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Public Assessment Report

Name of the Product:

Ivabradine Richter

5 mg, 7.5 mg film-coated tablets

(ivabradine)

Procedure number: HU/H/0431/001-002/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date: 5 January 2017

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 Richter 5 mg and 7.5 mg film-coated tablets. The holder of the marketing authorisation is Gedeon Richter Plc..

The active substance is ivabradine. Each Ivabradine Richter 5 mg and 7.5 mg film-coated tablet contains 5 mg or 7.5 mg ivabradine (as hydrobromide), respectively.

The other ingredients are lactose anhydrous, mannitol (E421), maltodextrin, croscarmellose sodium, silica, colloidal anhydrous (E551), magnesium stearate, Opadry 200F240001 Pink, poly(vinyl alcohol) (E1203), talc (E553b), titanium dioxide (E171), macrogol 3350 (E1521), methacrylic acid – ethyl acrylate copolymer (1:1), iron oxide yellow (E172), iron oxide red (E172) and sodium hydrogen carbonate (E500).

The 5 mg film-coated tablets are pale orange, oval, biconvex. Their a dimension is approximately 8.6 mm x 4.5 mm, with a "V"-shaped break-mark on edges, one side engraved with "CK3" and the other side without engraving. These film-coated tablet can be divided into equal doses.

The 7.5 mg film-coated tablets are pale orange, round, biconvex. Their diameter is approximately 6 mm, one side engraved with "CK4" and the other side without engraving.

The film-coated tablets are packaged in OPA/Al/PVC//Aluminium cold blisters, in cardboard carton.

Ivabradine Richter film-coated tablet (further on: Ivabradine Richter) 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 the heart cannot pump enough blood to the rest of the body. The most common symptoms of heart failure are breathlessness, fatigue, tiredness and ankle swelling.

Ivabradine, the active substance of Ivabradine Richter 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 Richter 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.

Note: this medicine is subject to additional monitoring. This will allow quick identification of new safety information. Patients can help by reporting any side effects they may experience.

What patients need to know before taking Ivabradine Richter?

Those who
- are allergic to ivabradine or any of the other ingredients of this medicine;
- has a resting heart rate before treatment that 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 that is exclusively imposed by their pacemaker;
- suffer from severe liver problems;
- 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

must not take Ivabradine Richter.

Warnings and precautions

Those 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

must talk straight away to their doctor before or while taking Ivabradine Richter.

Paediatric population

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

Other medicines and Ivabradine Richter

Patients who are taking, have recently taken or might take any other medicines must inform their doctor accordingly. It is particularly important if they are taking any of the following medicines, as a dose adjustment of Ivabradine Richter 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 Richter with food and drink

During treatment with Ivabradine Richter grapefruit juice should be avoided.

Pregnancy and breast-feeding

Those who are pregnant, think they may be pregnant or are planning to have a baby should not take Ivabradine Richter.

Those who are pregnant and have taken Ivabradine Richter, talk to their doctor.

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

Those who are breast-feeding should not take Ivabradine Richter. They must consult their doctor if they are breast-feeding or intending to breast-feed as breastfeeding should be discontinued if taking Ivabradine Richter.

Driving and using machines

Ivabradine Richter 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.

Ivabradine Richter contains lactose

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

How to take Ivabradine Richter?

Ivabradine Richter should be taken during meals.

The 5 mg tablet can be divided into equal doses.

Those who are being treated for stable angina pectoris

The starting dose should not exceed one tablet of Ivabradine Richter 5 mg twice daily. If the patient still has angina symptoms and if he/she have 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 patient. The usual dose is

one tablet in the morning and one tablet in the evening. In some cases (e.g. if the patient is elderly), the doctor may prescribe half the dose i.e., one half 5 mg tablet of Ivabradine Richter 5 mg (corresponding to 2.5 mg ivabradine) in the morning and one half 5 mg tablet in the evening.

Those who are being treated for chronic heart failure

The usual recommended starting dose is one tablet of Ivabradine Richter 5 mg twice daily increasing if necessary to one tablet of Ivabradine Richter 7.5 mg twice daily. The doctor will decide the right dose for the patient. The usual dose is one tablet in the morning and one tablet in the evening. In some cases (e.g. if the patient is elderly), the doctor may prescribe half the dose i.e., one half 5 mg tablet of Ivabradine Richter 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 Richter has been taken than it should have been?

A large dose of Ivabradine Richter could make the patient feel breathless or tired because the heart slows down too much. If this happens, the doctor must be contacted immediately.

What to do if taking Ivabradine Richter has been forgotten?

If a patient forgets to take a dose of Ivabradine Richter, he/she should take the next dose at the usual time. A double dose to make up for the forgotten dose should never be taken.

May the patient stop taking Ivabradine Richter?

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.

If the patient thinks that the effect of Ivabradine Richter is too strong or too weak, the doctor should be discussed.

Possible side effects

Like all medicines, Ivabradine Richter 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 heartbeats.

How to store Ivabradine Richter?

This medicine does not require any special storage conditions but it should 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 Ivabradine Richter 5 mg and 7.5 mg film-coated tablets. The procedure was finalised at 9 September 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 State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Germany, Spain and the United Kingdom) concerned the generic version of ivabradine 5 mg and 7.5 mg film-coated tablets (Ivabradine Richter tablets).

The applicant and the future holder of marketing authorisation was Gedeon Richter Plc.

The application has been filed pursuant to Article 10(1) of Directive 2001/83/EC and therefore, with the exception of two bioequivalence studies, no new clinical or preclinical data, other than supporting literature, were submitted, which is acceptable for generic applications. The applicant has adequately demonstrated bioequivalence between the product and reference products. The originator products were Corlentor 5 mg and 7.5 mg film-coated tablets by Les Laboratoires Servier, France, approved in 2005 in the European Economic Area.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Ivabradine Richter 5 mg and 7.5 mg film-coated tablets (Gedeon Richter Plc.).

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 Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

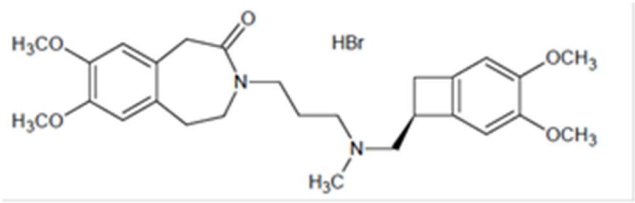
This chemical-pharmaceutical assessment report concerns the application of Ivabradine Richter 5 mg and 7.5 mg film-coated tablets via a decentralized procedure according to Article 10(1) of Directive 2001/83/EC (i.e. a generic application). The products have been developed by Gedeon Richter Plc. The reference products are Corlentor 5 mg and 7.5 mg tablets (containing 5 and 7.5 mg ivabradine hydrochloride as active ingredient, respectively) which were the original products of Les Laboratoires Servier.

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the 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 hydrobromide

Structure:



The active substance is white or almost white powder; freely soluble in dichloromethane, soluble in dimethyl formamide and methanol, sparingly soluble in acetonitrile, slightly soluble in deionized water, very slightly soluble in acetone and ethanol and practically insoluble in isopropanol. 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 drug substance is adequate.

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

Ivabradine hydrobromide is not official in the European Pharmacopoeia (Ph. Eur.). Therefore, an in-house specification has been set for the drug substance, which includes the following tests: appearance, particle size, identification, bromide identification, chiral identification, loss on drying, sulphated ash, heavy metals, related substances, chiral purity, residual solvents, assay, bromide content and microbiological purity.

The presented specification is in accordance with the Ph. Eur. general monograph on *Substances for Pharmaceutical Use* and the International Council on Harmonisation (ICH) Q6A guideline. The specification reflects all relevant quality attributes of the drug substance and was found to be adequate to control its quality. 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 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 hydrobromide as drug substance in 5 and 7.5 mg doses pharmaceutically equivalent and bioequivalent to the reference medicinal products Corlentor 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 strength: pale orange coloured, oval, biconvex film-coated tablets, with a dimension of approximately 8.6 mm x 4.5 mm, with a “V”-shaped break-mark on edges, one side engraved

with "CK3" and the other side without engraving. The film-coated tablet can be divided into equal doses.

7.5 mg strength: pale orange coloured, round, biconvex film-coated tablets, with a diameter of approximately 6 mm one side engraved with "CK4" and the other side without engraving.

The excipients used in the finished product were silica, colloidal anhydrous, magnesium stearate, croscarmellose sodium, maltodextrin, mannitol, lactose, anhydrous and Opadry 200F240001 Pink (sodium hydrogen carbonate, methacrylic acid – ethyl acrylate copolymer (1:1), makrogol 3350, poly(vinyl alcohol), titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172) and talc).

The excipients used comply with their respective Ph. Eur. monographs. Yellow and red iron oxides comply with USP/NF and E172. 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 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 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 3 years with no special storage conditions is approved.

The Summary of Product Characteristics, Patient Information (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 drug 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 products.

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 non-clinical 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.

III.2 Pharmacology

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

Ivabradine can interact also with the retinal current I_h which closely resembles cardiac I_f.

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.

This product and the reference products have different salt compositions. The reference products are hydrochlorides, Ivabradine Richter products are hydrobromide salts of ivabradine. Based on literature data provided by the applicant, the use of hydrobromide salt of ivabradine is not of toxicological concern in this medicinal product considering the therapeutic doses.

III.5 Ecotoxicology/environmental risk assessment (ERA)

Since Ivabradine Richter 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 Ivabradine Richter is a generic product, there is no need for further 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 similar extent via faeces and urine. About 4% of an oral dose is excreted unchanged in urine.

IV.2.2 Bioequivalence studies

To support the marketing authorisation application two bioequivalence studies were performed with Ivabradine Richter 5 mg and 7.5 mg film-coated tablets (Gedeon Richter) and the relevant strengths of the innovator product, Corlentor 5 mg and 7.5 mg film-coated tablets (Les Laboratoires Servier).

Bioequivalence study with the 7.5 mg strength

Design of this investigation was a pivotal, single-dose, randomized, single-centre, open-label, laboratory blind, two-stage, two-period, two-treatment, two-sequence, crossover bioequivalence study of ivabradine with an adequate washout period between two periods, in healthy adult subjects under fed condition.

As the pharmacokinetic behaviour of ivabradine in the literature is ambiguous, an adaptive sequential design was used as allowed in the EMA bioequivalence guideline in force (CPMP/EWP/QWP/1401/98 Rev.1, 2010).

Blood samples were taken. Determination of ivabradine in plasma samples was performed using a validated LC/MS/MS method.

The pharmacokinetic parameters studies were:
- primary: AUC_t, C_{max}
- other: T_{max}, AUC_{inf}, λ (terminal elimination rate constant), AUC(res%), $T_{1/2}$.

Bioequivalence criteria:
- At Stage 1 the Test product could be considered bioequivalent to the Reference product if the ln-transformed Test/Reference LS (least-squares) mean ratio and their 94.12% confidence intervals of the primary pharmacokinetic parameters fall entirely within the acceptance range of 80.00 – 125.00 for ivabradine using an α level of 0.0294 (according to Potvin's Method B, internationally accepted literature).
- If bioequivalence was not demonstrated at Stage 1, the study could have proceeded onto Stage 2 if the power was determined to be less than 80%. (If the power were greater than 80% the study would be stopped as it would be failed to demonstrate bioequivalence).

In order to demonstrate bioequivalence at Stage 2, the calculated 94.12% confidence interval for the ratio of the primary pharmacokinetic parameters should fall entirely within the acceptance range of 80.00 – 125.00% for ivabradine using α level of 0.0294. The results are shown in the next Table.

Pharmacokinetic parameter	Geometric mean ratio (Test/Reference)	94.12% Confidence intervals	CV%
AUC_{0-t}	103.86	98.70 – 109.30	15.56
C_{max}	99.22	89.97 – 109.43	30.33

Both study drugs were well tolerated by all subjects involved in the study. No new safety concerns related to administered formulations were raised during the conduct of the study.

Conclusion on this bioequivalence study: results derived from the combined (Stage 1 and Stage 2) analyses of log-transformed primary efficacy parameters (C_{max}, AUC_t) for ivabradine showed that the Test/Reference ratios of LS (least-squares) mean values and their 94.12% confidence intervals also were entirely included within the acceptance range of 80% - 125% at α level of 0.0294 (Potvin et al, 2008). Thus, results supported the bioequivalence between the Test- and Reference products.

On the basis of results of this bioequivalence study the single dose of the Ivabradine Richter 7.5 mg film-coated tablets (Test product) and a single dose of Corlentor 7.5 mg film-coated tablets (Les Laboratoires Servier, Reference product) are considered bioequivalent in healthy adult subjects under fed condition.

Bioequivalence study with the 5 mg strength

Design of this investigation was a pivotal, single-dose, randomized, single-centre, open-label, laboratory blind, two-stage, two-period, two-treatment, two-sequence, crossover bioequivalence study of ivabradine with an adequate washout period between two periods, in healthy adult subjects under fed condition.

As the pharmacokinetic behaviour of ivabradine in the literature is ambiguous, an adaptive sample size sequential design was used as allowed in the EMA guidance on bioequivalence studies (CPMP/EWP/QWP/1401/98 Rev. 1).

Blood samples were taken. Determination of ivabradine in plasma samples was performed using a validated LC/MS/MS method.

The pharmacokinetic parameters studies were:
- primary: AUC_t, C_{max}
- other: T_{max}, AUC_{inf}, λ (terminal elimination rate constant), AUC(res%), $T_{1/2}$.

Bioequivalence criteria:
- At Stage 1 the Test product could be considered bioequivalent to the Reference product if the ln-transformed Test/Reference LS (least-squares) mean ratio and their 94.12% confidence intervals of the primary pharmacokinetic parameters fall entirely within the acceptance range of 80.00 – 125.00 for ivabradine using an α level of 0.0294 (according to Potvin's Method B mentioned above).
- If bioequivalence was not demonstrated at Stage 1, the study could have proceeded onto Stage 2 if the power was determined to be less than 80%. (If the power were greater than 80% the study would be stopped as it would be failed to demonstrate bioequivalence).

In order to demonstrate bioequivalence at Stage 2 (if applicable), the calculated 94.12% confidence interval for the ratio of the primary pharmacokinetic parameters should fall entirely within the acceptance range of 80.00 – 125.00% for ivabradine using α level of 0.0294.

The results are shown in the next Table.

Pharmacokinetic parameter	Geometric mean ratio (Test/Reference)	94.12% Confidence intervals	CV%
AUC_{0-t}	100.82	95.88 – 106.01	13.58
$AUC_{0-\infty}$	100.89	95.96 – 106.08	13.55
C_{max}	96.69	85.71 – 109.09	33.28

Both study drugs were well tolerated by all subjects involved in the study. No new safety concerns related to administered formulations were raised during the conduct of the study.

Conclusion on this bioequivalence study: results derived from analysis of log-transformed primary efficacy parameters (C_{max}, AUC_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%. Thus, results supported the bioequivalence between the Test- and Reference products.

On the basis of results of bioequivalence study the single dose of the Ivabradine Richter 5 mg film-coated tablets (Test product) and a single dose of Corlentor 5 mg film-coated tablets (Les Laboratoires Servier, Reference product) are considered bioequivalent in healthy adult subjects under fed condition.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for this application.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for this application.

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 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 intra-ventricular conduction defects

Pharmacovigilance Plan: routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Richter's products containing ivabradine 5 mg and 7.5 mg. No additional activities are proposed.

Risk Minimisation Measures: routine measures (i.e. wording in Summary of Product Characteristics, Package Leaflet and classification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Richter's product containing ivabradine 5 mg and 7.5 mg. No additional activities are proposed. For any further information on risk minimisation, please 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 generic products.

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

To support the application the applicant has adequately demonstrated bioequivalence between Ivabradine Richter 5 mg and 7.5 mg film-coated tablets and the reference products Corlentor 5 mg and 7.5 mg film-coated tablets.

There is no objection against granting the marketing authorization from clinical points of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The present application concerns Ivabradine Richter 5 mg and 7.5 mg film-coated tablets, generic versions of ivabradine. The applicant and the future holder of authorisation is Gedeon Richter Plc.

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 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.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The reference products were Corlentor 5 mg and 7.5 mg film-coated tablets (Les Laboratoires Servier). To support the application the applicant has adequately proved bioequivalence between Ivabradine Richter and the reference products.

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 Member States have granted marketing authorisation for Ivabradine Richter 5 mg and 7.5 mg film-coated tablets.

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 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