15 September 2016
EMA/73167/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ivabradine Zentiva

International non-proprietary name: ivabradine

Procedure No. EMEA/H/C/004117/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ADR	Adverse Drug Reaction
AE	adverse event
AESI	AEs of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANSM	National Agency for the Safety of Medicine and Health Products
AP	Applicant's Part of ASMF
API	Active Pharmaceutical Ingredient
APPM	Association of Paediatric Palliative Medicine Master Formulary
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AST	aspartate aminotransferase
AUC	Area Under the plasma Concentration
AUC0-inf	Area Under the plasma Concentration-time curve from time zero to infinity
AUC0-t	Area Under the plasma Concentration-time curve from time zero to t hours
BA	BioAvailability
BCT	Blinded combination therapy
BE	Bioequivalence
BID	bis in die (twice daily)
BMI	Body Mass Index
BPI	Brief Pain Inventory
BNFc	British National Formulary for Children
BUN	blood urea nitrogen
CI	confidence interval
CIOMS	Suspect Adverse Reaction Report Form
Cl	Clearance
CLcr	creatinine clearance
Cmax	maximum plasma concentration
CMH test	Cochran-Mantel-Haenszel test
CoA	Certificate of Analysis
CP	cerebral palsy
CPPs	Critical process parameters
CQAs	Control quality attributes
CRO	Certified Research Organisation
CSF	cerebrospinal fluid
CV	Coefficient ov Variation
CYP450	cytochrome P450
DAP	Drug Analysis Print
DDI	Drug-drug interactions
DHCP	Direct Healthcare Professional Communication
DMF	Drug Master File = Active Substance Master File
DoE	Design of experiments
DP	Decentralised (Application) Procedure
DP	Drug product
DS	Drug substance
DSC	Differential Scanning Calorimetry
EC	Europena Commission
ECG	Electrocardiogram
EEG	electroencephalogram
eGFR	estimated glomerular filtration rate
eGFRCKD-EPI	estimated glomerular filtration rate based on the Chronic Kidney Disease Epidemiology Collaboration equation
eGFRMDRD	estimated glomerular filtration rate based on the Modification of Diet in

	Renal Disease equation
ECHO	echocardiography
EMA	European Madicines Agency
EoS	End os Study
ERA	endothelin receptor antagonist
ERT	enzyme replacement therapy
ESI	Electro Spray Ionisation
ETA	endothelin receptor antagosinsts
EU	European Union
FAV	Final Assessment Visit
FEV1	Forced expiratory volume in one second
FMEA	Failure mode and effects analysis
FPM	Finish Product Manufacturer
FT-IR	Fourier Transform Infrared Spectroscopy
GABA	Gamma-aminobutyric acid
GAD	Generalised Anxiety Disorder
GC	Gas Chromatography
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
GL-3	globotriaosylceramide
GLA	gene encoding α-Gal A
GLP	Good Laboratory Practice
GMP	Good manufacturing practice
GP	Glycopyrronium
GSRS	Gastrointestinal Symptoms Rating Scale
Hb	Haemoglobin
HCl	hydrochloride
HCP	Health Care Professional
HCT	hematocrit
HDPE	High Density Polyethylene
HEK	human embryonic kidney
HPLC	High pressure liquid chromatography
HR	Hazard Ratio
HRD	human recommended dose
CHMP	Committee for Human Medicine Products
IAR	infusion-associated reaction
IC	interstitial capillary
IC GL-3	interstitial capillary GL-3
ICD	Informed Consent Document
ICMR	Indian council of medical research
ICSR	Individual Case Safety Report
IEC	Independent Ethics Committee
IgG	immunoglobulin G
ICH	International Conference on Harmonisation
IMP	Investigated Medicinal product
IMS	International Marketing Sales
INN	International Non-proprietary Name
IP	investigational product
IPC	In-process control
IR	Incidence Rate
IR	Immediate-release or Infra-red
IRB	Institutional Review Board
ISR	Incurred Sample Reanalysis
IS-normalized MF	Internal Standard-normalised Matrix Factor
ITT	Intention To Treat
IV	Intravenous
JP	Japanese Pharmacopeia
JPE	Japanese Pharmaceutical Excipients
K2EDTA	dipotassium ethylenediaminetetraacetic acid

K_i	dissociation constant for binding of inhibitor to enzyme
KF Karl Fischer titration	
LC-MS/MS	liquid chromatography coupled with tandem mass spectrometry
LDPE	Low density polyethylene
LFT	Liver Function tests
LLOQ	Lower Limit of Quantification
LOA	Letter of Access
LOD	Limit of Detection
LOD Loss on drying	
LOQ	(1) Limit of Quantification, (2) List of Questions
LV	left ventricular
LVEDP	Left ventricular end diastolic pressure
LVH	Left ventricular hypertrophy
LVMi	Left ventricular mass index
lyso-Gb3	globotriaosylsphingosine
MA	Marketing Authorisation
MAA	Marketing Authorization Application
MAH	Marketing Authorisation holder
mBMRS	modified Behavioural and Medical Rating Scale
M.D.	Medical Doctor
MDRD	Modification of Diet in Renal Disease equation
mGFR	measured glomerular filtration rate
$mGFR_{iohexol}$	glomerular filtration rate as measured by plasma clearance of iohexol
mGFRiohexol	glomerular filtration rate measured by the plasma clearance of unlabelled iohexol
MHRA	Medicines and Healthcare Products Regulatory Agency
mITT	Modified Intended To Treat
mITT-amenable	patients with amenable mutations in the AT1001-011 mITT population
mPAP	Mean Pulmonary Artery Pressure
MR	Medical Representative
MRI	Magnetic resonance imaging
MS	Mass Spectrometry
mTDS	modified 9-point Teacher's Drooling Scale
MWD	minute walk distance
NAION	Non-Arteritic Anterior Ischemic Optic Neuropathy
NCA	National Competent Authority
ND	Not detected
NHS	National Health Service
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NSAID	Non-Steroidal Anti-Inflammatory Drug
NYHA	New York Heart Association
OECD	Organisation for Economic Co-operation and Development
OLE	open-label extension
OOS	
OPA Oriented polyamide film	Out of Specifications

OTC	Over-the-counter
PAH	Pulmonary Arterial Hypertension
PBMC	peripheral blood mononuclear cell
PCA	prescription cost analysis data
PCD	Photo-Contact Dermatitis
PCTFE	Polychlorotrifluoroethene
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamics
PDE	Permitted Daily Exposure
PDE-5	phosphodiesterase type-5
PE	Polyethylene
PEC	Predicted Enviromental Concentration
P-gp	P-glycoprotein
Ph.Eur.	European Pharmacopoeia
PhV	Pharmacovigilance
PIL	Patient Information Leaflet
PIP	Paediatric Investigational Plan
PK	pharmacokinetic
PMS	Post Marketing Surveillance
PP	Polypropylene
PRO	Patient-Reported Outcome
PS	Photo-Sensitivity
PSMF	Pharmacovigilance Systém Master File
PSUR	Periodic Safety Update Report
PT	Preferred Term
PTH	Pituitary thyroid hormone
PUMA	Paediatric Use Marketing Authorisation
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
PVOD	Pulmonary Veno-Occlusive Disease
PVR	Pulmonary vascular resistance
QA	Quality Assurance
QbD	Quality by design
QC	Quality Control (samples)
QD	quaque die (once daily)
QOD	every other day
QOD	quaque otra die (once every other day)
QOS	Quality Overall Summary
QP	Qualified Person
QTc	QT interval corrected for heart rate
QTPP	Quality target product profile
Rf	Retention factor
RH	Relative Humidity
rhα-Gal A	recombinant human α-Gal A
RMM	Risk Minimization Measure

RMS		Reference Member State
RR		Reporting Rate
RRT		Relative retention time
RSD		Relative standard deviation
Rt		Retention time
SAE		serious adverse event
SAO2		oxygen saturation
SEM		standard error of the mean
SF-36v2		Short Form Health Survey with 36 questions, version 2
SGLT1		sodium glucose cotransporter 1
SGOT		Serum glutamic oxaloacetic trnasaminase
SGPT		Serum glutamic pyruvic trnasmainase
Shire HGT		Shire human genetic therapies
SME		small, or medium-sized enterprise
SmPC		Summary of Product Characteristics
SMQ		Standardised MedDRA Querie
SOC		System Organ Class
SOP		Standard Operating Procedure
SPC		Summary of Product Characteristics
STD		Standard Deviation
T/R		Test/Reference
$t_{1/2}$		terminal elimination half-life
TEAE		treatment-emergent adverse event
THF	Tétrahydrofurane	
TID		tris in die (three times a day)
TLC		Total lung capacity
t_{max}		time to maximum plasma concentration
tmax		time of occurrence of Cmax
TSE		Transmissible spongiform encephalopathy
TTC		Threshold of toxicological concern
ULN		upper limit of normal
USP		United States pharmacopoeial
UV		Ultraviolet
VAS		visual analogue scale
Vss		volume of distribution
WBC		white blood cell
WCI		Worst Case Imputation
WEU		Well Established Use
WHO		World Health Organization
WRI		worst rank imputation
WT		wild type
XRD		X-Ray Diffraction
XRPD		X-ray powder diffraction
α-Gal A		alpha-galactosidase A
µCi		Microcurie

µM	Micromolar

Not all abbreviations might be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zentiva, k.s. submitted on 4 November 2015 an application for marketing authorisation to the European Medicines Agency (EMA) for Ivabradine Zentiva, 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 20 November 2014.

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 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 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 (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 requirement

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
- Community Marketing authorisation number: EU/1/05/316/012
- Bioavailability study number(s): 2014-3595 (IVABRL07375)

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: Radka Montoniová

- The application was received by the EMA on 4 November 2015.
- The procedure started on 4 December 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 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 20 May 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 June 2016
- During the PRAC meeting on 8 July 2016, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.

  During the CHMP meeting on 21 July 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 01 September 2016..
- 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 Zentiva.

2. Scientific discussion

2.1. Introduction

The proposed product is an immediate release film-coated 5mg 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 Procorolan 7,5 mg film-coated tablets containing the same active substance in the same pharmaceutical form.

Ivabradine is an anti-anginal and anti-ischaemic agent, which selectively and specifically inhibits the I*f* current in the sino-atrial node and provides heart rate reduction without altering other cardiac parameters, including conduction, and without directly affecting other haemodynamic parameters. The positive effect of ivabradine on angina pectoris symptoms and its ability to reduce myocardial ischemia make it an important agent in the management of patients with stable CAD or chronic HF as documented by current clinical practice guidelines [Ponikowski et al. 2016; Montalescot et al. 2013; NICE 2011].

The generic medicinal product has applied for all the indications of the reference medicinal product. The indications applied and approved by the CHMP are:

<u>Symptomatic treatment of chronic stable angina pectoris</u>

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 from 2.5 to 7.5 mg twice daily.

Symptomatic treatment of chronic stable angina pectoris

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, 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. 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 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 or 7.5 mg ivabradine (as hydrochloride) as active substance. The 5 mg tablet can be divided into equal doses.

Other ingredients are:

For the tablet core: mannitol, crospovidone, magnesium stearate.

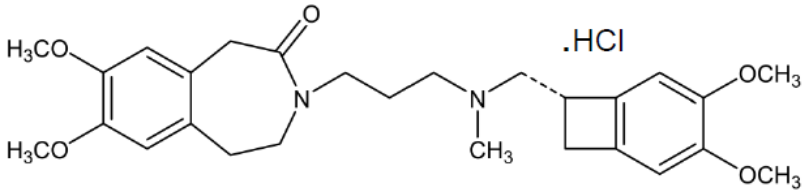
For the film coating: hypromellose, titanium dioxide, macrogol 400, glycerol.

The product is available in OPA/Alu/PVC-Alu 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-{[((7S)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl] methyl amino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride corresponding to the molecular formula $C_{27}H_{36}N_2O_5$.HCl. It has a relative molecular mass of 505.05 g/mol and the following structure:



The active substance is a white to slightly yellow hygroscopic powder, soluble in water and methanol, practically insoluble in THF.

The active substance exhibits stereoisomerism due to the presence of one chiral centre. The desired isomer is the S-form. The R-isomer is controlled routinely as an impurity in the active substance by a stereo-selective analytical method.

Polymorphism has been observed for the active substance. A list of 29 polymorphic forms, mentioned in the literature, has been presented together with their XRD patterns, DSC information and for some of them also manufacturing process. The active substance manufacturer consistently manufactures the same polymorphic form. Undesired conversion of crystalline form was observed in stability (refer to "Stability"). Further based on the investigations that were carried out, appropriate control strategy was put in place to prevent undesired change in the polymorph during active substance manufacture and stability. Polymorphic form of the active substance is also controlled in the active substance specifications.

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.

The active substance is synthesized by one manufacturer in eleven main steps using well defined starting materials with acceptable specifications. The originally proposed starting materials were re defined during the procedure at the request of CHMP to ensure that enough of the process is conducted under GMP. The chiral centre is generated during the process. The synthetic strategy and process design such as reagent selection, process parameters and in-process controls ensure the desired configuration at the chiral centre.

Reprocessing of active substance is described and considered acceptable.

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

The structure of the active substance has been confirmed by the following methods: ^{1}H- and ^{13}C- NMR, FT-IR, mass spectra, XRPD, elemental analysis and specific optical rotation. 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. Genotoxic impurities were investigated and appropriate control strategy was put in place.

The active substance is packaged appropriately.

Specification

The active substance specification includes tests and limits for the following parameters: appearance (Ph. Eur.), solubility (Ph. Eur.), identity (IR, chloride test Ph. Eur.), assay (HPLC), related substances (HPLC), R-isomer (HPLC), genotoxic impurity (HPLC), 1 bromo-3-chloro propane (GC), residual solvents (GC), water content (KF), heavy metals (Ph. Eur.), sulphated ash (Ph. Eur.), chloride content (potentiometric titration), specific optical rotation (Ph. Eur.), polymorphism (XRD) and particle size (laser diffraction).

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 are provided for three production scale batches of the active substance. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided on three production scale batches of active substance manufactured by the proposed manufacturer according to the proposed process and stored in a container closure system representative of that intended for the market for 9 months under long term conditions at 25 ºC / 60% RH and intermediate conditions at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines. Stability data were also provided on three production scale batches of active substance manufactured by the proposed manufacturer according to the initial process and stored for 24 months under long term conditions at 25 ºC / 60% RH and for 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

The following parameters were tested: appearance, water content, R-isomer, assay, related substances, genotoxic impurity Benzocyclobutane and polymorphism. The analytical methods used were the same as for release and were stability indicating.

An out of specification results for polymorphism was observed for one of the three supportive stability batches (initial process). In view of this failure, the stability studies were reinitiated. During investigation it was also decided to improve packaging step. The results of the re-initiated stability studies indicated that the active substance batches (initial process) are complying with the stability specification including test for polymorphism at 6 months accelerated and 18 months long-term stability station. However at 24 months long-term stability two of the three batches did not comply with the test for polymorphism by XRD.
Further, the first three production scale batches of ivabradine hydrochloride active substance manufactured by making minor changes in the manufacturing process were also kept for stability studies. Out of the three batches, one batch did not comply with the test for polymorphism at 3 months accelerated stability. An appropriate control strategy was put in place with regard to

preventing the undesired change in the polymorph. The retest period and storage precaution was also reconsidered in accordance with the stability results. Furthermore as both polymorphs observed are hydrates, they also have similar characteristics and there is no change in the quality of the finished product. Moreover it has been confirmed that only the expected form is presented in the finished product (refer to “Stability of the product”).

Forced degradation studies including photostability studies according to the ICH Q1B have been provided. No decrease was observed for assay with exception of treatment with acid heat and oxidative heat treatment. As for related substances method, no significant degradation as observed with exception of acid heat treatment and oxidative heat treatment. The substance has been shown to be stable under light conditions.

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 18 months with the storage condition “store below 25 ºC” in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product comes as oblong, one side and both edges scored white film coated tablet 5 mg and white to off white, round film coated tablet 7.5 mg.

The aim was to develop a stable and robust formulation, bioequivalent to the reference product Procoralan. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards with the exception of the film coating, although it is composed of a mixture of compendial components. 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. The formulation of the test product differs from that of the reference product. The reference product contains lactose monohydrate, maize starch, maltodextrin, silica (colloidal anhydrous) and magnesium stearate and the tablet core is coated with an aqueous film coat which consists of hypromellose, titanium dioxide, macrogol 6000, glycerol, magnesium stearate, yellow iron oxide and red iron oxide. For the proposed finished product the compatibility of the active substance with the excipients was based on stability studies. A detailed account of the development of the formulation was presented with clear explanations provided for the changes made at each point. The role, the choice of the excipients and their concentration has been satisfactorily justified.

Direct compression is used to manufacture the finished product. The manufacturing process consists of blending, compression and coating step. Manufacturing process optimisation was described. The overage used during the coating process was satisfactorily justified.

The proposed finished products Ivabradine 5 mg film coated tablet and Ivabradine 7.5 mg film coated tablet are manufactured by the same manufacturing process, the composition is qualitatively the same and quantitatively proportional.

Influence of tablet hardness was investigated. It was observed that tablet hardness increase does not have a significant effect on dissolution. Influence of active substance particle size distribution on

dissolution was investigated. The results confirmed the limit choice for the active substance specifications.

Data demonstrating the absence of polymorphic form change during the manufacturing process of the proposed finished product were provided. Possible change of the active substance polymorphic form during storage was studied. Polymorphism of the reference product was also investigated. Several polymorphic forms were observed depending on the batch. Different reference product batches and proposed finished product batches were investigated for similarity of dissolution profiles at different media (pH 1, pH 4.5, pH 6.8). Based on the results it was concluded that different polymorphic forms have no effect on dissolution profile and bioequivalence of products. It was observed that polymorphic structure was not critical for finished product quality.

Ivabradine 5 mg film coated tablet contains break-mark. Three finished product batches were tested according to Ph. Eur. breakability test. Results comply with Ph. Eur. requirements. Content uniformity of half tablet was also investigated on one batch. Results complied with requirements. Dissolution profile of half tablet was also evaluated with release media to show similarity. Dissolution profiles of Ivabradine 5 mg film coated tablet, Ivabradine 5 mg film coated half tablet and Ivabradine 7.5 mg film coated tablet were evaluated at pH 1. Profiles were found similar. The compliance of subdivision of tablet was demonstrated sufficiently.

A bioequivalence study was performed with the 7.5 mg strength showing bioequivalence between of the proposed finished product and the reference medicinal product. The formulation used for the bioequivalence study is the same as that intended for marketing. Based on the comparison of dissolution profiles of Ivabradine 7.5 mg film coated tablet and Procoralan 7.5 mg film coated tablet, where for both products more than 85 % of active substance is dissolved in 15 minutes in pH 1, pH 4.5 and pH 6.8, it was concluded that dissolution profiles are similar. A biowaiver was requested for the 5 mg strength based on the result from BE-study with 7.5 mg strength. Dissolution profiles of Ivabradine 7.5 mg and 5 mg film coated tablet were compared and it was observed that they are similar in pH 1, pH 4.5 and pH 6.8. All the conditions for biowaiver for additional product strengths as stated in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98) are fulfilled; therefore the bioequivalence results of the 7.5 mg strength can be extended to the 5 mg strength.

The development of the dissolution method is described and the discriminatory power has been demonstrated with regard to the amount of applied film coating and minimal changes in the tablet composition.

The impurity profiles of both generic and reference products in all strengths are similar.

The primary packaging is OPA/Alu/PVC-Alu blisters. The material complies with 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 five main steps: sieving, blending, compression, film coating and packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies on three pilot scale batches of each strength. 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 pharmaceutical form. Adequate justification for holding times of bulk intermediates (coating solution, tablet cores, and film-coated tablets prior to packaging) has been provided.

Validation will be performed post-approval on the first three consecutive production scale batches of each strength as per a protocol, which has been presented and is considered acceptable.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form: appearance (visual examination), identification (HPLC, UV, TiO_2 test), average film coated tablet weight (Ph.Eur.), subdivision of tablets (Ph. Eur.), LOD (Ph.Eur.), disintegration (Ph.Eur.), assay (HPLC), uniformity of dosage units-content uniformity (Ph.Eur.), dissolution, impurities (HPLC), microorganism count (Ph.Eur.) and polymorphism (XRD).

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 were provided for three production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data were provided for three pilot scale batches of finished product of 5 mg strength stored under long term conditions for 18 months at 25 ºC / 60% RH, under intermediate conditions for 12 months at 30 ºC / 65% RH and for 18 months at 30 ºC / 75% RH, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

Stability data were provided for three pilot scale batches of finished product of 7.5 mg strength stored under long term conditions for up 18 months at 25 ºC / 60% RH, under intermediate conditions for 12 months at 30 ºC / 75% RH and for up to 18 months at 30 ºC / 75% RH, and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines.

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 according to the shelf-life specifications described in the previous section. The analytical procedures used are stability indicating.

Out of specifications results were observed for the polymorphic form of two batches at 6 months at 40 °C/75 % RH and for three batches at 12 months at 30 °C/75 % RH. The results for polymorphism are in line with specification criteria in long term stability condition (25 °C ± 2 °C/60 ± 5 % RH). For the 7.5 mg strength, 18 months stability data is available only for one batch (12 month is available for the other two batches). Since the formulation of 7.5 mg and 5 mg tablets are proportional, based on available stability results it is expected that the stability of the 7.5 mg strength will not differ from the stability of the 5 mg strength. These finding dictated the product shelf life and storage conditions.

In addition, one batch of 7.5 mg strength was tested under daylight at 25 ºC / 60% RH according to ICH Q1B Guideline (directly exposed product, product in primary package and complete package

product). Parameters tested were: appearance, assay, dissolution, impurities and polymorphism. Based on the results the finished product is not light sensitive.

Based on available stability data, the proposed shelf-life of 18 months with the following storage precautions: “Store below 25 °C” and “Store in the original package in order to protect from moisture.” as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No 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. Polymorphism has been observed for the active substance. The active substance manufacturer consistently manufactures the same polymorphic form (crystalline form II which is also a hydrated form). Undesired conversion of crystalline form II to form γ was observed in stability of the active substance and finished product. Further based on the investigations that were carried out, it was understood that the water content and storage conditions have an impact on the polymorph. Hence appropriate control strategy was put in place to prevent undesired change in the polymorph during active substance and finished product manufacture and stability. 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

None.

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.

Pharmacodynamic, pharmacokinetic and toxicological properties of ivabradine are well known. As ivabradine is a widely used, well-known active substance, no further studies are required. Overview based on literature review is, thus appropriate. 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

The Environmental Risk Assessment was submitted according to the *EMA Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 21*)*. Since Ivabradine Zentiva is intended for generic substitution, this should not lead to an increased exposure to the environment. Also the $PEC_{surfacewater}$ was calculated to be 0.0003 µg/l (total EU worst case scenario), which is acceptable. Since the $PEC_{surfacewater}$ was calculated to be below 0.01 µg/l and considering the fact, that ERA is not deemed necessary for products which are intended as a substitute for other identical products on the market, the approach of the applicant was considered acceptable. As per *EMA Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 21*)* if the $PEC_{SURFACEWATER}$ value is below 0.01 µg/L(3), and no other environmental concerns are apparent, it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

2.3.3. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Ivabradine Zentiva 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 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.

The applicant provided a clinical overview outlining the pharmacokinetics and pharmacodynamics as well as efficacy and safety of ivabradine hydrochloride based on published literature. The SmPC is in line with the SmPC of the reference product.

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**)* in their current version, 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.

According to the statement in the study report, the BE study was performed as per the protocol and in compliance with the requirements of current GCP, and in particular with the requirements of ICH Guideline for Good Clinical Practice, according to the principles of GCP having their origin in the Declaration of Helsinki, ethical requirements of Article 8.3 (i b) of Directive 2001/83/EC and ethical requirements of Directive 2001/20/EC.

Exemption

The applicant applied for marketing authorization for two different strengths of ivabradine containing film-coated tablets: 5 mg and 7.5 mg. Bioequivalence was demonstrated for the highest strength (i.e. 7.5 mg). In vivo bioequivalence study waiver was sought for the lower strength of 5 mg based on the consideration of the general biowaiver criteria as specified in the *EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).*

Drug products Ivabradine 5 mg film coated tablet and Ivabradine 7.5 mg film coated tablet are manufactured by the same manufacturing process, the composition is qualitatively the same and quantitatively proportional. Dissolution profiles of Ivabradine 5 mg film coated tablet and Ivabradine 7.5 mg film coated tablet are similar in all dissolution media.

Clinical studies

To support the application, the company has submitted one bioequivalence study No. IVABRL07375 - a single-dose, open-label, single-center, randomized, two-period, two-treatment, two-sequence, crossover comparative bioavailability study conducted in forty healthy volunteers under fed conditions.

Table 1. Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BE	2014-3595/ IVABRL07375	5.3.1.2	Determine bioequivalence between a new (generic) drug product and a marketed reference product under fed conditions	Crossover	One Film Coated Tablet, 7.5 mg, Oral	40 (39 completed)	Healthy Subjects	Single-dose	Complete: Full Report

2.4.2. Pharmacokinetics

Study IVABRL07375: A single-dose, open-label, single-center, randomized, two-period, two-treatment, two-sequence, crossover comparative bioavailability study of two formulations of Ivabradine 7.5mg film-coated tablets conducted under fed conditions.

Sponsor of the Study:	Zentiva, k.s., Czech Republic

CRO:	Pharma Medica Research Inc., Canada

Methods

Study design

This was a single-dose, open-label, single-center, randomized, two-period, two-treatment, two-sequence, crossover comparative bioavailability study conducted in forty healthy volunteers under fed conditions.

After an overnight fast of at least 10 hours, subjects consumed a high-fat, high-calorie breakfast. Approximately half of the breakfast was consumed starting 15 minutes prior to drug administration. The other half was consumed within 30 minutes of starting the first half of the breakfast, after the administration of assigned drug product.

A single 7.5 mg dose (one tablet) of the assigned drug product was administered according to the randomization scheme with 240 mL (±5 mL) of room temperature water. Subjects consumed the entire 240 mL (±5 mL) of water during the drug administration process.

The washout period between drug administrations for each subject was at least 7 days.

The blood pressure and pulse rate were measured prior to drug administration and at 3 and 7 hours post-dose. The temperature of each subject was measured daily during confinement.

Test and reference products

Product Characteristics	Test product	Reference Product
Name	Ivabradine 7.5 mg, film coated tablet	Procoralan 7.5 mg, film coated tablet
Strength	7.5 mg	7.5 mg
Dosage form	Film Coated Tablets	Film Coated Tablets
Marketing Authorization Holder		Les Laboratoires Servier 50, rue Carnot 92284 Suresnes cedex – France
Manufacturer	Zentiva, k.s. U kabelovny 130 10237 Praha 10 Czech Republic (Responsibility: secondary packaging, labelling, testing, storage, release and distribution to CRO) Zentiva Sağlık Ürünleri San ve Tic. A.Ş. Küçükkarıştıran mah. Merkez sok. No:223/A, 39780, Büyükkarıştıran/Lüleburgaz Kırklareli Turkey (Responsibility: fabrication, primary packaging, testing, storage)	Servier (Ireland) Industries Ltd Gorey Road Arklow - Co. Wicklow – Ireland
Batch number	P03032015	197167
Batch size (Biobatch)	100 000 FCT	
Measured content(s)[1] (% of label claim)	101.24%	99.13%
Commercial Batch Size	100 000 – 1 000 000 FCT	
Expiry date (Retest date)	16.09.2015	09/2017
Location of Certificate of Analysis	Appendix 16.1.6	Appendix 16.1.6
Member State where the reference product is purchased from:		Germany
This product was used in the following trials:	2014-3595 (Zentiva study number IVABRL07375)	2014-3595 (Zentiva study number IVABRL07375)

[1] List for each active substance for fixed combinations

Ivabradine Zentiva 7.5mg film-coated tablet manufactured by Zentiva, k.s. has been compared to Procoralan 7.5mg film-coated tablet manufactured by Servier Industries Ltd.

Population studied

Forty (40) male and female, healthy, non-smoker subjects with a mean body mass index 25.6 kg/m^2 (range 18.5 – 29.3), and mean age 39 years (range: 18-54) who voluntarily signed the informed consent were included in the study. Thirty-nine (39) subjects finished both periods that were included into pharmacokinetic dataset.

Dropouts - subject No. 8 was dropped due to positive urine test for tricyclic antidepressants, prior to Period 2.

Protocol deviations - one subject came late (9 minutes) to the clinical facility on the check-in day prior Period 2.

Concomitant medication - subject 25 took two 200 mg tablets of ibuprofen on 11 May 2015 (96 hours after dosing).

Analytical methods

Ivabradine was determined by achiral HPLC method using tandem mass spectrometry detection (PMRI-1492-14 v.00). Ivabradine and internal standard (Rac-ivabradine-d_6) were extracted from K_2EDTA plasma by protein precipitation extraction. Plasma samples were precipitated with a mixture of organic solvents and supernatant was diluted and transferred for LC-MS/MS analysis. Fully automated extraction can be also performed by the Hamilton Star Lab Automated System. The calibration range was from 0.100 to 100 ng/mL using a plasma sample volume of 0.100 mL.

Certificates of analysis for ivabradine hydrochloride and Rac-ivabradine-d6 were attached to the Analytical report. The calibration standards and QC samples were prepared from different stock solutions.

A minimum of sixteen (16) QC samples (four at each concentration level) were included in each analytical batch. Samples were analysed in 9 analytical batches each of them containing blank and zero samples, nine calibration standards, four sets of QC samples at four levels and samples from mostly 6 subjects. To ensure that there is no carryover between injections, blank samples were monitored. There was one minor protocol deviation with no impact on the study outcome.

Bioanalytical method validation

The validation results of a high performance liquid chromatographic method using tandem mass spectrometry detection for determination of ivabradine in human plasma were presented in the Validation Report. The method was validated at Pharma Medica Research Inc., Bioanalytical Division in June 2014. The long term stability data of ivabradine in solutions and in human plasma were submitted. Certificates of analysis for ivabradine hydrochloride and Rac-ivabradine-d6 were attached to the Validation report. Ivabradine undergoes extensive metabolism. The major metabolic pathways include O-demethylation, N-demethylation and dehydrogenation. Under experimental conditions these metabolites will not reverse back to ivabradine.

Pharmacokinetic variables

The following PK parameters were estimated for ivabradine using a non-compartmental approach in SAS (version 9.3): AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $T_{1/2}$. These are adequate and in line with the *EMA Guideline on the investigation of bioequivalence (*CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ***).

Statistical methods

Randomization

Subjects were randomly assigned to one treatment sequence according to a predetermined computer-generated randomization scheme (procedure PLAN in SAS®).

Blinding

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

Determination of Sample Size

Sample size was estimated to be 36 subjects. Four (4) extra subjects were included into the study to account for potential dropouts. Therefore, 40 subjects were enrolled into this study.

Statistical Analysis

Descriptive statistics for the PK parameters of ivabradine were presented. The PROC GLM procedure from SAS version 9.3 was used.

Analysis of variance (ANOVA) was performed on log-transformed AUC_t and C_{max} parameters. The significance of the sequence, period treatment and subject (sequence) effects (all fixed) was tested.

Based on the log-transformed parameters, the following criteria were used to evaluate the bioequivalence between the test and reference products: The 90% CIs of the relative mean AUC_t and C_{max} of the test to reference products should be between 80.00 and 125.00%.

Results

Table 1: Summary of Study Results Based on Plasma Ivabradine Levels

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-t)}$ (ng-h/mL)	108.24	58.63	106.37	52.97
C_{max} (ng/mL)	34.68	15.21	30.80	13.28
T_{max}* (h)	1.00 (0.25 – 3.50)		1.25 (0.50 – 2.67)	
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours			
C_{max}	maximum plasma concentration			
T_{max}	time for maximum concentration (* median, range)			

Table 2: Statistical analysis for Ivabradine (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
$AUC_{(0-t)}$ (ng-h/mL)	99.72%	(94.52%, 105.21%)	14.08
C_{max} (ng/mL)	112.73%	(103.02%, 123.35%)	23.89
* estimated from the Residual Mean Squares			

Safety data

There were totally 22 adverse events involving 15 subjects. All adverse events were judged to be mild in severity. Subject 25 experienced vomiting (96 hours after dosing). This adverse event was not considered to be associated with the drug treatment and subject 25 did not withdraw from the study. Following adverse events were reported: sleepiness (6), dizziness (3), catheter site reaction (2), bradycardia (2), vomiting (1), cut on right side of forehead (1), chills (1), muscle fatigue (1), ringing in ear (1), chest discomfort (1), hypertension (1), runny nose (1), sinus congestion (1).

Conclusions

Based on the presented bioequivalence study, Ivabradine Zentiva, 7,5 mg film-coated tablet was considered bioequivalent with Procoralan 7,5 mg film-coated tablet.

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 are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

To support this application, the company has submitted one bioequivalence study and review of pre-clinical and clinical data. In this application, an essential similarity was claimed to the original medicinal product Procoralan, which was also used as reference product in bioequivalence study.

Submitted bioequivalence study was a single-dose, randomized, crossover, study comparing two formulations of ivabradine 7.5 mg film-coated tablets under fed conditions. The study has been declared to be conducted in GCP setting, and list of GCP inspections of individual sites have been submitted.

To submit one bioequivalence study was considered acceptable since the application concerns an oral immediate release formulation (film-coated tablets) and the kinetics of ivabradine is linear over and oral dose range of 0.5 – 24 mg. The reference medicinal product is recommended to be taken during a meal; therefore bioequivalence study under fed conditions is optimal to demonstrate bioequivalence between test and reference medicinal products. Considering expected time to peak concentration (1 – 2 hours after administration) sufficient number of blood samples was taken to identify the C_{max}. The plasma elimination half-life of ivabradine is 2 hours hence the sampling time of 12 hours is considered sufficient. This is further supported by the fact, that in no individual subject the extrapolated AUC was higher than 20%. The washout period of 7 days is appropriate. The inclusion and exclusion criteria are considered acceptable. Food, alcohol, herbal/natural products, nutritional supplements, caffeine and xanthine containing products, grapefruit products and other medication restrictions were also adequate. The reason for drop-out is in line with the protocol and is considered acceptable.

Concomitant medication (2 tablets of ibuprofen 200 mg), taken 96 hours after dosing, could not affect results of the study as the dosing period was only 12 hours. The pharmacokinetic variables were adequate and in line with the *EMA Guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **)*. Statistical methods are acceptable according to *EMA Guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr **)*. The 90% confidence interval for the ration of the Test and Reference products fell into the acceptance range of 80.00 – 125.00% both for AUC0-t and Cmax. No pre-dose concentrations were detected. One subject reached T_{max} at the first sampling point. Since this issue occurred only in one case it is deemed that it should have not affected the study validity. Sequence and period effect were not significant. The test and reference products had a comparable safety profile in terms of the nature of events and overall proportion of subjects who experienced AEs. No unexpected AEs have been observed.

The applicant has also requested biowaiver for 5 mg strength. Drug products Ivabradine 5 mg film-coated tablet and Ivabradine 7.5 mg film-coated tablet are manufactured by the same manufacturing process, the composition is qualitative same and quantitatively proportional. Dissolution profiles of Ivabradine 5 mg film- coated tablet and Ivabradine 7.5 mg film-coated tablet are similar in all dissolution media. Regarding the linear kinetics of ivabradine in proposed strengths, the biowaiver is acceptable.

Based on the presented bioequivalence study, Ivabradine Zentiva, 7,5 mg film-coated tablet is considered bioequivalent with Procoralan, 7,5 mg film-coated tablet.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Ivabradine was provided and was accepted by the CHMP. In addition, to support this application, the company has submitted one bioequivalence study. Based on the presented bioequivalence study, Ivabradine 7,5 mg film-coated tablet manufactured by Zentiva, k.s., Czech Republic, was considered bioequivalent with Procoralan 7,5 mg film-coated tablet. The applicant has also requested biowaiver for 5 mg strength and this was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

2.5. Risk management plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Atrial fibrillation • Phosphenes / blurred vision • Bradycardia • Blood pressure increase in hypertensive patients • 2nd and 3rd degree AVB • ECG QT interval prolonged
Important potential risks	• Supraventricular tachyarrhythmias (SVT) other than atrial fibrillation • Immune system disorders • Severe ventricular arrhythmia • Myocardial infarction
Missing information	• Use in children and adolescent (below 18 years old) • Use in pregnant and lactating women • Use in patients with severe hepatic insufficiency • Use in patients with severe renal impairment • Chronic heart failure patients with intraventricular conduction defects

Pharmacovigilance plan

Not applicable

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Atrial fibrillation	Proposed text in SmPC Contraindications (AV-block of 3rd degree, sino-atrial block, pacemaker dependent, sick sinus syndrome, resting heart rate below 70 bpm prior to treatment) are reported in section 4.3. Warning in section 4.4 that: • Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and therefore not recommended in patients with atrial fibrillation. • In patients treated with ivabradine the risk of developing atrial fibrillation is increased. • Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their physician if these occur. Advice in section 4.4 to consider the possibility of non-urgent DC-cardioversion 24 hours after the last dose of ivabradine. Atrial fibrillation listed as common side effect amongst the cardiac disorders in section 4.8. Incidence of atrial fibrillation in clinical	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	studies is reported in section 4.8. Prescription only medicine.	
Phosphenes / blurred vision	Proposed text in SmPC Section 4.7 informs about impaired driving ability due to visual symptoms have been reported. Ivabradine may cause transient luminous phenomena consisting mainly of phosphenes. Precaution when using machines or diving veichles should be taken. Explanation in section 4.8 that the most common adverse reactions with ivabradine, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product. Luminous phenomena (phosphenes) listed as very common side effect amongst the eye disorders and duly described in section 4.8. Blurred vision listed as common side effect amongst the eye disorders in section 4.8. The pharmacodynamic mechanism through which ivabradine causes phosphenes is reported in section 5.1. Prescription only medicine	None proposed
Bradycardia	Proposed text in SmPC Recommended doses are reported in section 4.2. Warning to adjust treatment posology even suspending therapy in case patient experiences symptoms related to bradycardia. Precautions for patients with low heart rate are described in section 4.4. Statement in section 4.4 that there is no evidence of risk of (excessive)	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	bradycardia on return to sinus rhythm when pharmacological cardioversion is initiated in patients treated with ivabradine. Pharmacodynamic and Pharmacokinetic interactions potentially increasing the risk of arrhythmia and bradycardia are described in section 4.5. Explanation in section 4.8 that the most common adverse reactions related to ivabradine, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product. Bradycardia listed as common side effect amongst the nervous system disorders. Expalnation that overdose may lead to severe and prolonged bradycardia and the way to treat the latter are provided in section 4.9. Statement in section 5.1 that the main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. Percentage of people reporting bradycardia as adverse event during one study is reported in Clinical efficacy and safety paragraph. Prescription only medicine	
Blood pressure increase in hypertensive patients	Proposed text in SmPC Warning in section 4.4 that during a clinical study some transient episodes of increased blood pressure occurred shortly after blood pressure treatment was modified. The percentage of patients that experienced these episodes was higher in people treated with	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	ivabradine than in people treated with placebo. Thus when treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval. Uncontrolled blood pressure listed as common adverse reaction amongst vascular disorders in section 4.8. Prescription only medicine	
2nd and 3rd degree AVB	Proposed text in SmPC AV-block of 3rd degree listed as contraindication in section 4.3. Warning in section 4.4 that ivabradine is not recommended in patients with AV-block of 2nd degree. AV 2nd and 3rd degree block listed as very rare adverse reaction amongst cardiac disorders in section 4.8. Prescription only medicine	None proposed
ECG QT interval prolonged	Proposed text in SmPC Warning in section 4.4 that the use of ivabradine in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided. Heart rate reduction, as caused by ivabradine, may exacerbate QT prolongation. QT prolonging medicinal products are listed in section 4.5. The concomitant use of these products with ivabradine should be avoided since QT prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is needed.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	ECG prolonged QT interval listed as uncommon adverse reaction amongst investigations in section 4.8. Prescription only medicine	
Supraventricular tachyarrhythmias (SVT) other than atrial fibrillation	Proposed text in SmPC Warning in section 4.4 that ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and likely loses its efficacy when a tachyarrhythmia occurs (e.g. ventricular or supraventricular tachycardia). Ivabradine is therefore not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function. Supraventricular extrasystoles listed as uncommon adverse reaction amongst cardiac disorder in section 4.8. Prescription only medicine	None proposed
Immune system disorders	Proposed text in SmPC Eosinophilia listed as common adverse reaction amongst blood and lymphatic system disorders in section 4.8. Prescription only medicine	None proposed
Severe ventricular arrhythmia	Proposed text in SmPC Warning in section 4.4 that ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and likely loses its efficacy when a tachyarrhythmia occurs (e.g. ventricular or supraventricular tachycardia). Ivabradine is therefore not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function. Chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	block right) and ventricular dyssynchrony should be monitored closely. Ventricular extrasystoles listed as common adverse reaction amongst cardiac disorder in section 4.8. Prescription only medicine	
Myocardial infarction	Proposed text in SmPC Acute myocardial infarction listed as contraindication in section 4.3. Warning in section 4.4 that ivabradine is indicated only for symptomatic treatment of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death). Prescription only medicine	None proposed
Use in children and adolescent (below 18 years old)	Proposed text in SmPC Section 4.2 states that the safety and efficacy of ivabradine for the treatment of chronic heart failure in children aged below 18 years have not yet been established. Result from clinical studies in pediatric patients are shown in section 5.1. The long-term effects of ivabradine on growth, puberty and general development as well as the long- term efficacy of therapy with ivabradine in childhood to reduce cardiovascular morbidity and mortality have not been studied. As written in section 5.2 the pharmacokinetic profile of ivabradine in paediatric chronic heart failure patients aged 6 months to less than 18 years is similar to the one described in adults	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	when a titration scheme based on age and weight is applied. Same similarity between paediatric and adult population has been observed for the PK/PD relationship. Prescription only medicine	
Use in pregnant and lactating women	Proposed text in SmPC Section 4.3 informs that ivabradine is contraindicated in pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures. As stated in section 4.6 there are no or limited amount of data from the use of ivabradine in pregnant women. Therefore, ivabradine is contraindicated during pregnancy. Animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contraindicated during breast-feeding. Preclinical safety data are reported in section 5.3. Prescription only medicine	None proposed
Use in patients with severe hepatic insufficiency	Proposed text in SmPC Posology for patients with hepatic impairment is described in section 4.2. Severe hepatic insufficiency is listed amongst contraindications in section 4.3. As shown in section 5.2 in patients with mild hepatic impairment unbound AUC of ivabradine and the main active metabolite were about 20% higher than in subjects with normal hepatic function. No data are available in patients with severe hepatic impairment.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Prescription only medicine	
Use in patients with severe renal impairment	Proposed text in SmPC As stated in section 4.2 no data are available in patients with creatinine clearance below 15 mL/min. Ivabradine should therefore be used with precaution in this population. Section 5.2 informs that the impact of renal impairment (creatinine clearance 15 – 60 mL/min) on ivabradine pharmacokinetic is minimal, in relation with the low contribution of renal clearance (about 20%) to total elimination for both ivabradine and its main metabolite. Prescription only medicine	None proposed
Chronic heart failure patients with intraventricular conduction defects	Proposed text in SmPC Section 4.1 informs about approved use of ivabradine for the treatment of chronic heart failure. Warning in section 4.4 that chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be monitored closely. Prescription only medicine	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 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 Zentiva. In the absence of any conditions imposed on Ivabradine Zentiva, 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *EMA Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3. Benefit-risk balance

This application concerns a generic version of ivabradine hydrochloride film-coated tablet. The reference product Procoralan is indicated for symptomatic stable angina pectoris in adult patients whose heart rate is over or equal 70 beats per minute in adult patients who do not tolerate or cannot take heart medicines called beta-blockers or in combination with beta-blockers in patients whose condition is not fully controlled with a betablocker and in chronic heart failure in adult patients whose heart rate is over or equal to 75 beats per minute. It is used in combination with standard therapy, including beta-blocker therapy or when beta-blockers are contraindicated or not tolerated.

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 with the following design: a single-dose, open-label, single-centre, randomized, two-period, two-treatment, two-sequence, crossover comparative bioavailability study conducted in forty healthy volunteers under fed conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Study in fed status was considered acceptable as per requirements in the SmPC of the reference medicinal product. Dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Ivabradine 7.5mg film-coated tablets manufactured by Zentiva, k.s., met the protocol-defined criteria for bioequivalence when compared with the Procoralan 7.5 mg film-coated tablets. The point estimates and their 90% confidence intervals for the parameters $AUC_{0-t,}$, 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 product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are 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 Zentiva 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 beats per minute (bpm).
Ivabradine is indicated:

- in adults unable to tolerate or with a contraindication 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 (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.