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 patient information leaflet 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*.

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	Assessment report attached