23 March 2017
EMA/263015/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ivabradine Accord

International non-proprietary name: ivabradine

Procedure No. EMEA/H/C/004241/0000

Note

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

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Administrative information

Name of the medicinal product:	Ivabradine Accord
Applicant:	Accord Healthcare Ltd Sage House 319 Pinner Road North Harrow Middlesex HA1 4HF UNITED KINGDOM
Active substance:	Ivabradine hydrochloride
International non-proprietary name/Common name:	ivabradine
Pharmaco-therapeutic group (ATC Code):	cardiac therapy, other cardiac preparations (C01EB17)
Therapeutic indication(s):	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 betablocker 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)
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	5 mg and 7.5 mg
Route(s) of administration:	Oral use
Packaging:	blister (alu/alu)
Package size(s):	100 x 1 tablets (unit dose), 112 x 1 tablets (unit dose), 14 x 1 tablets (unit dose), 28 x 1 tablets (unit dose), 56 x 1 tablets (unit dose), 84 x 1 tablets (unit dose) and 98 x 1 tablets (unit dose)

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List of abbreviations

ACE : Angiotensin converting enzyme

AF : Atrial fibrillation

ASMF : Active Substance Master File

AT1 : Angiotensin I

AUC : Area under the curve

BCS : Biopharmaceutics Classification System

BID : Two times a day

BNP : Brain natriuretic peptide

bpm : Beats per minute

CAD : Coronary artery disease

CCS : Canadian Cardiovascular Society

CHF : Chronic heart failure

CFR : Coronary flow reserve

Cmax : Maximum plasma concentration of drug

CNS : Central nervous system

CQA : Critical Quality Attribute

CSS : Clinical summary score

CYP : Cytochrome P450

CV : Coefficient of Varience

DNA : Deoxy ribonucleic acid

ETT : Exercise tolerance test

EU : European Union

g : Gram(s)

h : Hour(s)

HCN : Hyperpolarization-activated cyclic nucleotide-gated channel

HF : Heart failure

HPLC : High performance liquid chromatography

HQoL : Health related quality of life

HR : Heart rate

hSAN : human sino-atrial nodes

i.p. : Intraperitoneal

i.v. : Intravenous

IC_{50} : Half maximal inhibitory concentration

I_f : Funny current

IPC : In-process control

KCCQ : Kansas City Cardiomyopathy Questionnaire

KF : Karl Fischer titration

kg : Kilograms

L : Liter(s)

LD_{50} : Median lethal dose

LVEF : Left ventricular ejection fraction

LVWth : Left ventricular (LV) wall thickening

M : Molar

MAA : Marketing Authorization Application

mg : Milligrams

MHRD : The maximum recommended human dose

MI : Myocardial infarction

ml or mL : Milliliter

mRNA : Messenger ribonucleic acid

MVO_2 : Myocardial oxygen consumption

NADPH : Nicotinamide adenine dinucleotide phosphate (reduced form)

ng : Nanograms

OSS : Overall summary score

PDR : Physician desk reference

Ph. Eur. : European Pharmacopoeia

PMI : Potentially mutagenic impurities

QOL : Quality of life

QTPP : Quality target product profile

s.c. : Sub-cutaneous

SmPC : Summary of product characteristics

TED : Total exercise duration

TSE : Transmissible spongiform encephalopathies

VF : Ventricular fibrillation

VT : Ventricular tachycardia

XRPD : X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 9 November 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Ivabradine Accord, 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 25 June 2015.

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 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 contra-indication to the use of beta-blockers

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

Information on paediatric requirements

Not applicable

Information relating to 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: 074-14

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: Eleftheria Nikolaid

- The application was received by the EMA on 9 November 2015.

- The procedure started on 4 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 23 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 01 April 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 October 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 November 2016.
- During the PRAC meeting on 1 December 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 15 December 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 21 February 2017.
- During the meeting on 23 March 2017, 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 Accord.

2. Scientific discussion

2.1. Introduction

The proposed product is an immediate release film-coated 5 mg and 7.5 mg tablets containing ivabradine hydrochloride as active substance. Ivabradine hydrochloride is a chemical substance and the dosage form has been developed as generic product to the centrally authorised product Procoralan containing the same active substance in the same pharmaceutical form.

Ivabradine acts by inhibiting the I_f 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.

Ivabradine was first introduced into the market in Europe eight years ago as Procoralan film coated tablets. Current Marketing Authorization Application (MAA) is based on "essential similarity" to the original product in accordance with Article 10(1) (a) (iii) of Directive 2001/83/EC.

This MAA is made on the basis that ivabradine film-coated tablets 5/7.5 mg is essentially similar to Procoralan 5/7.5 mg film-coated tablets marketed by Les Laboratoires Servier, France. The indications sought are the same as those for Procoralan 5/7.5 mg film-coated tablets.

One bioequivalence study comparing ivabradine film-coated tablets 7.5 mg against Procoralan 7.5 mg film-coated tablets under fed conditions was conducted and submitted within current MAA and was considered pivotal.

The proposed indications are:

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 β-blockers*

or

- *in combination with β-blockers in patients inadequately controlled with an optimal β-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 β- blocker therapy or when β-blocker therapy is contraindicated or not tolerated.

The recommended dose range is 2.5 or 7.5 mg twice daily.

Symptomatic treatment of chronic stable angina pectoris

It is recommended that the decision to initiate or titrate treatment takes a place with the availability of serial heart measurements, ECG or ambulatory 24-hour monitoring. The starting dose of ivabradine should not exceed 5 mg twice daily in patients aged below 75 years. After three to four weeks of treatment, if 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 to the next higher dose in patients receiving 2.5 mg twice daily or 5 mg twice daily. 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.

In addition, discontinuation of treatment should be considered if there is only limited symptomatic response and when there is no clinically relevant reduction in resting heart rate within three months. If, during treatment, heart rate decreases below 50 bpm at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the lowest dose of 2.5 mg twice daily (one half 5 mg tablet twice daily). After dose reduction, heart rate should be monitored (see section 4.4). Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dose reduction.

Treatment of chronic heart failure

The treatment has to be initiated only in patient with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic heart failure. The usual recommended starting dose of ivabradine is 5 mg twice daily. After 2 weeks of treatment, the dose can be increased to 7.5 mg twice

daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

If during treatment, heart rate decreases persistently below 50 bpm at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. If heart rate increases persistently above 60 bpm at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5 mg twice daily or 5 mg twice daily. Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist.

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 (E470b), pregelatinised starch (maize) and colloidal hydrated silica.

Ingredients of the film-coating are: polyvinyl alcohol (E1203), titanium dioxide (E171), macrogol 4000, talc (E553b), yellow iron oxide (E172) and red iron oxide (E172).

The product is available in aluminium/aluminium perforated unit dose blisters, as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

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 molecular weight of 505.05 g/mol and the following structure:

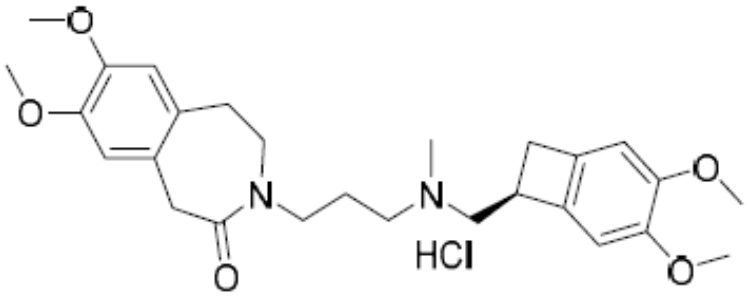

Figure 1. Chemical structure of ivabradine hydrochloride.

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

The active substance is a white to slightly yellow hygroscopic powder, soluble in water, solutions of physiological pH and dimethyl sulfoxide. It is freely soluble in methanol and dichloromethane.

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 in the specifications of the active substance.

Polymorphism has been observed for ivabradine hydrochloride. Seven crystalline forms have been identified and δd-form has been selected for further development. It has been demonstrated that the active substance manufacturing process consistently produces crystalline δd-form 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 two manufacturers are responsible for different steps of its production.

Ivabradine hydrochloride is synthesized in a two-branch convergent process using two commercially available well defined starting materials with acceptable specifications. The branches consist of six and four chemical synthesis steps respectively, followed by a coupling reaction and purification and salt formation. The starting materials were re-defined during the procedure, at the request of CHMP, in order to ensure that critical steps 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 on impurities with mutagenic potential is presented and followed which was deemed acceptable and in line with Guideline ICH M7. Reprocessing is claimed for a part of manufacturing process. At the time of opinion the recommended criteria for deciding when the reprocessing can be performed and data showing that reprocessing has been validated related to specific reprocessing procedures applied was not provided, however it is considered that this minor unresolved quality issue has no impact on the Benefit/Risk ratio of the product. The CHMP recommends that this is addressed in future quality development.

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 transparent polyethylene (LDPE) bag under nitrogen and tightly sealed with strip seal. The primary sealed transparent polyethylene bag is packed in second transparent polyethylene bag containing activated silica under nitrogen and tightly closed with strip seal. The secondary packed material is again packed in transparent polyethylene bag containing activated silica under nitrogen and tightly closed with

strip seal. The finally container is an aluminium can containing activated silica under nitrogen. 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, solubility (Ph. Eur.) identification including polymorphic δd-form (IR, HPLC, XRD), chlorides (Ph. Eur.), water content (KF), sulfated ash (Ph. Eur.), heavy metals (Ph. Eur.), clarity of solution (ph. Eur.), enantiomeric purity (HPLC), related substances (HPLC), assay (HPLC), residual solvents (GC), hydrochloric acid content (titration), palladium content (ICP-OES), particle size distribution (laser diffraction) and microbiological examination (Ph. Eur.).

Impurities are all limited to below the qualification threshold as per ICH Q3A. Detailed calculations of purge and fate of the different identified potentially mutagenic impurities (PMI) under the conditions of the manufacturing process have been provided and the control strategy for PMI was considered acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. As part of related substances, enantiomeric purity and residual solvents method validation, the applicant provides the signal to noise ratio values which are greater than 3. At the time of opinion the recommended recalculation of this ratio was not done, however it is considered that this minor unresolved quality issue has no impact on the Benefit/Risk ratio of the product. The CHMP recommends that this is addressed in future quality development. 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.

The active substance specifications are based on the active substance critical quality attributes (CQA).

Stability

Stability data on six production scale batches and on three laboratory scale batches of active substance stored in a container closure system representative of that intended for the market, for up to eighteen months under long term conditions at 5±3 °C and for up to six months under accelerated conditions at 25±2 °C / 60±5% 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 acidic, alkaline medium, with oxidising agent, heat, UV and fluorescent light degradation and humidity degradation were also provided on one batch.

The following parameters were tested: description, identity including polymorphic δd-form, water content, clarity of solution, enantiomeric purity, related substances, assay and microbiological examination. 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.

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 12 months in the proposed air tight container at 2-8 °C and protected from moisture.

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 salmon coloured, oblong shaped, approximately 8.50 mm by 4.50 mm in size, scored on both sides film-coated tablet and debossed with “FK” on one side and “2” on other side of the tablet. The 7.5 mg strength is presented as salmon coloured, triangular shaped, approximately 7.30 mm by 6.769 mm in size film-coated tablet and debossed with “FK” on one side and “1” on other side of the tablet. The different strengths of the film-coated tablets differ in shape, dimensions, scoring (5 mg film-coated tablets can be divided into equal doses) and debossing.

Pharmaceutical development of the finished product contains QbD elements. 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 and the following Quality Target Product Profile (QTPP): immediate release film-coated tablet for oral administration in 5 and 7.5 mg strengths, packed in alu-alu blisters; immediate release enabling T_{max} in 2 h; bioequivalence to the reference medicinal product; meeting the same or compendial or other applicable quality standards and stability of at least 24 months at room temperature. The following critical quality attributes (CQA) are defined: physical attributes of appearance, size, scoring and friability; assay; content uniformity; degradation products and dissolution. The CQAs were identified based on the performed risk-assessments. The formulation development has been evaluated through the use of design of experiments.

Since the active substance is freely soluble across the physiological pH (BCS Class I), 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. The active substance particle size is controlled in the active substance specifications due to its impact of manufacturability of the finished product.

The formulation of Ivabradine Accord 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 the tablet core (the reference medicinal product additionally contains maltodextrin) and film-coating (PVA based in Ivabradine Accord and hypromellose based in the reference medicinal product). 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, pH 6.8 phosphate buffer and purified water. In-line with the reference product, Ivabradine Accord 5 mg film-coated tablets have been developed as scored tablets. Study related to subdivision of tablets was performed and found acceptable.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards and legal requirements. 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. To assess discriminatory power of the dissolution method, a trial batch was manufactured. The discriminatory power of the dissolution method has been demonstrated, as the modified formulation failed to meet specifications.

Standard direct compression has been selected as the manufacturing process for the film-coated tablets due to ease of manufacturing and good compatibility of the ingredients. Blending time, lubrication step, hardness and

coating step 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.

A bioequivalence study was performed showing bioequivalence between Ivabradine Accord 7.5 mg film-coated tablets and the reference medicinal product. Based on the acceptable study, a request for a waiver of bioequivalence study on the remaining strength (5 mg) was submitted and found acceptable an in line with the Guideline on the Investigation of Bioequivalence. 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 alu-alu blisters and/or PPCP container used as bulk transportation packaging. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and a hold time study for bulk container and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: sifting, blending, compression, coating and packaging. A common blend is used for both tablet strengths. The critical steps include blending, 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, average weight of the tablet (weighing), identification (UV, HPLC), water content (KF), dissolution (HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), related substances (HPLC), microbiological quality (Ph. Eur.) and resistance to crushing. The specification for the 7.5 mg strength is identical other than the description, average weight of the tablets and resistance to crushing.

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 two 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.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data on two commercial scale batches of each strength of finished product stored under long term conditions for 18 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 the same parameters as for release. The analytical procedures used are the same as used for release and are stability indicating.

No significant changes have been observed under long term or accelerated conditions.

Forced degradation studies on samples treated under alkaline, acidic, oxidation, water and heat stress conditions, UV light conditions have been performed as part of the validation of the analytical methods, demonstrating that they are stability indicating. The results demonstrated an increase in impurities under alkaline, acidic, oxidation, water and heat stress conditions. No major degradation is observed in UV degradation study.

In addition, samples from one batch of each of the film-coated tablet strengths were 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 (description, assay and related substances), demonstrating their photostability.

Based on available stability data, the proposed shelf-life of 2 years 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.

At the time of the CHMP opinion, there were two minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

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. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The CHMP recommends to complement the dossier by (a) providing criteria for deciding when the active substance reprocessing can be performed and (b) evidencing that reprocessing has been validated by real data related to specific reprocessing procedures applied.

The CHMP recommends to recalculate limits of detection of the active substance analytical methods for related substances, enantiomeric purity and residual solvents so that the signal to noise ratio equals 3.

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.

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 the applicant as the introduction of Ivabradine Accord manufactured by Accord Healthcare Ltd was 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 was expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

This application concerns a generic application and the data submitted are considered relevant and sufficient.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Ivabradine Accord was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional non-clinical studies were not considered necessary.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablet 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 considered 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 (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), EMA Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98),* as well as the *EMA Guideline on Bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)* were 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

Bio-waiver for remaining strength (Ivabradine film-coated tablets 5 mg)

Based on the bio-equivalence study for Ivabradine film-coated tablets 7.5 mg, a request for bio-waiver for the remaining strength i.e. 5 mg was placed based on the following general requirements:

a) All the strengths i.e. 5 mg and 7.5 mg of proposed pharmaceutical products are manufactured by the same manufacturing process,

b) The qualitative composition of the Ivabradine film-coated tablets 5 mg is same as that of Ivabradine film-coated tablets 7.5 mg.

c) The composition of both strengths i.e. 5 mg and 7.5 mg are quantitatively proportional i.e. the ratio between the amount of each excipient to the amount of active substance(s) is same for all the strengths.

d) In-vitro dissolution data on all the strengths confirms the adequacy of waiving additional in vivo bioequivalence testing.

It is stated in the *EMA Guideline on the Investigation of Bioequivalence (Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)* that for products where all the above conditions a) to d) are fulfilled and the products show linear pharmacokinetics, it is sufficient to establish bioequivalence with only one of the strengths. The proposed formulations fulfil all the above criteria, thus 7.5 mg strength has been selected as a BE investigation strength.

The dissolution profiles comparison of Ivabradine film-coated tablets 5 mg and bio-batch i.e. Ivabradine film-coated tablets 7.5 mg showed more than 85% of drug release within 15 minutes, so dissolution profiles are considered similar without any mathematical calculation for similarity. Hence, the dissolution profiles can be

acceptable and it proves that test product (5 mg strengths) is similar to the test product (7.5 mg strength, bio-batch).

Linear pharmacokinetics of Ivabradine

The pharmacokinetics of ivabradine is linear over an oral dose range of 0.5-24 mg (as indicated in the SmPC for Procoralan). Also in a study, healthy non-smoking volunteers were randomly assigned to 1 of 3 treatment groups based on treatment with 5, 10 or 20 mg of ivabradine. After a single dose, the subjects assigned to the 3 dose groups received repeated oral doses of ivabradine BID for 6 days. The results show that after the single dose, plasma ivabradine Cmax and AUC increased approximately linearly with dosage (Jiang J et al. 2013).

Clinical studies

To support the application, the applicant has submitted one bioequivalence study (074-14).

Tabular overview of clinical studies

Protocol No.	Study Title
074-14	An open label, balanced, randomized, two treatment, two sequence, two period, single oral dose, crossover bioequivalence study of two products of Ivabradine 7.5 mg film-coated tablets in normal healthy, adult, human subjects under fed condition

2.4.2. Pharmacokinetics

Study No. 074-14 An open label, balanced, randomized, two treatment, two sequence, two period, single oral dose, crossover bioequivalence study of two products of Ivabradine 7.5 mg film-coated tablets in normal healthy, adult, human subjects under fed condition<NUMBER>:

Methods

Study design

Clinical Facility, Bio-analytical, Pharmacokinetic, Bio-statistics & Programming, Quality Assurance and Clinical Laboratory Services at:

Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India.

The study was an open label, balanced, randomized, two-treatment, two-period, two sequence, single oral dose, crossover, bioequivalence study in healthy, adult, human subjects under fed conditions, with a screening period of 28 days prior to the dosing in Period-I.

After an overnight fast of at least 10 hours, the subjects were served standardized high fat high calorie vegetarian breakfast, which they consumed within 30 minutes. A single oral dose (7.5 mg) of either the test product or the reference product was administered to the subjects at 30 minutes after serving the breakfast. The IMP was administered in sitting posture with 240 mL of drinking water at ambient temperature. The investigational medicinal product (IMP) administration was as per the randomization schedule and under open-label conditions.

A washout period of 07 days was maintained between the successive dosing days.

In each study period, 22 blood samples, including one pre-dose blood samples, were collected from each subject except for the discontinued/withdrawn subjects to analyze the pharmacokinetic profile of the test as well as the reference product.

During the study, venous blood samples were collected at pre-dose and at 0.25, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00, 5.00, 6.00, 8.00, 10.00, 12.00, 16.00 and 24.00 hours post dose.

Test and reference products

Table 1. Tests and Reference product information of project no. 074-14

Product Characteristics	Test Product	Reference Product
Name	Ivabradine film-coated tablets 7.5 mg	Procoralan 7.5 mg film-coated tablets
Strength	7.5 mg	7.5 mg
Dosage Form	Film-coated tablet	Film-coated tablet
Manufactured by	Intas Pharmaceuticals Ltd., India	Servier (Ireland) Industries Ltd, Gorey Road, Arklow- Co. Wicklow - Ireland
Batch No./Lot No.	S03464	196359
Batch Size (Bio batch)	170,000 tablets	
Measured Content(s)[1] (% of Label Claim) /Assay %	102.7%	99.7%
Commercial Batch Size	170,000 tablets 1,400,000 tablets	
Expiry Date	02/2017	09/2017
Location of Certificate of Analysis	<Module 5, study-reports, Vol 1 of 3>	<Module 5, study- reports, Vol 1 of 3>
Member State where the Reference Product is purchased from		United Kingdom

[1] List for each active substance for fixed combinations

Ivabradine Accord 7.5 mg film-coated tablets manufactured by Intas Pharmaceuticals Ltd., India (batch No. S03464) has been compared to Procoralan 7.5 mg film-coated tablets manufactured by Servier (Ireland) Industries Ltd (Batch No: 196359).

Population studied

The subjects who participated in the study were non-smoker, healthy, adult, male, in the age range of 18 to 45 years (both inclusive) living in India. They had a Body Mass Index (BMI) between 18.5 and 27.0 (both inclusive), calculated as weight in kg/height in m2. Body weight should be more than 50 kg.

A total of 61 subjects (Subject Nos. 1001-1056, 2002, 2020, 2040, X-1 and X-2) were enrolled in Period-I of the study. On the day of check-in for Period-I, prior to check-in, Subject Nos. 1002, 1020 and 1040 discontinued from the study on their own accord. They were replaced with next available volunteer having ASN 29, ASN 40

and ASN 64 respectively. The subjects were then allotted Subject Nos. 2002, 2020 and 2040 respectively. Hence, a total of 58 subjects (Subject Nos. 1001, 2002, 1003-1019, 2020, 1021-1039, 2040, 1041-1056, X-1 and X-2) were checked in for the study. Subject Nos. X-1 and X-2 were checked in for the study, in order to compensate for any dropouts prior to dosing in Period-I. After being checked-in, Subject No. 1047 was withdrawn from the study on the grounds of protocol non-compliance. He was replaced with Subject No. X-2 who was later allotted Subject No. 2047. Subject No. 1054 discontinued from the study on his own accord. He was replaced with Subject No. X-1 who was later allotted Subject No. 2054.

Hence, as per the protocol, 56 subjects (Subject Nos. 1001, 2002, 1003-1019, 2020, 1021-1039, 2040, 1041-1046, 2047, 1048-1053, 2054, 1055, 1056) were dosed in Period-I of the study.

Subject No. 1006 was withdrawn from the study on medical grounds in Period-II. Subject No. 1022 was withdrawn from the study on the grounds of protocol non-compliance in Period-II. Subject No. 1027 discontinued from the study on his own accord in Period-II. In all, 53 subjects (1001, 2002, 1003-1005, 1007-1019, 2020, 1021, 1023-1026, 10281039, 2040, 1041-1046, 2047, 1048-1053, 2054, 1055, 1056) completed the clinical phase of the study successfully.

Analytical methods

Sponsor of the study: Intas Pharmaceuticals Ltd, India 2nd Floor, Chinubhai Center, Ashram Road, Ahmedabad-380 009 Gujarat, India.

Site of Sample Analysis : Lambda Therapeutic Research Ltd., Plot No. 38, Near Silver Oak Club, S. G. Highway, Gota, Ahmedabad-380 061, Gujarat, India.

Date of First Sample Collection : 25 July 2015

Date of Completion of Analysis : 21 August 2015

The plasma samples (pharmacokinetic samples) were received from Clinical Facility, Lambda Therapeutic Research Limited, Ahmedabad, India, in frozen condition in boxes containing adequate amount of dry ice. The received samples at bioanalytical facility were transferred to the freezer maintained at -65 ± 10°C for the final storage. Before analysis, all the samples were verified.

Anticoagulant	K_2EDTA
Number of subjects (as per protocol)	56
Number of sampling time-points (as per protocol)	22
Details of sampling time-points (as per protocol)	0.000 (pre-dose) and at 0.250, 0.500, 0.750, 1.000, 1.250, 1.500, 1.750, 2.000, 2.250, 2.500, 2.750, 3.000, 3.500, 4.000, 5.000, 6.000, 8.000, 10.000, 12.000, 16.000 and 24.000 hours post-dose
Number of periods (as per protocol)	02
Total number of samples (as per protocol)	2464 (56 subjects X 22 time-points X 02 period)
Samples not received/lost	66 (refer to Table No. 07)

3 from the 56 subjects were withdrawn / discontinued from the study in Period II and therefore 3x22=66 samples were missing

It appeared that the applicant has performed the standard validations for the analytical method. However, there were certain issues that needed to be clarified by the applicant such as the high value of the upper limit of the intra-day accuracy (113.3%), the low recovery values for ivabradine (92.6, 90.6 and 90.5% for LQC, MQC & HQC standards) in relation with quite higher recovery value of the Internal Standard (97.9%) as well as the lower claimed acceptance limit of 30%. In addition the applicant was asked to provide chromatographs with both peaks of Ivabradine and IS depicted on them and justify the resolution of the relevant peaks. The questions were raised in an effort to clarify and fully identify any potential flaws in the analytical method that could have a significant impact on the results. In addition the questions were raised to remove any doubts on that the sequence effect was a pure chance finding of the study and not a systematic error of the analytical procedure. The responses of the applicant were in accordance with the general widely known practice and thus were considered sufficient.

Pharmacokinetic variables

Efficacy was primarily assessed by the pharmacokinetic properties of the test and the reference formulations by measurement of Ivabradine concentration in plasma.

The following pharmacokinetic parameters were calculated:

Primary pharmacokinetic parameters: Cmax, AUC0-t and AUC0-∞

Secondary pharmacokinetic parameters: Tmax, λz, t1/2 and AUC_%Extrap_obs

These pharmacokinetic parameters were calculated for Ivabradine by non-compartmental model using WinNonlin Professional Software Version 5.3 (Pharsight Corporation, USA).

The pharmacokinetic variables chosen for demonstration of bioequivalence were considered appropriate.

Statistical methods

Descriptive statistics were calculated and reported for all pharmacokinetic parameters of Ivabradine. ANOVA, power and ratio analysis for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ were computed for Ivabradine. Using two-one sided tests for bioequivalence, 90% confidence intervals for the ratio of the geometric least-squares means between drug formulations were calculated for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for Ivabradine. ANOVA model was to be included Sequence, Subject (Sequence), Formulation and Period as fixed effects. Each analysis of variance was to be included calculation of least-squares means, the difference between adjusted formulations means and the standard error associated with the differences.

An F-test was to be performed to determine the statistical significance of the effects involved in the model at a significance level of 5% (alpha = 0.05). The power of the study to detect 20% difference between test and reference formulations was to be calculated and reported for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of Ivabradine. Ratio of geometric least squares means of test and reference formulations was to be calculated and reported for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for Ivabradine. Intra-subject variability was to be calculated and reported for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for Ivabradine. Any missing samples (M) or non-reportable (NR) concentration values were to be disregarded in pharmacokinetic and statistical analysis.

Using two one-sided tests for bioequivalence, 90% confidence intervals for the ratio of geometric least squares means between drug formulations were to be calculated for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ for Ivabradine.

Blinding

This was an open-label study. Blinding was not applicable.

Determination of Sample Size

Based on the available literature data, the intra-subject variability observed for primary pharmacokinetic parameter Cmax was found to be ~ 23%, the sample size computation was determined using SAS by considering the following assumptions:

T/R ratio = 90.0-110.0%

Intra-Subject C.V (%) ~ 23%

Significance Level = 5%

Power ≥ 80% ☐

Bioequivalence Limits = 80.00 – 125.00 %

Based on the above estimates and considering dropouts and/or withdrawals, a sample size of 56 subjects was considered to be sufficient to establish bioequivalence between formulations with adequate power for pivotal study.

All statistical analyses for Ivabradine were performed using PROC GLM of SAS® Version 9.3 (SAS Institute Inc., USA). Selection of PK parameters, determination of sample size, statistical evaluation of the PK parameters and the acceptance ranges for bioequivalence were in accordance with the *EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1 Cor**)*. The statistical methods chosen were considered adequate.

Results

A tabular summary of the bioequivalence study is given below and a study summary is included at the end of this clinical overview. In this study of Ivabradine film-coated tablets 7.5 mg, the 90% confidence interval lay within the accepted range of 80.0-125.0 for Cmax, AUC0-t, and AUC0-∞. Thus, the study has demonstrated that a single dose of the applicant's Ivabradine film-coated ts 7.5 mg is bioequivalent to a single dose of Procoralan 7.5 mg film-coated tablets.

Table 2. Relative Bioavailability Results for Ivabradine (N = 53)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	33.997	34.307	99.1	93.63 - 104.88	17.5	100.0
$lnAUC_{0-t}$	194.740	191.328	101.8	97.43 - 106.33	13.5	100.0
$lnAUC_{0-\infty}$	198.093	194.770	101.7	97.31 - 106.29	13.6	100.0

The relative bioavailability analyses (i.e. geometric least squares means, ratio, 90% confidence interval, intra subject CV and power) of Test Product-T vs. Reference Product-R for Ivabradine are summarized in the following table:

Table 3. Relative bioavailability results for Ivabradine (N=53)

Relative Bioavailability Results for Ivabradine (N = 53)

Parameters	Geometric Least Squares Means			90% Confidence Interval	Intra Subject CV (%)	Power (%)
	Test Product-T	Reference Product-R	Ratio (T/R)%			
lnC_{max}	33.997	34.307	99.1	93.63 - 104.88	17.5	100.0
$lnAUC_{0-t}$	194.740	191.328	101.8	97.43 - 106.33	13.5	100.0
$lnAUC_{0-\infty}$	198.093	194.770	101.7	97.31 - 106.29	13.6	100.0

ANOVA p-values for Ivabradine are summarized in the following table:

Table 4. ANOVA p-values for Ivabradine

ANOVA p-values for Ivabradine

Parameters	ANOVA (p-value)			
	Formulation	Sequence	Period	Subject (Seq)
lnC_{max}	0.7896	0.0004	0.1656	<0.0001
$lnAUC_{0-t}$	0.5011	0.0002	<0.0001	<0.0001
$lnAUC_{0-\infty}$	0.5237	0.0002	<0.0001	<0.0001

Note: p-value is statistically significant if it is < 0.05.

Based on the above table, **formulation effect** is found to be statistically insignificant for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of Ivabradine.

Sequence effect is found to be statistically significant for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of Ivabradine. The cause for significant sequence effect could not be found with certainty. Under special circumstances the significant sequence effect can be ignored. The study [1] was a single dose study [2] was in healthy volunteers, [3] was not comparing an endogenous substance, [4] had an adequate washout and [5] used appropriate design and analysis. Moreover, study met bioequivalence criteria successfully. Hence, it was agreed that this sequence effect was just statistically significant and could be ignored.

Period effect is found to be statistically insignificant for ln-transformed pharmacokinetic parameter Cmax but it is found to be statistically significant for ln-transformed pharmacokinetic parameters AUC0-t and AUC0-∞ of Ivabradine. In the study, clinical conditions were kept identical in both periods of the study, and there were no

pre-dose concentrations observed. The decision of bioequivalence was based on the 90% confidence interval by Schuirmann two one sided 't' test which was within the acceptance criteria i.e. 80.00 to 125.00%. It was considered that this significant period effect for ln-transformed pharmacokinetic parameters AUC0-t and AUC0-∞ was just statistically significant and could be ignored.

Subject (Sequence) effect was found to be statistically significant for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of Ivabradine. Since each subject was assigned only one sequence, subjects were nested within sequence. This Subject (Sequence) effect was tested by the Residual and should be highly significant. This significance was an indication that the purpose of using the crossover design has been realized in that the between-subject variance was significantly larger than the residual. The above mentioned justification provided by the applicant was further discussed and further justifications were required. The statistical significance of the sequence effect for both Cmax and AUC was quite high 0.004 and 0.002 respectively. The additional justifications presented by the applicant were considered sufficient.

Safety data

One (01) significant AE was reported in Period-II. The AE was reported after administration of Test Product-T. The AE was moderate in nature. The causality assessment was judged as unrelated for the AE. The subject was withdrawn from the study on medical grounds. He was treated appropriately and followed up until resolution of this AE. There was no death or serious adverse event during the conduct of the study.

This patient reported to the clinical facility with complaint of multiple abrasions over back of thigh and back of trunk. He informed that he had fallen down on road at approximately 10:00 hours on 31 July 2015 and had complaints of pain and swelling over affected local sites. The adverse event was sudden at onset, occurred as single episode and moderate in nature. He was withdrawn from the study on medical grounds. He was treated with medication and was followed up until resolution of his AE. His adverse event was resolved at 17:00 hours on 05 August 2015. The adverse event was moderate in nature and the relationship of the adverse event to the study drug was considered to be unrelated.

In general, the clinical portion of the study was completed with one (01) significant AE. The investigational products were well tolerated by healthy subjects, as a single dose administration. There were no clinically significant findings in the vital signs assessment, ECG recordings or the laboratory tests in any of the subjects in the study.

Conclusions

Based on the presented bioequivalence study Ivabradine Accord was considered bioequivalent with Procoralan.

2.4.3. Pharmacodynamics

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

2.4.4. Post marketing experience

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

2.4.5. Discussion on clinical aspects

Statistical analysis of the bioequivalence (BE) study was performed on the pharmacokinetic data for 53 subjects (56 subjects on test treatment and 53 subjects on reference treatment). The applicant presented that the 90% confidence interval of the test/reference ratio from the ANOVA of the log-transformed AUC0-t, AUC0-∞-, and Cmax were within the acceptance criteria of 80.00-125%.

The CHMP noted also additional publication that has compared the pharmacokinetic profile of ivabradine under fasting conditions (*Choulwar Amol K*, Mungantiwar Ashish A., Chintamaneni Meena "A comparative, Bioequivalence study to evaluate the safety and pharmacokinetic profile of single dose Ivabradine 7.5mg Tablets in healthy, adult, human subjects under fasting condition" Research Journal of Pharmacy and Technology Year : 2012, Volume : 5, Issue : 5 First page : (658) Last page : (666) Print ISSN : 0974-3618. Online ISSN : 0974-360X).*

The SmPC dosing recommendations provide recommendations for administration in the fed state and the post-prandial investigation of BE was acceptable.

However, a strong **sequence effect** has been observed. The sequence effect could be caused by three confounded sources (i.e. the sources cannot be distinguished): (i) **the true sequence effect** (difference in mean of TR- mean of RT), (ii) **the differential carry-over effect** of the two drugs into the next period: the response on the second period depends on the response in the first period and this dependency differs depending on which of the two treatments was given during the first period, (iii) **the drug by period interaction**: the difference between drugs is different for the two periods. Therefore, if a significant sequence effect is found, the 90% CI for T/R could be biased due to possible **differential carry-over effect**. A properly designed and executed study should lack of differential carry-over effect or **product by period interaction**. When an **adequate wash-out** period exists, the carry over effects are usually eliminated. When a sequence effect is presented, then, the results from the first period only should be analysed. In this case, one-half of the data wwould be lost (second period) and there would be less chance to detect bioequivalence. The explanations provided initialy by the applicant covered only the case of differential carry-over effect (without excluding the validity of bioanalysis).

The applicant explained that **the cause for significant sequence effect could not be found with certainty**. Therefore under special circumstances the significant sequence effect can be ignored. The study [1] was a single dose study [2] was in healthy volunteers, [3] was not comparing an endogenous substance, [4] had an adequate washout and [5] used appropriate design and analysis. Moreover, study meets bioequivalence criteria successfully. Hence, this sequence effect is just statistically significant and can be ignored." The applicant provided further explanations that were accepted by the CHMP.

The statistical significance of the sequence effect for both Cmax and AUC was quite high: 0.004 and 0.002, respectively. A well designed study should not contain a sequence effect. The factors contributing to this can be a combination of the three factors mentioned above (i, ii and iii). Since, excluding the carry-over pharmacokinetic effect, it was not clear which factor contributed to the effect observed, the results of both, first and second periods, should be analysed for demonstration of bioequivalence.

Subject (Sequence) effect was found to be statistically significant for ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of Ivabradine. Since each subject was assigned only one sequence, subjects were nested within sequence. This Subject (Sequence) effect was **tested by the residual** and should be highly significant. This significance was an indication that the **purpose of using the crossover design has**

been realized in that **the between-subject variance was significantly larger than the residual**. The clarifications presented by the applicant were considered sufficient.

Concerning the **validation of the analytical report** there were certain issues identified that were further discussed and clarified. According to the validation report the **intra-day accuracy** ranged from 98.1 to 113.3%. The applicant was requested to justify and discuss the **high value of the upper limit (113.3%)**.

The **recovery values for ivabradine** (**92.6, 90.6 and 90.5%** for LQC, MQC & HQC standards) **were low** and quite lower compared to the respective value of the recovery of the **Internal Standard [ISTD] (97.9%)**.

In addition the **acceptance limits** were claimed to be 30-115%. The **lower limit (30%)** was asked to be better justified.

Also, the ivabradine and IS peaks were presented in separate chromatographs. The applicant was asked to provide **chromatographs with both peaks of Ivabradine and ISTD depicted on them**. In addition taking into account the **close values of the retention times** of the drug and ISTD the applicant was requested to discuss the resolution of the relevant peaks, since this could not be identified from the analytical validation study report.

In responses provided the applicant has referred to (1) **the entire method validation** that was performed before start of the subject sample analysis AND (2) **the experiments concerning the system suitability and the auto sampler carry-over effect** that was performed before subject sample analysis (pre-study validation). The results of both experiments were well within the acceptance criteria. In addition, during the conduction of the study, required set of quality control samples were analyzed along with each analytical run ("in-study validation") and the relevant results were presented in the bioanalytical report. 20% of chromatograms of serially selected subjects (including chromatograms of calibration curve standards and quality control samples) have been appended to the bio-analytical report. The applicant has submitted within responses **100% of chromatograms** of subjects as requested. In addition to that **incurred sample reproducibility (ISR) experiment** was also performed and provided by the applicant. Those data of ISR were also considered as "in-study validation".

The applicant agreed that the **intra-day accuracy** of lower limit of quantification of the quality control (LLOQ QC) samples for P&A I was slightly on higher side **(113.3 %)** and therefore results of P&A batch of method validation were checked again. The intra-day % accuracy of lower limit of quantification LLOQ QC samples for another 2 P&A batches were 96.2 % and 102.1 %. These data revealed that there was no spiking error observed (i.e. spiking on higher side). Drug area responses for LOQ QC samples were slightly on higher side, which resulted into higher % accuracy. However, it was agreed with the applicant that this does not have any impact on final outcome of the results as intra-day accuracy of LOQ QC for P&A I was also within acceptance range of 85-115 % and also inter-day (Global) % accuracy for LOQ QC samples were 103.8 %. Based on the results of entire method validation, it was concluded that there is **no issue of accuracy and precision** in this method.

The applicant checked again the results obtained from **recovery experiment**. The mean recovery of drug and IS were 91.2% and 97.8% respectively and both were quite close to each other. The **difference between drug and ISTD recovery was only around 6-7%** which could be considered insignificant considering the fact that recovery was generated in biological matrix. The difference in recovery may be attributed to variations due to various factors such as complexity of biological matrix, extraction process, endogenous compounds, etc. Further the difference might also be attributed to the fact that the internal standard was externally added to the spiked QC samples. In addition to above, the applicant confirmed that the back calculated concentrations were

calculated based on the peak area ratio of drug and ISTD area response. And if the generated concentrations are precise and accurate, the difference in recovery of drug and ISTD should not have any impact. In current case, the concentrations generated during the method validation study were precise and accurate, (which was reflected in data presented in two tables: Table no. 04 of method validation report # MV(I)-138-15 and Table no. 03 of bio-analytical report of study #074-14). From the above data, it was confirmed that the minor difference in recovery of drug and ISTD (but consistence recoveries) had no impact on the study. This clarification was accepted by the CHMP.

The applicant agreed that the retention time of drug and ISTD were similar i.e. 2.4 minutes. However, it was noted that during currently discussed study quantification of drug and ISTD were done using LC-MS/MS (mass spectrometric detector). The quantification in LC-MS/MS was purely done on the basis of m/z ratio (i.e. mass transitions), which differ from drug to drug (i.e. according to their molecular weight). In current study, Drug and ISTD MRM channels were separated based on their parent /daughter masses and hence chromatograms of Drug and ISTD were not possible to generate in one channel. Considering the quantification of drug and ISTD were done in different MRM channels (for drug : m / z 469.20 > 177.20 and for ISTD m / z 475.20 > 177.20), resolution of drug and ISTD peak were not applicable as both peaks were generated in separate channel.

The CHMP agreed that the responses of the applicant were in accordance with the general widely known practice and thus are considered sufficient.

2.4.6. Conclusions on clinical aspects

The choice of parameters, fed state and sample size for the bioequivalence demonstration were considered all acceptable. However, there were certain issues with the validation of the analytical report identified that created concerns and were discussed further. In addition a sequence effect was identified and the initial justification of the applicant was not considered sufficient. Therefore, despite the fact that the applicant presented that the two products, test and reference were shown to be bioequivalent, this was only considered acceptable after the issues related to the sequence effect were resolved. In order to be able to come to a conclusion the CHMP requested that the following concerns in the clinical part of the dossier have to be addressed: (1) submission of all validation chromatographs (both in-study and pre-study validation chromatographs) in addition to the clarifications requested in the analytical methods section AND (2) further discussion on the highly statistical significant sequence effect.

The applicant provided additional clarification and submitted within his responses 100% of chromatograms of subjects as requested. The CHMP accepted the clarifications provided by the applicant.

A summary of the literature with regard to clinical data of Ivabradine Accord was provided and was accepted by the CHMP. This was in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk management plan

Safety concerns

Important identified risks	• Bradycardia [1], [2] • Phosphenes /Blurred vision [1], [2] • Second and Third degree atrioventricular blocks (AVB II and III) [1], [2] • Increased blood pressure in hypertensive patients [1], [2] • Atrial fibrillation (AF) [1], [2] • ECG prolonged QT interval [1]
Important potential risks	• Supra-ventricular tachyarrhythmia (SVT) other than AF [1], [2] • Immune disorders [1], [2] • Severe ventricular arrhythmia [1] • Myocardial infarction [1]
Missing information	• Safety in children and adolescents (< 18 years old) [1], [2] • Safety in pregnant and lactating women [1], [2] • Safety in severe hepatic insufficiency patient [1], [2] • Safety in severe renal impairment patient [1], [2] • Safety in chronic heart failure patients with intraventricular conduction defects [1], [2]

[1] Proposed SmPC & PIL of Ivabradine Accord 5 mg and 7.5 film-coated tablets.

[2] Safety concerns are derived from European Medicines Agency, Assessment report (EPAR) of Ivabradine for procedure number EMEA/H/C/000597/II/0018 dated 16 March 2012.

Pharmacovigilance plan

The Applicant did not propose any additional pharmacovigilance activities. Only routine pharmacovigilance activities are proposed, with the objective to evaluate and further characterize the risks in terms of demographic profile of population at risk and establish relationship with the administered dose, duration etc.

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, 4.8 and 4.9 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Other routine risk minimisation measures including the prescription only status of the product.	
Important identified risk: Phosphenes /Blurred vision	Section 4.4, 4.7 and 4.8 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed.
Important identified risk: Second and Third degree atrioventricular blocks (AVB II and III)	Section 4.3, 4.4, and 4.8 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed.
Important identified risk: Increased blood pressure in hypertensive patients	Section 4.4, and 4.8 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Atrial fibrillation (AF)	Section 4.4 and 4.8 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed.
Important identified risk: ECG prolonged QT interval	Section 4.4, 4.5 and 4.8 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed.
Important potential risk: Supra-ventricular tachyarrhythmia (SVT) other than AF	Section 4.4 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed.
Important potential risk: Immune disorders	Section 4.3 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	including the prescription only status of the product.	
Important potential risk: Severe ventricular arrhythmia	Section 4.4 and 4.8 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed.
Important potential risk: Myocardial infarction	Section 4.3 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed.
Missing information: Safety in children and adolescents (< 18 years old)	Section 4.2 and 5.1 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed.
Missing information: Safety in pregnant and lactating women	Section 4.3, 4.6 and 5.3 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety	None proposed.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	concern. Other routine risk minimisation measures including the prescription only status of the product.	
Missing information: Safety in severe hepatic insufficiency patient	Section 4.2, 4.3 and 5.2 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing information: Safety in severe renal impairment patient	Section 4.2 and 5.2 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing information: Safety in chronic heart failure patients with intraventricular conduction defects	Section 4.1, 4.2, 4.4, 5.1 and 5.2 of Ivabradine proposed SmPC and corresponding sections of PIL have information on this safety concern. Other routine risk minimisation measures including the prescription only status of the	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	product.	

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

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.

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 did 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 formed the pivotal basis with an open label, balanced, randomized, two treatment, two sequence, two period, single oral dose, crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. Pharmacokinetic and statistical methods applied were adequate. The test formulation of Ivabradine Accord met the protocol-defined criteria for bioequivalence when compared with the 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 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product was therefore concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, was of the opinion that no additional risk minimisation activities were required beyond those included in the product information.

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 Accord 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 contra-indication to the use of beta-blockers

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