15 September 2016
EMA/648588/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ivabradine JensonR

International non-proprietary name: ivabradine

Procedure No. EMEA/H/C/004217/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse Event
Alu	aluminium
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
AUC ratio	The ratio of AUC_{0-t} to $AUC_{0-\infty}$ expressed in (%) percentage
AUC_{0-72}	The area under the plasma concentration versus time curve from time 0 to 72 hours
$AUC_{0-\infty}$	The area under the plasma concentration versus time curve from time 0 to infinity
AUC_{0-t}	The area under Plasma concentration versus time curve from time 0 to t, where t = time of last measurable concentration
BMI	Body Mass Index
CC	Calibration curve
CFU	Colony-forming unit
C_{max}	Maximum measured plasma concentration over the time span specified
CoA	Certificate of analysis
CRC	Clinical Research Centre
CV%	Percentage Coefficient of Variation
CV	Captured volume
DSC	Differential scanning calorimetry
EC	Ethics Committee
EEA	European Economic Area
ER	Environmental Risk
ERA	Environmental Risk Assessment
EU	European Union
f2	The similarity factor
GC	Gas chromatography
GCP	Good Clinical Practice
GLM	General Linear Models
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCl	Hydrochloric Acid
HDPE	High Density Polyethylene
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMR	Indian Council of Medical Research
ID	Identification
IDHAC	3-(3-Chloropropyl)-7,8-dimethoxy-1,3-dihydro-2*H*-3-benzazepin-2-one
IPC	In-process controls
IR	Infra-Red Spectroscopy
ISR	Incurred Sample Reanalysis
ITHAC	3-(3-Chloropropyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-2*H*-3-benzazepin-2-one
K_2EDTA	Di Potassium Ethylene Diamine Tetra Acetic Acid
K_{el}	Apparent first – order terminal elimination rate constant
KF	Karl Fischer
Kg/m^2	Kilogram per square meter
LC	Liquid chromatography
LDPE	Low Density Polyethylene
LOQ	Limit of quantitation

LQCT	Last measurable blood sampling point
LSM	Least Square Mean
MAH	Marketing Authorisation Holder
Mg	Milligram
min	Minute
Ml	Milliliter
MS	Mass Spectrometry
N	Number of subjects
ng	Nanogram
NKEL	Number of points used in calculation of terminal elimination rate constant
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
No	Number
ºC	Degree Celsius
OOS	Out of specification
OPA	Ortho-phthalaldehyde
Ph.Eur.	European Pharmacopoeia
PMI	Potentially mutagenic impurities
PVC	Poly vinyl chloride
QCs	Quality Control Sample
QP	Qualified Person
rpm	Revolutions per minute
SAS	Statistical Analysis Software
SICBA	[((7*S*)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl]methylamine
SmPC, SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
$t_{1/2}$	Apparent first-order terminal elimination half-life calculated as $0.693/K_{el}$
TLIN	Time point at which log linear elimination begins
T_{max}	Time of the maximum measured plasma concentration
UPLC	Ultra Performance Liquid Chromatography
USP	United States Pharmacopoeia
UV	Ultraviolet light
WFI	Water for injections
XRPD	X-ray powder diffraction

Please note that not all of these abbreviations might be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Mylan S.A.S submitted on 11 November 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Ivabradine Mylan, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 April 2015.

On 15 July 2016, the applicant name was changed from Mylan S.A.S to JensonR+Limited. Subsequently, the product name was changed from Ivabradine Mylan to Ivabradine JensonR.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

Symptomatic treatment of chronic stable angina pectoris

Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 bpm. Ivabradine is indicated:

- in adults unable to tolerate or with a contra-indication to the use of beta-blockers

- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

Treatment of chronic heart failure

Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including betablocker therapy or when beta-blocker therapy is contraindicated or not tolerated (see section 5.1).

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Procoralan instead of non-clinical and clinical unless justified otherwise

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Procoralan 5 mg, 7.5 mg film-coated tablets
- Marketing authorisation holder: Les Laboratoires Servier, France
- Date of authorisation: 25-10-2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/05/316/001-007, EU/1/05/316/008-014

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: : Procoralan 5 mg, 7.5 mg film-coated tablets
- Marketing authorisation holder: Les Laboratoires Servier, France
- Date of authorisation: 25-10-2005
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/05/316/001-007, EU/1/05/316/008-014

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Procoralan 7.5 mg film-coated tablets
- Marketing authorisation holder: Les Laboratoires Servier, France
- Date of authorisation: 25-10-2005
- Marketing authorisation granted by:
  - Community
- Bioavailability study number: 14-VIN-785

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Piotr Fiedor

- The application was received by the EMA on 11 November 2015.
- The procedure started on 4 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 February 2016.The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 3 March 2016.
- During the meeting on 1 April 2016, the CHMP agreed on the consolidated List of Questions to be

sent to the applicant. The final consolidated List of Questions was sent to the applicant on 1 April 2016.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 July 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 August 2016.
- During the PRAC meeting on 2 September 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 15 September 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Ivabradine JensonR.

2. Scientific discussion

2.1. Introduction

The present application is made under Article 10(1) generic application, i.e. Ivabradine JensonR 5 mg and 7.5 mg, film-coated tablets is a generic version of the already approved reference product Procoralan 5 mg and 7.5 mg film-coated tablets by Les Laboratoires Servier that contains the active substance Ivabradine hydrochloride.

Ivabradine acts by inhibiting the If current, which modulates pacemaker activity in the sino-atrial node, providing heart rate reduction. Ivabradine is intended for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥70 bpm and it is indicated in adults unable to tolerate or with a contra-indication to the use of beta-blocker or in combination with beta-blockers in patients with inadequately controlled with an optimal beta-blocker dose. Ivabradine is 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 starting dose of ivabradine should not exceed 5 mg twice daily. After three to four weeks of treatment, if the patient is still symptomatic, if the initial dose is well tolerated and if resting heart rate remains above 60 bpm, the dose may be increased. The maintenance dose should not exceed 7.5 mg twice daily. If there is no improvement in symptoms of angina within 3 months after start of treatment, treatment of ivabradine should be discontinued.

It has applied for all the indications of the reference product.

The application consists of one Bioavailability study for the higher strength 7.5mg film coated tablet to that of the reference product and an application for a biowaiver for the lower strength 5mg film coated tablet according to the according to the *EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)*.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 5 mg or 7.5 mg of ivabradine (as hydrochloride) as active substance.

Other ingredients of the tablet core are: anhydrous lactose, magnesium stearate, maltodextrin, microcrystalline cellulose, hydroxypropyl cellulose, and colloidal anhydrous silica. Ingredients of the film-coating are: hypromellose, titanium dioxide, macrogol 400, yellow iron oxide (E172), red iron oxide (E172), polysorbate 80.

The product is available in cold form blisters (OPA/Alu/PVC), cold form perforated unit dose blisters (OPA/Alu/PVC), PVC/Aclar-Alu blisters, PVC/Aclar-Alu perforated unit dose pack, and HDPE bottle with opaque polypropylene screw cap with aluminium induction sealing liner with wad and desiccant, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The information on ivabradine hydrochloride is provided according to the Active Substance Master File (ASMF) procedure.

The chemical name of ivabradine hydrochloride is 3-[3-({[(7*S*)-3,4-dimethoxybicyclo[4.2.0]octa-1(6),2,4-trien-7-yl]methyl}(methyl)amino)propyl]-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepin-2-one, hydrochloride corresponding to the molecular formula $C_{27}H_{37}ClN_2O_2$ and has a relative molecular mass of 505.05 and the following structure:

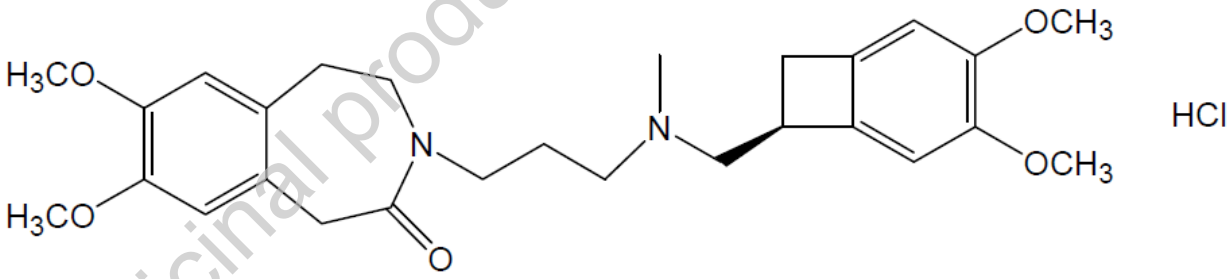

Figure 1. Chemical structure of ivabradine hydrochloride.

The structure of the active substance was elucidated by a combination of mass spectrometry, infrared absorption spectrophotometry, and nuclear magnetic resonance spectrometry. A screening of crystalline forms was performed using X-Ray Powder Diffraction (XRPD).

The active substance is a white or almost white powder, freely soluble in water and solutions of physiological pH. It is freely soluble in methanol and slightly soluble in acetone. The active substance is not hygroscopic according to Ph. Eur, general text 5.11.

Ivabradine hydrochloride exhibits stereoisomerism due to the presence of one chiral centre. The chiral centre is generated under substrate control during the synthetic process. Enantiomeric purity is

controlled routinely by chiral HPLC as in-process control (IPC) during synthesis, in the specifications of the SICBA HCl isolated intermediate, and in the specifications of the active substance.

Polymorphism has been observed for ivabradine hydrochloride. Several crystalline forms have been described in the literature, some of them being hydrates or solvates. The active substance manufacturer discovered a new polymorphic form (Form IV) not previously described which has been patented. Form IV has been characterised by XRPD, differential scanning calorimetry (DSC) and infrared (IR) absorption spectrophotometry. It has been demonstrated that the active substance manufacturing process consistently produces crystalline Form IV of the active substance. Polymorphic form is controlled in the specifications of the active substance.

There is no monograph of ivabradine hydrochloride in the European Pharmacopoeia.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

One source of the active substance is used although three manufacturers are responsible for different steps of its production.

Ivabradine hydrochloride is synthesized in seven main steps using commercially available well defined starting materials with acceptable specifications. The starting materials were re-defined during the procedure, at the request of CHMP, in order to ensure that critical steps (in particular those generating potentially mutagenic impurities (PMI) and enough of the synthetic process are included in the dossier, thereby ensuring the quality of the active substance throughout its lifecycle. As a result of this, a new manufacturer was added to the dossier and the QP declaration was updated. An extensive discussion and risk assessment on impurities with mutagenic potential is presented and followed which was deemed acceptable and in line with ICH M7.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials, and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in a double low-density polyethylene (LDPE) bag within a polyethylene (HDPE) drum. The primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance, identity including polymorphic Form IV (IR), chlorides (Ph. Eur.), enantiomeric purity (LC), related substances (LC), residual solvents (GC), assay (potentiometry), water content (KF), sulfated ash (Ph. Eur.), and particle size distribution (laser diffraction).

Impurities are all limited to below the qualification threshold according to ICH Q3A. A risk assessment on the impact of potentially mutagenic impurities (PMI) has been performed in line with ICH M7. Detailed calculations of purge and fate of the different identified PMI under the conditions of the manufacturing process have been provided and the control strategy of PMI was considered acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three productions scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on five production scale batches and on an additional development batch of active substance from the proposed manufacturers stored in a container closure system representative of that intended for the market, for up to three years under long term conditions at 30 ºC / 65% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH, according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions including heat (80 ºC for 30 days), light (24 hours), dissolved in neutral (methanol), acidic [mixture of methanol and concentrated hydrochloric acid (99:1 v/v)] and alkaline medium [mixture of methanol and 2 M potassium hydroxide (90:10 v/v)] and with oxidising agent [mixture of methanol and 33 % hydrogen peroxide solution (90:10 v/v)] were also provided on one batch.

The following parameters were tested: appearance, identity including polymorphic Form IV and enantiomeric purity (IR), chlorides (Ph. Eur.), related substances (LC), assay (potentiometry), and water content (KF). The analytical methods used were the same as for release and were stability indicating.

Data from long term, accelerated, and photostability studies demonstrate little or no change over time and all tested parameters were within the specifications.

With regards to the forced degradation studies, ivabradine hydrochloride is stable in the solid state under the impact of high temperature or extreme light irradiation. In dissolved state at room temperature, the active substance is stable against hydrolysis in neutral or alkaline media. Degradation occurs in acidic medium or in presence of an oxidising agent.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of three years in the proposed container. The active substance does not require any special storage conditions.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as immediate release film-coated tablets. The 5 mg strength is presented as pink, oval, biconvex film-coated scored tablets, approximately 7.9 mm by 4.15 mm in size and debossed with "I 5" on one side and "M" on other side of the tablet. The 7.5 mg strength is presented as pink, round, bevelled edge, biconvex film coated tablets, approximately 6.65 mm in diameter debossed with "I 7" on one side and "M" on other side of the tablet. The different strengths of the film-coated tablets are distinguishable by their shape, size, and debossing.

The aim of the pharmaceutical development was to develop a generic version of the reference product, Procoralan film-coated tablets, with equivalent performance in clinical use. Other requirements were a robust and scalable manufacturing process and suitable stability in the commercial pack.

Since the active substance is freely soluble across the physiological pH, control of polymorphic form and particle size are not critical to ensure a consistent performance *in vivo*. The impact of finished product manufacturing process on the polymorphic form of the active substance has been studied and it has been demonstrated that it remains stable throughout the shelf-life. Physical characterisation studies of the active substance demonstrated “very poor” to “very, very poor “ powder flow properties, therefore particle size distribution is controlled in the specifications of the active substance. In addition, it has been demonstrated that there is no significant effect of changes in particle size distribution of ivabradine hydrochloride active substance on the dissolution profile.

The formulation of Ivabradine JensonR is based on the formulation of the reference medicinal product. Both formulations are qualitatively similar in terms of excipients, with minor differences in the composition of diluents, binder, and disintegrant: Ivabradine JensonR uses anhydrous lactose and microcrystalline cellulose as diluents, low-substituted hydroxypropyl cellulose as a binder, and uses no disintegrant, whilst the originator uses lactose monohydrate as a diluent and maize starch as a disintegrant. The differences in the formulation were deemed not significant based on the comparative dissolution profiles in different media (0.1N HCl,, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer covering the pH range of pH 1.2 - pH 6.8) and the bioequivalence study.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. A series of binary active substance-excipient compatibility studies was performed and the results demonstrated good compatibility.

The developed dissolution method is in line with Ph. Eur. requirements. The discriminatory power of the dissolution method has been demonstrated and it was shown that the standard release method is able to discern changes in the manufacturing process and in the formulation.

Dry granulation and direct compression have been selected as the manufacturing process for the film-coated tablets due to ease of manufacturing and good compatibility of the ingredients. Blending time and compression (hardness range) were optimised during the development before the scale-up of the process. The manufacturing process used to manufacture the clinical batches used in bioequivalence study is the same as the one used to manufacture commercial batches.

As mentioned above, a bioequivalence study was performed showing bioequivalence between the clinical formulation and the proposed commercial formulation. In addition, bioequivalence was demonstrated between 7.5 mg Procoralan and Ivabradine JensonR film-coated tablets. A strength biowaiver for 5 mg strength was considered justified as the generic product strengths are dose proportional in terms of the film-coated tablet contents, are manufactured using the same process and manufacturer, exhibit similar dissolution profiles across the physiological pH range and pharmacokinetics of ivabradine is linear over an oral dose range of 0.5 – 24 mg..

The primary packaging is cold form blisters (OPA/Alu/PVC), cold form perforated unit dose blisters (OPA/AL/PVC), PVC/Aclar-Alu blisters, PVC/Aclar-Alu perforated unit dose pack, and HDPE bottle with opaque polypropylene screw cap with aluminium induction sealing liner with wad and desiccant. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: preparation of the blend, sifting and blending of the components, compression, coating, and packaging. The critical steps include preparation of the powder blend, compression of the tablets, coating of the tablets and packaging operations. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and the pharmaceutical form.

Product specification

The finished product release specifications, shown below for the 5 mg film-coated tablet, include appropriate tests for this kind of dosage form and include tests for description, identification (UV, HPLC), colour identifications for titanium dioxide and iron oxide (colour reaction), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), related substances (HPLC), water content (KF), microbiological quality (Ph. Eur.), and uniformity of mass for subdivided tablets (Ph. Eur.). The specification for the 7.5 mg strength is identical other than the description and assay (actual amount).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for three commercial scale batches of each film-coated tablet strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three commercial scale batches of each strength of finished product stored under long term conditions for 12 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH, according to the ICH guidelines, were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, dissolution, related substances, water content, microbiological quality, and uniformity of mass for subdivided tablets.

No significant changes have been observed under long term or accelerated conditions. Observed physical change was small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

Forced degradation studies on samples treated under alkaline (2N NaOH solution), acidic (2N HCl solution), oxidation (10% H_2O_2 solution), water and heat stress conditions (at 60 °C, 2 hours), exposed to humidity (25 °C / 90% RH) and heat (105 °C) and UV and white light conditions have been performed as part of the validation of the analytical methods, demonstrating that they are stability indicating.

In addition, one batch of 7.5 mg film-coated tablets was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No out of specification

results was observed in any of the tested parameters (assay, related substances, and dissolution), demonstrating their photostability.

In-use stability study was performed on 5 mg film-coated tablets strength for 180 days. The results showed no significant changes and a 180 days in-use shelf-life after first opening of bottles is considered acceptable.

Based on available stability data, the proposed shelf-life of 2 years and 180 days after first opening of the bottle as stated in the SmPC (section 6.3) is acceptable. This medicinal product does not require any special storage conditions.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

No other excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by JensonR+ Limited as the introduction of Ivabradine JensonR is considered unlikely to result in any significant increase in the combined sales volumes for all ivabradine hydrochloride containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased. The CHMP agreed with this justification.

2.3.3. Discussion on non-clinical aspects

The range of non-clinical data presented in the dossier is typical for a generic application and include no new studies. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology of ivabradine was provided, which was based on up-to-date and adequate scientific literature.

Ivabradine was authorised in 2005 and is well-known substance. Its pharmacodynamic, pharmacokinetic and toxicological properties are well characterised. This generic application contains the same salt of the active substance as the reference medicinal product. Therefore, CHMP agreed that no further studies were required and that a summary of the literature with regard to non-clinical data of ivabradine was appropriate.

Introduction of the medicinal product onto the market is unlikely to result in any significant increase in the combined sales volumes for all ivabradine products, and would thus not be expected to have an adverse effect upon the environment. With this regard and on the basis of *CHMP Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (CPMP/SWP/4447/00)*, a formal environmental risk assessment was not considered necessary - the ERA was expected to be similar and not increased.

2.3.4. Conclusion on the non-clinical aspects

The CHMP considered that the non-clinical data provided are adequate to support the clinical use of ivabradine.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for Ivabradine JensonR 5 mg and 7.5 mg film coated tablets containing ivabradine hydrochloride. To support the marketing authorisation application the applicant conducted one bioequivalence study with cross-over design under fed conditions. This study was the pivotal study for the assessment.

No CHMP scientific advice pertinent to the clinical development was given for this medicinal product.

For the clinical assessment the *EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)* as well as the *EMA Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)* are of particular relevance.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

The application for marketing authorisation was based on demonstrating bioequivalence of the test product Ivabradine 7.5 mg film-coated Tablets of Mylan Laboratories Limited, India with the approved reference product Procoralan (Ivabradine) 7.5 mg film-coated tablets of Les Laboratoires Servier. Justification for requesting bio-waiver for the lower strength i.e. Ivabradine 5 mg film-coated tablets, film-coated tablets, was prepared according to general bio-waiver criteria as specified in the *EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)*. The biowaiver to extrapolate the bioequivalence conclusion from study 14-VIN-785 with the Ivabradine 7.5 mg film-coated tablets of JensonR to the 5 mg strength was considered acceptable as it satisfied the biowaiver criteria.

Clinical studies

To support the application, the applicant has submitted one bioequivalence study.

Table 3. Tabular overview of clinical studies

Type of Study	Study Number	Location of Study Report	Objectives of Study	Study Design and Type of Control	Test product(s); dosage regimen; route of administration	No. of subjects	Healthy subjects or patients	Duration of treatment	Study status; Type of Report
BE	14-VIN-785	Clinical Study Report& PK Report and Adverse Event Listing **Clinical Study (5.3.1.2)** CRFs and Individual Subjects **Individual CRF (5.3.7)** **Literature References (5.4)**	To compare the rate and extent of absorption of Ivabradine 7.5 mg film-coated Tablets of Mylan Laboratories Limited, India and Procoralan (Ivabradine) 7.5 mg film-coated tablets of Les Laboratoires Servier, 50, rue Carnot 92284, Suresnes cedex, France in healthy, adult, human subjects under Fed condition. To evaluate the safety and tolerability of Ivabradine 7.5 mg film-coated Tablets in healthy, adult, human subjects.	An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover bioequivalence study in healthy, adult, human subjects under fed condition. Treatment controlled	One tablet formulation, single dose, oral administration	Planned - 34 Enrolled- 34 Completed- 33 Analyzed- 33 Withdrawn-01	Healthy adult human subjects	Single-Dose	Completed; Abbreviated
PK	Not Applicable								
PD	Not applicable								
Efficacy	Not Applicable								

2.4.2. Pharmacokinetics

Study 14-VIN-785: An open label, balanced, randomized, single-dose, two-treatment, two-sequence, two period, crossover bioequivalence study of Ivabradine 7.5 mg film-coated tablets of Mylan Laboratories Limited, India and Procoralan (Ivabradine) 7.5 mg film-coated tablets of Les Laboratoires Servier, France in healthy, adult, human subjects under fed condition.

Methods

Study design

This was an open label, balanced, randomized, single-dose, two treatment, two-sequence, two-period crossover bioequivalence study of Ivabradine 7.5 mg film-coated tablets with the reference product Procoralan (Ivabradine) 7.5 mg film-coated tablets of in healthy, adult, human subjects under fed condition. The study was conducted from the 15 June 2015 to 25 June 2015 in Veeda Clinical Research Pvt. Ltd., India. The two study periods were separated by a washout period of 7 days. A randomized block design was adopted while the randomization scheme was generated using SAS® (SAS Institute

Inc., USA).

The meal consisted of a high-fat and high-calorie (approximately 800-1000 calories consisting of cheese sandwich, glass of whole milk, egg omelette in butter, fried chicken, fried potato and tomato chutney) was to be finished 30 minutes prior to administration of the drug formulation.

The analytical portion of the bioequivalence study Project No. 14-VIN-785 was conducted at the Bioanalytical Laboratory of the CRC- Mylan Laboratories Ltd., India, from 01st September 2015 to 11th September 2015 determining plasma Ivabradine & N-desmethyl Ivabradine concentrations in the clinical samples from the Fed Bioequivalence study.

A total of twenty (20) blood samples (6.0ml) per subject were collected during each period. The pre-dose (O.OOhr) blood sample was collected within one hour before dosing. The post-dose blood samples were be drawn at 0.33, 0.67, 1.00, 1.33, 1.67, 2.00, 2.33, 2.67, 3.00, 3.50, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours after dosing in each period.

Test and reference products

Ivabradine 7.5 mg film coated tablets manufactured by Mylan Laboratories Limited, Aurangabad-431136, India. (batch No. 2008571, manufacturing date Feb-2015; exp. date Jan-2017, assay of 98.5% w/w, batch size of test product 140,000 tablets, commercial batch size of 1,400,000 tablets.) has been compared to Procoralan® 7.5 mg film coated tablet manufactured by Les Laboratoires Servier, 50, rue Carnot 92284, Suresnes cedex, France (Batch No. 911867., exp. date Jun 2015, assay of 96.5% w/w) that has been centrally authorised in Europe since the 25 October 2005.

Population(s) studied

A total of 34 Asian male subjects were enrolled in the study. Weight of the subjects was within the normal range according to the Body Mass Index (18.5 to 30.0 kg/m2) with a minimum of 45 kg weight while the subjects' age was in the range of 18 to 45 years (including both, average age 33 years). 33 subjects completed the study. These 33 subjects were analysed in the bio-analytical phase. 1 subject was withheld from analysis (Subject No.: 01). The 33 subjects were considered for pharmacokinetic and statistical analysis.

The Applicant presented the literature source (Vlase et al. 2010) of intra-subject CV for 10 mg (20%) and for 5 mg (22.9%) of Ivabradine. Based on this data, the ISCV of 22% was considered for sample size calculation in the present study. The predicted sample size was also confirmed in the study data #14-VIN-785, in which ISCV for Cmax is 20.80%.

The sample size calculations was conducted to establish power (1-β) above 90 % and based on foundations in accordance with the guidelines. Although the description state in the protocol required some details (description how sample size was calculated - eg. used algorithms).

Analytical methods

The analytical portion of the bioequivalence study Project No. 14-VIN-785 was conducted at the Bioanalytical Laboratory of the CRC- Mylan Laboratories Ltd. India, from 01st September 2015 to 11th September 2015 determining plasma ivabradine & N-desmethyl ivabradine concentrations in the clinical samples from Fed Bioequivalence study.

The analysis was performed according to Analytical Method Procedure No. “AMP-176-00” on an API 4000 LC/MS/MS system using ivabradine-D6 & N-desmethyl ivabradine-D6 as internal standards (IS). The interface used with the API 4000 LC/MS/MS system was a Turbo ionspray®. The positive ions were measured in MRM mode. The Lower limit of quantitation (LLOQ) was 0.499 ng/mL for ivabradine and 0.099 ng/mL for N-desmethyl ivabradine and the upper limit of quantitation (ULOQ) was 79.913 ng/mL for ivabradine and 9.874 ng/mL for N-desmethyl ivabradine

Calibration curve standards (CC) and quality control (QC) samples met the acceptance criteria for all the runs used for the final data, demonstrating satisfactory performance of the method during the analysis of study subject samples.

Temperature of deep freezers, in which plasma samples of 14-VIN-785 (P 01 & 02) were stored, was found to have fluctuated and not maintained at -78±8°C. Stability data demonstrate that analyte is stable even at a temperature as high as -20 ±5°C, which covers the excursions noted during storage of the clinical samples in this study.

A statement of GLP compliance was provided and the study followed the *EMA Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**).

Pharmacokinetic variables

Pharmacokinetic measurement: From the time/concentration values, the primary variables are C_{max} and AUC_{o-t} and the secondary variables are AUC_{o-inf}, T_{max}, AUC_%Extrap_obs, $t_{1/2}$ and K_{el} for ivabradine and N-desmethylated ivabradine were calculated and these are used in the statistical analysis to compare the relative bioavailability of the two products. WinNonlin® Enterprise Software Version 5.3 or higher was used as the PK analysis software.

The pharmacokinetic parameters C_{max}, AUC_{0-t} and AUC_{0-inf} for ivabradine and N-desmethylated ivabradine were estimated to evaluate bioavailability.

Standards for bioequivalence

Based on the statistical results of 90% confidence interval of the geometric least square mean ratio for the pharmacokinetic parameters Cmax and AUC0-t of ivabradine the conclusions were drawn whether test formulation is bioequivalent to reference formulation under fed condition. Acceptance range for bioequivalence is 80.00%-125.00% for 90% confidence intervals of the geometric least square means ratio for Cmax and AUC0-t of ivabradine.

Statistical methods

Statistical software used in the study was SAS® software for windows, release 9.2 (SAS Institute Inc., Cary NC, USA).

Sample size calculation was based on the method described in “Sample Size Determination for Bioequivalence assessment Using a Multiplicative Model” by Dieter Hauschke, Volker W. Steinijans, Edgar Diletti, and Margin Burke (1992), Journal of Pharmacokinetics and Biopharmaceutics, Vol. 20, No. 5. 1992 and used a power of 90%, α of 0.05, T/R ratio of 105% and ISCV of 22%.

The main types of summary statistics for continuous data were calculated and presented for the primary pharmacokinetic parameters. Ratio of geometric least squares means was calculated and reported for ln-transformed parameters Cmax, AUC0-t and AUC0-∞ for ivabradine.

Analysis of variance was carried out for ln-transformed Cmax, AUC0-t and AUC0-∞ for ivabradine using PROC GLM. ANOVA model included fixed effects of Sequence, Treatment, Period and Subject (Sequence). Subject nested into sequence was used as error term for checking the significance of sequence.

Intra-subject variability and power was calculated and reported for ln-transformed pharmacokinetic parameters C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for ivabradine using root mean square error computed by PROC GLM.

Data from metabolite N-desmethylated ivabradine was presented as supportive data, with individual and mean concentrations, individual and mean pharmacokinetic parameters reported.

The statistical methodology used in the studies is justified and consistent with the principles of the *EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)*.

Results

Table 4. Pharmacokinetic parameters for Ivabradine (non-transformed values)(N=33)

	Test (T)		Reference (R)	
	arithmetic mean	**SD**	**arithmetic**	**SD**
$AUC_{(0-t)}$	180.054	70.0659	184.976	69.0817
$AUC_{(0-\infty)}$	184.256	70.4924	189.576	70.1161
C_{max}	38.719	15.4079	39.932	15.8684
T_{max}*	1.670	(0.67-3.50)	1.330	(0.67-5.00)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours>			
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours>			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 5. Pharmacokinetic parameters for N-desmethylated Ivabradine (non-transformed values) (N=33)

	Test (T)		Reference (R)	
	arithmetic mean	**SD**	**arithmetic**	**SD**
$AUC_{(0-t)}$	41.333	8.8200	42.383	7.9010
$AUC_{(0-\infty)}$	54.655	10.9353	55.980	9.4895
C_{max}	4.554	1.2385	4.670	1.2456
T_{max}*	1.670	(0.67-4.50)	1.330	(0.67-5.00)
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours>			
AUC_{0-72h}	area under the plasma concentration-time curve from time zero to 72 hours>			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

The geometric least squares mean of Test Formulation (T) and Reference Formulation (R), its ratio (T/R)%, intra-subject variability and 90% confidence intervals the Geometric least square mean ratio (T/R) obtained from the analysis of ln-transformed parameters Cmax, AUC_{0-t} and AUC_{0-inf} are summarized in the following table.

Table 6. Statistical analysis for Ivabradine (ln-transformed values)(N=33)

Pharmacokinetic parameter	Geometric Mean Ratio Test[T]/Reference [R]	Confidence Intervals	Intrasubject CV%*

Pharmacokinetic parameter	Geometric Mean Ratio Test[T]/Reference [R]	Confidence Intervals	Intrasubject CV% *
$AUC_{(0-t)}$	97.12	91.08% - 103.57%	15.49
$AUC_{(0-inf)}$	97.06	91.02% - 103.50%	15.47
C_{max}	96.93	88.95%-105.63%	20.8
* estimated from the Residual Mean Squares			

Moreover the Applicant presented the geometric means and ratios of means for Cmax, AUC0-t and AUC0-∞ of N-desmethylated ivabradine (summarized in the table below).

PK Parameters (Unit)	Geometric Means and It's Ratio		
	Test Product (T)	Reference Product (R)	(T/R) (%)
C_{max} (ng/mL)	4.375	4.495	97.33
AUC_{0-t} (hr*ng/mL)	40.369	41.627	96.98
AUC_{0-inf} (hr*ng/mL)	53.557	55.159	97.10

The AUC_%Extrap_obs for ivabradine and N-desmethylated ivabradine were not higher than 20%. For AUC_{0-t} and C_{max} of ivabradine the 90% confidence interval for the ratio of the test and reference products fell within the acceptance range of 80.00% to 125.00%.

The 90% confidence interval for geometric least square mean ratio of (T/R) is within the acceptance range of 80.00% to 125.00% for primary pharmacokinetic parameters C_{max} and $AUC0_{-t}$, required for concluding bioequivalence between the test and reference formulations. The statistical assessment of the main effects (in ANOVA model) showed that one effect was significant. Significant period effect justification for ln-transformed parameters AUC0-t and AUC0-inf was provided by applicant.

Results presentation provided in the documentation was clear and well prepared. Based on the results obtained in the bioequivalence study study 14-VIN-785, the ivabradine 7.5 mg film-coated tablets of Mylan Laboratories Limited and Procoralan (ivabradine) 7.5 mg film-coated tablets of Les Laboratoires Servier, in healthy, adult, human subjects were judged to be bioequivalent under fed condition.

Safety data

Both the study products were found to be safe and well tolerated. There were no serious adverse events (AEs) reported in this study. The adverse event was not life threatening or required the subjects to be hospitalized. One subject (subject number 15) reported adverse event after administration of test product and three subjects (subject number 01, 15 and 17) reported adverse event after administration of reference product. Of the 4 adverse events reported during the study, 1 was considered probable and 3 were considered unrelated to investigational products. 1 related adverse event occurred following administration of reference product.

Conclusions

Based on the presented bioequivalence study Ivabradine JensonR 7.5mg film coated tablets is considered bioequivalent with Procoralan 7.5 mg film-coated tablets.

The results of study 14-VIN-785with 7.5mg formulation can be extrapolated to the other strength 5 mg, according to conditions in the Guidelines.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Additional data

The results of in vitro dissolution tests at three different buffers were reported. The sampling time points were sufficient. 12 units of the product, each tested batch were used. The comparative dissolution test regarding the biowaiver for ivabradine 5 mg strength was conducted according to recommendations of the *EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).* Bearing in mind that more than 85% of the labelled amount of the drug was released within 15 minutes from each tested formulations (all the batches) in all three mediums covering pH of 1.2 to 6.8, the dissolution profiles were considered as similar without further mathematical calculations.

2.4.5. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.6. Discussion on clinical aspects

To support the application, the applicant has submitted one bioequivalence study. The bioequivalence of the applied formulation versus the reference product has been investigated on the 7.5 mg strength (study 14-VIN-785).

The bioequivalence study was open label, balanced, randomized, single dose, laboratory-blind, two period, two sequence, crossover study comparing the test formulations of Ivabradine 7.5 mg film-coated tablets with the approved reference product Procoralan (Ivabradine) 7.5 mg film-coated tablets. Sample size was estimated with an intra-subject CV% for primary pharmacokinetic parameters not exceeding 22%. The Applicant presented the literature source (Vlase et al. 2010) of intra-subject CV for 10 mg (20%) and for 5 mg (22.9%) of ivabradine. Based on this data, the ISCV of 22% was considered for sample size calculation in the present study. Assuming an expected ratio of C_{max} and AUC within 95% to 105%, the necessary sample size was estimated to be 30 subjects to show a bioequivalence with a power of at least 90% at 5% level of significance. Expecting certain dropouts and/ or withdrawals, 4 additional subjects were included to the study.

The subjects fasted overnight for at least 10 hours before scheduled time of start of high-fat, high calorie breakfast. Investigational product (allocated as per the randomization schedule) was administered orally to each subject according to the randomization schedule. The sampling points and the sampling scheme were adequate. The total duration of clinical phase of the study was 11 days. A washout period of seven days was kept between each consecutive dosing period to minimize the carry over effects and to eliminate the drug from the body. Ivabradine and N-desmethylated ivabradine were measured in human plasma using a validated LC/MS method. The pharmacokinetic parameters of ivabradine and N-desmethylated ivabradine were standard and adequate. The pharmacokinetic parameters Cmax, AUC_{0-t}, AUC_{0-inf}, T_{max}, $t_{1/2}$, K_{el} and AUC_%Extrap_obs for ivabradine and N-desmethylated ivabradine were calculated.

The primary pharmacokinetic parameters for ivabradine were: C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and for these values ratios of geometric least squares means and all descriptive statistics were calculated. Moreover the Applicant presented the geometric means and ratios of means for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ of N-desmethylated ivabradine.

Study results submitted by the applicant include statistical analysis appropriate to bioequivalence studies. Guidelines include provisions as to compare parameters in the analyses, so the use of ANOVA for primary endpoint was justified.

There was no subject in the study 14-VIN-785 detected as an outlier for the pharmacokinetic parameters. For AUC_{0-t} and C_{max} of ivabradine the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00% to 125.00%. The AUC_%Extrap_obs for ivabradine and N-desmethylated ivabradine were not higher than 20%. No pre-dose concentrations above the limit of quantification were detected and no subjects reached T_{max} of ivabradine at the first sampling point.

The Applicant has performed in vitro dissolution tests comparing the test and reference bio-batches used in bioequivalence study. In addition, the comparative dissolution test regarding the biowaiver for ivabradine
5 mg strength was conducted according to recommendations of the *EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)* and the dissolution profiles were considered as similar. Therefore, a bio-waiver for the 5 mg strength was accepted.

Analysis of variance was carried out for ln-transformed C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ for Ivabradine using PROC GLM. ANOVA model included fixed effects of Sequence, Treatment, Period and Subject (Sequence). Subject nested into sequence was used as error term for checking the significance of sequence. The sequence effect was tested at the $\alpha=0.10$ level of significance and all other main effects was tested at the $\alpha=0.05$ level of significance. Analysis of the main effects showed that one effect was significant. The significant period effect for AUC_{0-t} and AUC_{0-inf} was observed. A well-run study with consistent treatment of subjects should produce no significant period effects. The cause of that effect was investigated by the Applicant. Period effect may be due to a too short washout between periods (residual or carry-over effects), or they may reflect differing procedures of sample workup or storage, because for each subject usually all samples of all periods are analysed within the same run. They also may reflect an effect of the diet (Pabst, Jaeger, 1990). The Applicant presented discussion regarding reasons of the significant period effect. The Applicant claimed that the use of crossover design for bioequivalence (BE) studies allowed each subject to serve as his or her own control to improve the precision of the comparison. One of the assumptions underlying this principle was that carryover effects were either absent or equal for both formulations. If carryover effects were present in a crossover study and were not equal, the usual crossover estimate of μT-μR could be biased. One limitation of a conventional two-formulation, two-period, two-sequence crossover design was that the only statistical test available for the presence of unequal carryover effects was the sequence test in the analysis of variance (ANOVA). This was a between-subject test using subject nested in sequence as error term. Since, none of the PK parameter analysis had statistical significant sequence effect. No carryover effect or unequal carryover effect was confirmed for this study. Moreover, considering elimination half-life ($T_{1/2}$) of active drug and metabolite, wash out of 7 days was sufficient for the study. Hence, No carry over observed and also the residual error was insignificant.

Each analytical run consist of CC's/QC' and all the samples of periods were processed together and analysed under single curve and batch meets the criteria, no carry over was seen in period-1 pre-dose, which indeed demonstrate that there was no carry over in the assay method. In a few of the subjects period-2, the analyte response observed but the concentration was BLQ (Below limit of quantitation).

Hence, it was concluded that period effect is not due to bioanalytical assay method. All the subjects were served standardized meal menu during the period I & II. Hence diet differences were ruled out. At the time of generation of randomization was balanced. However at the end of study, subject no. 01 did not report to the facility in period 02 hence was withdrawn from the study. At the end of the study the observed number of subjects were 16 in sequence RT and 17 subjects in sequence TR. Due to this unbalance, period effect could be observed.

The Applicant acknowledged the observed statistically significant period effects for AUC_{0-t} and AUC_{0-inf}. However, the SAS GLM Procedure model utilized for analysis adjusts the period effects when estimating treatment effect. In the Applicant`s opinion the results presented in the report take any significant effects into account and adjusted for them in the statistical model utilized for determination of bioequivalence.

2.4.7. Conclusions on clinical aspects

The bioequivalence of the applied product Ivabradine, film-coated tablets, 7.5 mg with the respective strength of the reference product Procoralan film-coated tablets of Les Laboratoires Servier has been demonstrated in one bioequivalence study (study 14-VIN-785).

The study has been performed under fed conditions, which reflects recommendations in the brand leader's SPC for the administration of the product.

Presented study was designed and conducted according to assumptions and techniques suitable for bioequivalence studies (open label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period crossover scheme). The sample size was calculated to provide adequate power of bioequivalence analysis. The statistical methodology used in the studies is justified and consistent with the principles of guidelines on the investigation of bioequivalence.

In accordance with the study protocol the study meets the bioequivalence criteria as 90% confidence intervals for the ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} for ivabradine is within the acceptance range of 80.00% - 125.00% with power (1-β) 99.45 and 99.99 respectively.

The bioequivalence study appears to have been well conducted.

An acceptable justification for a biowaiver of Ivabradine Hydrochloride, 5 mg, film-coated tablets has been provided. According to the *EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)*, Ivabradine 5 mg film-coated tablets satisfy the conditions for waiver of bioequivalence studies conducted on the applied product 7.5 mg strength.

2.5. Risk management plan

Safety concerns

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 • Prolonged QT interval on ECG.
Important potential risks	• Supra-ventricular tachyarrhythmia 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 hepatic insufficiency • Use in patients with renal impairment • Use in chronic heart failure patients with intra-ventricular conduction defects.

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: bradycardia	Section 4.2, 4.3, 4.4, 4.5 and 4.8 of the SPC and section 2 and 4 of the PL has adequate information regarding this risk.	None
Important identified risk: phosphenes/blurred vision	Section 4.4, 4.7 and 4.8 of the SPC and section 2 and 4 of the PL has adequate information regarding this risk.	None
Important identified risk: 2nd and 3rd degree atrioventricular blocks (AVB II and III)	Section 4.3, 4.4, and 4.8 of the SPC and section 2 and 4 of the PL has adequate information regarding this risk.	None
Important identified risk: increase in blood pressure in hypertensive patients	Section 4.4, and 4.8 of the SPC and section 2 and 4 of the PL has adequate information regarding this risk.	None
Important identified risk: atrial fibrillation	Section 4.4, 4.5 and 4.8 of the SPC and section 2 and 4 of the PL has adequate information regarding this risk.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: prolonged QT interval or ECG	Section 4.4, 4.5 and 4.8 of the SPC and section 2 and 4 of the PL has adequate information regarding this risk.	None
Important potential risk: supra-ventricular tachyarrhythmia other than atrial fibrillation	Section 4.4, 4.5 and 4.8 of the SPC and section 2 and 4 of the PL has adequate information regarding this risk.	None
Important potential risk: immune disorders	No information regarding immune disorders is mentioned in SPC and PL of ivabradine.	None
Important potential risk: severe ventricular arrhythmia	Section 4.4, 4.5 and 4.8 of the SPC and section 2 and 4 of the PL has adequate information regarding this risk.	None
Important potential risk: myocardial infarction	Section 4.3, 4.4 and 4.5 of the SPC and section 2 and 4 of the PL has adequate information regarding this risk.	None
Missing information: use in children under 18 years old	Section 4.2 and 5.1 of the SPC and section 2 of the PL has some information regarding this missing information but limited.	None
Missing information: use in pregnancy and breastfeeding women	Section 4.3 and 4.6 of the SPC and section 2 of the PL has some information regarding this missing information but limited.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information: use in patients with hepatic insufficiency	Section 4.2 of the SPC and section 2 of the PL has some information regarding this missing information but limited.	None
Missing information: use in patients with renal impairment	Section 4.2 of the SPC and section 2 of the PL has some information regarding this missing information but limited.	None
Missing information: use in chronic heart failure patients with intra-ventricular conduction defects.	Section 4.4 and 5.1 of the SPC and section 2 of the PL has some information regarding this missing information but limited.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 2 is acceptable.

The Drug Utilisation Study (DUS) imposed on the reference medicinal product compares the characteristics of new users and the patterns of use of ivabradine before and after implementation of the risk-minimisation measures (Q1 2010-Q4 2013 vs Q2v 2015-Q1 2016). This comparison cannot be made for generic products since they were not available before implementation of the risk minimisation measures. Results from the DUS of innovator will become available in Q2 2017. Since the SmPC for the generic ivabradine products will be fully aligned with the SmPC of the reference product, the future results from DUS were considered applicable to the generic product as well. Consequently, at this time there is no need to perform separate studies.

It was considered that the obligation imposed for the reference medicinal product should not be imposed on Ivabradine JensonR. In the absence of any conditions imposed on Ivabradine JensonR, it was concluded that this product should not be included in the list of products subject to additional monitoring under the mandatory or optional scope criteria and will not display the black triangle in the SmPC and PL.

2.6. PSUR submission

The requirements for submission of periodic safety update reports for this medicinal product 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.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Procoralan. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of ivabradine hydrochloride film coated tablets. The reference product Procoralan is indicated for

Symptomatic treatment of chronic stable angina pectoris

Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ⩾ 70 bpm.
Ivabradine is indicated :
- in adults unable to tolerate or with a contra-indication to the use of beta-blockers
- or in combination with beta-blockers in patients inadequately controlled with an optimal beta blocker dose.

Treatment of chronic heart failure
Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ⩾ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. (see section 5.1).

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance. The applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis for authorisation with an open label, balanced, randomized, single-dose, two-treatment, two-sequence, two period, crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective EMA Guidelines. The study was conducted under fed conditions as it followed the recommendations of the SmPC of Procoralan for the tablet to be taken with food. The data for the ivabradine main metabolite were considered supportive, although it was noted that N-desmethylated ivabradine contributed in part to the overall activity of ivabradine. This suggested that the metabolite

is responsible for the initial bradycardic effect, whereas the parent compound is responsible for the duration of action, (Ragueneau, 1998). Choice of dose, sampling points, overall sampling time as well as the wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Ivabradine JensonR 7.5 mg film coated tablets met the protocol-defined criteria for bioequivalence when compared with Procoralan. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference medicinal product can therefore be concluded.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ivabradine JensonR is favourable in the following indication:

Symptomatic treatment of chronic stable angina pectoris

Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 bpm. Ivabradine is indicated:

- in adults unable to tolerate or with a contraindication to the use of beta-blockers
- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

Treatment of chronic heart failure

Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.