CBG MEB

Public Assessment Report

Scientific discussion

Carivalan 6.25 mg/5 mg, 6.25 mg/7.5 mg, 12.5 mg/5 mg, 12.5 mg/7.5 mg, 25 mg/5 mg and 25 mg/7.5 mg, film-coated tablets

(carvedilol/ivabradine hydrochloride)

NL/H/3546/001-006/DC

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This module reflects the scientific discussion for the approval of Carivalan 6.25 mg/5 mg, 6.25 mg/7.5 mg, 12.5 mg/5 mg, 12.5 mg/7.5 mg, 25 mg/5 mg and 25 mg/7.5 mg, film-coated tablets. The procedure was finalised on 9 November 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

A list of literature references is given on page 27.

List of abbreviations

CAD	Coronary Artery Disease
CCS	Canadian Cardiovascular Society
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHF	Chronic Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CNS	Central Nervous System
CV	Cardiovascular
EAE	Emergent Adverse Event
ECG	Electrocardiogram
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
ERG	Electroretinographic
ETT	Exercise Tolerance Test
FDC	Fixed Dose Combination
HF	Heart Failure
HR	Heart Rate
IC50	Half Maximal Inhibitory Concentration
ICH	International Conference of Harmonisation
IMS	Intercontinental Marketing Service
IV	Intravenous
LD50	Half Maximal Lethal Dose
LVEF	Left Ventricular Ejection Fraction
LVSD	Left Ventricular Systolic Dysfunction
MAH	Marketing Authorisation Holder
MDD	Mean Daily Dose
MI	Myocardial Infarction
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PO	Per Os
QoL	Quality of Life
RH	Relative Humidity
RMP	Risk Management Plan
RRR	Relative Risk Reduction
RS	Randomised Set
SAP	Stable Angina Pectoris
SEAE	Serious Emergent Adverse Event
SmPC	Summary of Product Characteristics
TED	total exercise duration
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Carivalan 6.25 mg/5 mg, 6.25 mg/7.5 mg, 12.5 mg/5 mg, 12.5 mg/7.5 mg, 25 mg/5 mg and 25 mg/7.5 mg, film-coated tablets from Les Laboratoires Servier.

Carivalan is indicated as substitution therapy in adult patients with normal sinus rhythm already controlled by ivabradine and carvedilol taken concomitantly at the same doses level for:

- The symptomatic treatment of chronic stable angina pectoris (SAP) in coronary artery disease patients.
- The treatment of chronic heart failure (CHF) (II-IV NYHA-class) with systolic dysfunction.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a fixed dose application. Fixed dose combinations (FDCs) contain active substances from medicinal products already authorised in the EEA but not hitherto used in combination for therapeutic purposes.

The individual active substances within Carivalan, ivabradine and carvedilol, are established active substances which have been included in cardioprotective agents. Ivabradine is registered by Les Laboratoires Servier through a centralised procedure (EMEA/H/C/000597-598) as Procoralan/Corlentor since 2005. Carvedilol is registered as Eucardic (NL License RVG 19808, 19809 and 14491) by Roche Nederland B.V. in the Netherlands since 1991 (25 mg) and 1997 (6.25 mg and 12 mg).

The concomitant use of the carvedilol and ivabradine in the treatment of SAP and CHF is well-known and common. The combination of ivabradine with a beta-blocker (e.g. carvedilol) in the symptomatic treatment of chronic SAP and CHF is clearly specified in the indication section of the ivabradine SmPC. Beta-1 selective agents are preferred due to lower side-effects and fewer precautions compared with non-selective beta-blockers. The 2013 European Society of Cardiology (ESC) guideline recommends the combination of beta-blockers with ivabradine for treatment of angina in patients in sinus rhythm, as well as the National Institute for Health and Care Excellence (NICE) therapeutic guideline in 2011. The 2016 ESC guidelines recommends that ivabradine should be considered to reduce the risk of HF hospitalisation in patients in sinus rhythm with an EF ≤35%, a HR remaining ≥70 bpm, and persisting symptoms (NYHA class II–IV) despite standard therapy, including beta-blocker. This combination is also supported by clinical data.
The proposed carvedilol/ivabradine FDC would allow a simplification of therapy by decreasing the number of individual dose units to be taken by patients from four to two and may improve patient compliance to treatment.

The clinical development programme consisted of four bioequivalence studies performed in accordance with the “Guideline on the investigation of bioavailability and bioequivalence” (CPMP/EWP/QWP/1401/98 Rev. 1/Corr, 2010) to demonstrate the bioequivalence between carvedilol/ivabradine FDC and the free combination, i.e. the two tablets administered concomitantly; and one interaction study. The combination of carvedilol and ivabradine is also supported by multiple clinical studies from scientific literature.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Germany, Denmark, Greece, Spain, Hungary, Italy, Latvia, Lithuania, Luxembourg, Malta, Norway, Poland, Portugal, Romania, Slovenia and Slovakia.

The marketing authorisation has been granted pursuant to Article 10b of Directive 2001/83/EC.

The proposed carvedilol/ivabradine FDC is intended for treatment of SAP and CHF as substitution therapy in adult patients. A PIP waiver was granted by the Paediatric Committee on 19 June 2015 for all subsets of the paediatric population (EMEA-001743-PIP01-14).

II. QUALITY ASPECTS

II.1 Introduction

Carivalan is a film-coated tablet containing carvedilol and ivabradine (as ivabradine hydrochloride), in six combinations:

- The 6.25 mg/5 mg strength is a white, hexagonal, film-coated tablet engraved with CI2 on one face and  on the other face. Each film-coated tablet contains 6.25 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
- The 6.25 mg/7.5 mg strength is a yellow, hexagonal, film-coated tablet engraved with CI3 on one face and  on the other face. Each film-coated tablet contains 6.25 mg of carvedilol and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).
- The 12.5 mg/5 mg strength is a white, elliptic, film-coated tablet engraved with CI4 on one face and  on the other face. Each film-coated tablet contains 12.5 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
- The 12.5 mg/7.5 mg strength is a yellow, elliptic, film-coated tablet engraved with CI5 on one face and  on the other face. Each film-coated tablet contains 12.5 mg of carvedilol and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).
- The 25 mg/5 mg strength is a white, octagonal, film-coated tablet engraved with CI6 on one face and  on the other face. Each film-coated tablet contains 25 mg of carvedilol and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
- The 25 mg/7.5 mg strength is a yellow, octagonal, film-coated tablet engraved with CI7 on one face and  on the other face. Each film-coated tablet contains 25 mg of carvedilol and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).

The film-coated tablets are packed in PVC/PVDC/aluminium blisters.

The excipients are:
Tablet core - Pregelatinised starch (maize), monohydrate lactose, microcrystalline Cellulose (E460), sodium croscarmellose (E468), maltodextrin, colloidal anhydrous silica (E551) and magnesium stearate (E470b).
Film-coating - glycerol (E422), hypromellose (E464), magnesium stearate (E470b), titanium dioxide (E171), iron oxide yellow (E172) (for 6.25 mg/7.5 mg, 12.5 mg/7.5 mg and 25 mg/7.5 mg) and Macrogol 6000 (E1521).

The different strengths are not dose-proportional.

II.2 Drug Substances

Carvedilol
The active substance is carvedilol, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Carvedilol is a white or almost white, crystalline powder. It is practically insoluble in water, slightly soluble in ethanol, and sparingly soluble in methylene chloride. The solubility in aqueous solutions is pH dependent. It contains a chiral centre, but exists as a racemate of its two enantiomeric forms. Carvedilol shows polymorphism; Form II is manufactured. The active substance is not hygroscopic.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with an additional requirement for ethyl acetate solvent residual content. The additional requirement as mentioned in the CEP is covered by the limit for loss on drying. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three full scale batches.

Stability of drug substance
The active substance is stable for five years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Ivabradine hydrochloride
The active substance is ivabradine hydrochloride, an established active substance that is not described in any Pharmacopoeia. Ivabradine hydrochloride is a white to slightly yellow powder, which is freely soluble in purified water, methanol and dichloromethane, soluble in ethanol and slightly soluble in acetone. The solubility in aqueous solutions, containing 0.15 M potassium chloride, is pH dependent. Ivabradine hydrochloride is hygroscopic. Ivabradine has the S-configuration.

Manufacturing process
Ivabradine hydrochloride is manufactured in a three step process from two intermediates. One intermediate is manufactured in one step, whereas the other intermediate is manufactured in a two step process. The starting materials are acceptable. No class-I solvents are use during the synthesis. Ivabradine hydrochloride has been adequately characterised and acceptable specifications have been adopted for the starting materials, the solvents and the reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three production scale batches.

Stability of drug substance
Stability data for ivabradine hydrochloride have been provided for three full scale batches. The batches were stored at 25°C/60% RH (36 months), 30°C/75% RH (36 months), and at 40°C/75% RH (six months). Storage under long-term and accelerated conditions did not show any up- or downward trends indicating that the batches remain stable throughout the tested period. The claimed retest period of three years is acceptable, based on available completed 36 months long-term stability studies. No specific temperature restrictions are required.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is justified and their functions explained. The compatibility of carvedilol with ivabradine hydrochloride was assessed and it was concluded that carvedilol and ivabradine hydrochloride could be used together in the same formulation without taking any particular precaution to separate them. First direct compression was tried as manufacturing process, however, this did not lead to homogeneous products therefore, wet granulation was selected for the manufacturing process of the tablet cores. The used excipients, and their ratios were optimised for blend characteristics, granulation behaviour, tabletting behaviour, and dissolution behaviour. The pharmaceutical development of the product has been adequately performed, and the choices of the packaging and manufacturing process are acceptable.

The test batches used in the bioequivalence studies (6.25 mg/7.5 mg, 12.5 mg/7.5 mg, and 25 mg/7.5 mg strengths) have the same quantitative composition and are manufactured according to the proposed manufacturing process. The batch sizes of the batches are acceptable given the proposed maximum batch size of the commercial batches. Analysis results for the batches of test and reference products used in the bioequivalence studies, have been provided demonstrating that their content did not differ more than 5%, thereby the batches are acceptable.

Comparative dissolution testing at 3 pH's has been successfully studied in support of bioequivalence study, and to support a biowaiver for the other strengths (6.25 mg/5 mg, 12.5 mg/5 mg, 25 mg/5 mg). At pH 1.2 and 4.5, the release of carvedilol from the tablets is more than 85 % within 15 minutes for all strengths. At pH 6.8 dissolution is slower, but the calculated similarity factor (f2) is more than 50 for the studied strength. The release of ivabradine from the tablets is more than 85 % within 15 minutes for all strengths throughout the physiological pH range.

Manufacturing process
The manufacturing process is a standard wet granulation. The drug substances are granulated together with part of the excipients, then the granulate is mixed with the external phase and the obtained blend is lubricated with the flow agent and the lubricant. The lubricated blend is compressed into tablets. Tablets are film-coated and packed. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three batches per strength at the smallest commercial scale. The product is manufactured using conventional manufacturing techniques. Process validation for intermediate and large commercial scaled batches will be performed post authorisation.

Control of excipients
The excipients, including all components of the coating systems, comply with the Ph.Eur. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, average mass, microbiological quality, identification and assay of drug substances, degradation products, uniformity of dosage units, and dissolution. The release and shelf-life requirements/limits are not identical. The limits for assay of drug substances and the limits for degradation products have been widened at end of shelf life compared to release to cover for degradation. The proposed specifications are acceptable. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods have been provided. Batch analytical data from three batches of each strength of the smallest industrial scale proposed and, in addition, for one batch of the largest industrial scale proposed for the 12.5 mg/7.5 mg strength and the 25 mg/5 mg strength, from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on three batches of each strength (total eighteen batches), of the smallest commercial scale, stored 18 months at 25°C/60% RH, 30°C/65% RH and 30°C/75% RH (*except for 6.25/7.5 mg strength: 18 months for 2 batches and 9 months for 1 batch*). Three batches of each strengths were stored 6 months at 40°C/75% RH. The conditions used in the stability studies are according to the ICH stability guideline. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. A shelf life of 24 months is acceptable, based on the provided data.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Carivalan has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substances and finished product.

No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Carvedilol
Carvedilol is a non-cardio selective beta-blocker. Carvedilol inhibited I_{kr}, I_{Ca}, I_{to}, and I_{Kur} *in vitro* with IC50 ranging 0.35-3.59 µM and I_{Ks} with half maximal inhibitory concentration (IC50) of 12.54 µM. Carvedilol had no significant effect on I_{k1} up to 30 µM. Carvedilol caused a prolongation of action potential duration in rabbit papillary muscles of 7-12% at 1 µM and of 12-24% at 3 µM. These concentrations are at least 100 times higher than the unbound therapeutic concentration of 0.003 µM at an oral dose of 50 mg. Carvedilol induced bradycardia, hypotension, an increase in the respiratory rate and a decrease in expiratory velocity in dogs, increased motility and decreased contractile amplitude and tonus in the intestines in rabbits, and central nervous system (CNS) effects (reduced awareness, motor activity and muscle tone, absence of righting reflex and ipsilateral flexor reflex and staggering gait) at high dose (300 mg/kg) per os (PO) in mice.

Ivabradine
Ivabradine is a selective and specific inhibitor of the cardiac pacemaker I_f current. In the hERG assay, ivabradine and its main metabolite (N-desmethylated derivative) inhibited channel function at high concentrations, with IC50 values of 4.85 and 15.8 µM, respectively. These values are approximately 240 and 3000 fold higher than the unbound plasma concentrations for ivabradine and its main metabolite, respectively, in patients taking 7.5 mg twice daily. No effect on QTc was observed in dogs. Visual symptoms have been reported in patients as a pharmacological effect secondary to the inhibition of the retinal hyper polarisation-activated current I_h that is structurally closely related to the target-cardiac I_f.

Combination carvedilol and ivabradine
No non-clinical studies were performed with the combination carvedilol/ivabradine. This is not necessary since the combination of ivabradine with beta-blockers is already approved.

III.2 Pharmacokinetics

Carvedilol
The bioavailability of carvedilol after oral administration was much lower in dogs (2.1%) compared with that reported in humans (25%). Carvedilol is more than 98% bound to plasma proteins. Carvedilol binds to the melanin of the uveal tract. Carvedilol crosses the placenta in rats. Carvedilol is extensively metabolised in rat, mice and dogs. Metabolic routes were glucuronidation of the parent compound and hydroxylation of the carbazolyl ring, with subsequent glucuronidation in dogs, hydroxylation of the carbazolyl ring, with subsequent glucuronidation in rats and glucuronidation of the parent compound and hydroxylation of either the carbazolyl or phenyl ring, with subsequent glucuronidation in mice. In rats, it was showed that carvedilol metabolites were secreted primarily in bile. In intact animals, the majority of the radioactivity was recovered in faeces, with only a small percentage excreted in bile.

Ivabradine
After oral administration over a large range of doses, ivabradine is rapidly and almost completely absorbed with a moderate bioavailability of ~40% due to first-pass effect. Plasma protein binding is moderate (60-70%). Ivabradine and metabolites rapidly equilibrate in most tissues, except in brain and testis where passage is very low. Slower removal from pigmented structures in the uveal tract is indicative of melanin binding, albeit reversible. Melanin binding in the eye, which is characteristic of many basic compounds (e.g., propranolol, bisoprolol), is not related to the electroretinographic (ERG) changes observed in dogs. Ivabradine was not phototoxic in the in vitro Neutral Red Uptake test. Ivabradine was also distributed into amniotic fluid of pregnant rats and was excreted in maternal milk of rats. Ivabradine was extensively metabolised in all animal species tested by oxidation via CYP450, mainly CYP3A4. Elimination of ivabradine mainly occurred via hepatic metabolism.

Combination carvedilol and ivabradine
No non-clinical interaction studies with carvedilol/ivabradine were performed. A clinical interaction study regarding the carvedilol/ivabradine combination is available. No additional non-clinical data are needed regarding pharmacokinetic interactions between carvedilol and ivabradine because this is an approved combination.

III.3 Toxicology

Carvedilol
Acute toxicity was investigated in mice, rats and dogs. Half maximal lethal dose (LD50) was >8000 mg/kg in mice and rats after oral administration. In mice, LD50 after intraperitoneal administration was 364 mg/kg. In rats, LD50 was 25 mg/kg after intravenous administration and 769 mg/kg after intraperitoneal administration. In dogs, oral LD50 was >1000 mg/kg. Intravenous LD50 in rabbits was 27 mg/kg.

Repeat-dose toxicity studies were performed in rats, up to 18 months, and in dogs, up to 12 months. An increase in bile duct hyperplasia was observed in rats and dogs and focal hepatocellular hyperplasia was noted in rats. A small increase in hepatic adenomas was observed in rats in the 18-month study. This was however not found in the carcinogenicity study in rats.

Carvedilol was negative when tested in a battery of genotoxicity assays, including the Ames and the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase assays for mutagenicity and the *in vitro* hamster micronucleus and *in vivo* human lymphocyte cell tests for clastogenicity. Carvedilol was not carcinogenic in mice and rats after treatment with up to 200 mg/kg and 74.7-169.5 mg/kg, respectively, via the diet.

Fertility was impaired at >6 times the human dose in mg/m^2. Increased post-implantation loss was observed in rats and rabbits and a decreased foetal body weight and delayed skeletal development in rats, at doses >3-6 times the human dose in mg/m^2. Increased mortality was observed in neonatal rats one week post-partum at >6 times the human dose in mg/m^2.

Under the current conditions, there are no new impurities for carvedilol.

Ivabradine
Acute toxicity studies were conducted in mice, rats and dogs. Qualitatively similar toxicity profiles were observed in mice and rats. The observed effects were behavioural changes in association with high plasma concentrations, and death (observed minimal lethal doses: mice: ≥742 mg/kg PO, ≥56 mg/kg intravenous (IV); rats: ≥557 mg/kg PO, ≥74 mg/kg IV). In dogs, the observed effects were neurobehavioral changes (maximum tolerated dose: between 11 and 22 mg/kg PO in a dose-escalation study, 9.3 mg/kg IV).

Repeat-dose studies were performed in rats and dogs, up to one year duration. The heart was the main target organ in both species. Heart rate reduction, the pharmacological effect of ivabradine, was evident from the lowest dose in the studies where it was measured. In the heart of rats, focal myocardial lesions were observed. The exposure at the no observed adverse effect level (NOAEL) was 2 times (males) and 9 times (females) the human exposure. In dogs, the main treatment-related findings were sinus bradycardia, sinoatrial block, sinoatrial arrest, first-degree atrioventricular block and second-degree atrioventricular block. These electrocardiogram (ECG) changes were seen at dose levels associated with mean plasma. C_{max} 20-fold above that in human at 7.5 mg twice daily. There were also some ventricular escape complexes and atrial or ventricular premature complexes at dose levels associated with mean plasma C_{max} at least 80-fold greater than in humans. No treatment-related ECG changes were noted at the end of the recovery period. There was no effect on QT-interval duration. Reversible ERG changes were observed in dogs. No ophthalmoscopic changes were observed and no pathological changes detected by light microscopy or by transmission electron microscopy in dogs exposed for one year to concentrations up to 70-fold those in patients. Furthermore, there were no other ophthalmological effects and no histopathological effects in the eyes of any studied species.

No evidence of mutagenicity or relevant clastogenic activity was observed from an exhaustive review and analysis of the data from a battery of *in vitro* and *in vivo* genotoxicity tests performed in accordance with International Conference on Harmonisation (ICH) guidelines. The tumorigenic potential of ivabradine was investigated in mice and rats over 104 weeks. There was no evidence of ivabradine-related carcinogenic effects in mice and rats.

Ivabradine did not affect fertility in male or female rats. Ivabradine was embryo toxic and teratogenic in rats and rabbits. Embryo toxic effects in rats comprised increased intrauterine and post-natal mortality, and teratogenic effects occurred in the heart at systemic exposure levels close to those in patients receiving therapeutic doses of ivabradine. Adverse effects in rabbits comprised three foetuses from three litters in two out of three separate studies, which had ectrodactylia; these were from dams exposed to 21 times the mean human AUC. Intrauterine and neonatal mortality could also have been associated with potentially lethal cardiac malformations, as indicated by some pups that died neonatal and had septal defects. In a pre- and postnatal development study in rats, increased post-natal mortality was observed.

IV studies revealed no evidence of local toxicity at the injection sites. No haemolytic risk was observed in human blood.

In a 4-week Wistar rat study, including lymphocyte subset analysis and plaque-forming cell assay using sheep red blood cells, no immunotoxicity of ivabradine was shown.

The potential phototoxicity of ivabradine was assessed using the *in vitro* Neutral Red Uptake test in cultured mouse Balb/c 3T3 fibroblasts. The results showed no cytotoxic effect observed after treatment of cells with ivabradine at concentrations up to 200 µM.

An in silico analysis with Derek software of potential impurities revealed a structural alert for mutagenicity (alkylating agent) for bromodiox and chloroethane. Bromodiox will be maintained below the Threshold of Toxicological Concern. Chloroethane is not used during the synthesis of ivabradine. For two degradation products shelf-life limits are proposed to be increased to 0.8%. Both impurities were sufficiently qualified at this limit.

Combination carvedilol and ivabradine
No non-clinical combination studies were performed with carvedilol and ivabradine. This is not necessary because it is an approved combination.

III.4 Ecotoxicity/environmental risk assessment (ERA)

No environmental risk assessment was provided. The fixed dose combination of carvedilol and ivabradine is intended for patients who are already controlled by carvedilol and ivabradine taken concomitantly at the same dose level. An increase in the environmental exposure to these compounds is not expected.

III.5 Discussion on the non-clinical aspects

For this fixed dose application, no new data regarding pharmacology, pharmacokinetics or toxicology have been provided. No new studies have been performed and none are considered necessary. This is acceptable, as both active substances are well known.

IV. CLINICAL ASPECTS

IV.1 Introduction

The two active substances are well-known and have an established efficacy and tolerability.

To support the application, the MAH submitted one interaction study and three bioequivalence studies with the 12.5 mg/7.5 mg, 6.25 mg/7.5 mg, 25 mg/7.5 mg tablets respectively. For the other strengths (6.25 mg/5 mg, 12.5 mg/5 mg, 25 mg/5 mg) a biowaiver was claimed. The studies are sufficient for this type of application. The clinical pharmacokinetic studies are shortly summarised below and the biowaiver is also discussed.

IV.2 Pharmacokinetics

IV.2.1 Bioequivalence studies

The objective of the three studies was to demonstrate the bioequivalence of ivabradine and carvedilol administered in single dose concomitantly as a fixed combination (Les Laboratoires Servier, France) or as a combination of marketed tablets of the two drugs; Procoralan (Les Laboratoires Servier, France) and Dilatrend (Roche, Germany):

- Study I - A bioequivalence study under fed conditions with the 12.5 mg/7.5 mg strength
- Study II - A bioequivalence study under fed conditions with the 6.25 mg/7.5 mg strength
- Study III - A bioequivalence study under fed conditions with the 25 mg/7.5 mg strength

The choice of the reference product
The choice of the reference product in the bioequivalence studies has been justified.
The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in the studies for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Bioequivalence study I
Design
This study was a single centre, open-label, randomised, single-dose, two-period, cross-over bioequivalence study in 64 healthy male (n=34) and female (n=30) subjects, aged 18-55 years. Each subject received a single dose (12.5 mg/7.5 mg) of one of the 2 carvedilol/ivabradine treatments. The treatment was orally administered with 240 ml of water 30 minutes after starting a high-fat, high-calorie breakfast. There were 2 dosing periods, separated by a wash-out period of at least 7 days.

Blood samples were collected pre-dose and at 10 min, 20 min, 40 min, 1h, 1h 20 min, 1h 40 min, 2h, 2h 20min, 2h 40 min, 3h, 3h 30 min, 4h, 5h, 6h, 8h, 10h, 12h, 16h, 24h, 30h, 36h after administration of the products.

The design of the study is acceptable. The pharmacokinetic studies were all performed in fed conditions in line with the recommendations for the reference products. Carvedilol is recommended to be taken with food in order to slow down the absorption and therefore to potentially lower any orthostatic effects. Ivabradine should also be taken during meals in order to decrease the intra-individual variability in exposure. The carvedilol/ ivabradine FDC is therefore also taken during meals.

Results
All subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 7.5 mg ivabradine under fed conditions.

Treatment N=64	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Treatment A	79.3	80.9	24.3	1.00 (0.33 - 3.5)	2.50
Treatment B	78.9	80.3	24.5	1.00 (0.33 - 3.0)	2.41
***Ratio (90% CI)**	1.01 (0.97 - 1.05)	--	0.99 (0.93 – 1.06)	--	--
CV (%)	13.60	--	22.61	--	--

Treatment A	fixed combination of ivabradine 7.5 mg and carvedilol 12.5 mg
Treatment B	concomitant administration of ivabradine 7.5 mg plus carvedilol 12.5 mg
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
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
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 12.5 mg carvedilol under fed conditions.

Treatment N=64	**AUC_{0-t}** ng.h/ml	**$AUC_{0-\infty}$** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h	**$t_{1/2}$** h
Treatment A	142.7	144.1	36.7	1.33 (0.67 - 4.0)	8.33
Treatment B	143.7	149.5	32.7	1.33 (0.33 - 5.0)	8.26
***Ratio (90% CI)**	0.99 (0.95 - 1.04)	--	1.12 (1.04 – 1.21)	--	--
CV (%)	16.07	--	26.00	--	--

Treatment A	fixed combination of ivabradine 7.5 mg and carvedilol 12.5 mg
Treatment B	concomitant administration of ivabradine 7.5 mg plus carvedilol 12.5 mg
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
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
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Ivabradine and carvedilol pharmacokinetic parameters were similar after administration of the fixed combination of ivabradine 7.5 mg and carvedilol 12.5 mg and concomitant administration of ivabradine 7.5 mg plus carvedilol 12.5 mg. The 90% confidence intervals for AUC_{last} and C_{max} of both active substances were fully included within the range of 80-125%.

Bioequivalence study II

Design

This study was a single centre, open-label, randomised, single-dose, two-period, cross-over bioequivalence study in 64 healthy male (n=35) and female (n=29) subjects, aged 18-55 years. Each subject received a single dose (6.25 mg/7.5 mg) of one of the 2 carvedilol/ivabradine treatments. The treatment was orally administered with 240 ml of water 30 minutes after starting a high-fat, high-calorie breakfast. There were 2 dosing periods, separated by a wash-out period of at least 7 days.

Blood samples were collected pre-dose and at 10 min, 20 min, 40 min, 1h, 1h 20 min, 1h 40 min, 2h, 2h 20 min, 2h 40 min, 3h, 3h 30 min, 4h, 5h, 6h, 8h, 10h, 12h, 16h, 24h, 30h, 36h after administration of the products.

The design of the study is acceptable. It is acceptable that the bioequivalence study was conducted under fed conditions.

Results

All subjects were eligible for pharmacokinetic analysis.

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 7.5 mg ivabradine under fed conditions.

Treatment N=64	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Treatment A	79.7	81.4	23.3	1.01 (0.33 - 3.5)	2.55
Treatment B	79.5	81.1	22.6	1.33 (0.33 - 3.5)	2.60
***Ratio (90% CI)**	1.00 (0.96 - 1.05)	--	1.03 (0.96 – 1.11)	--	--
CV (%)	15.21	--	25.62	--	--

Treatment A	fixed combination of ivabradine 7.5 mg and carvedilol 6.25 mg
Treatment B	concomitant administration of ivabradine 7.5 mg plus carvedilol 6.25 mg
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
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
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Table 4. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of 6.25 mg carvedilol under fed conditions.

Treatment N=64	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Treatment A	69.4	71.6	17.3	1.33 (0.33 - 3.5)	7.35
Treatment B	70.5	72.1	15.4	1.67 (0.67 - 3.5)	7.57
***Ratio (90% CI)**	0.98 (0.94 - 1.03)	--	1.13 (1.05 – 1.21)	--	--
CV (%)	14.31	--	24.5	--	--

Treatment A	fixed combination of ivabradine 7.5 mg and carvedilol 6.25 mg
Treatment B	concomitant administration of ivabradine 7.5 mg plus carvedilol 6.25 mg
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
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
$t_{1/2}$	half-life
CV	coefficient of variation

**ln-transformed values*

Ivabradine and carvedilol pharmacokinetic parameters were similar after administration of the fixed combination of ivabradine 7.5 mg and carvedilol 6.25 mg and concomitant administration of ivabradine 7.5 mg plus carvedilol 6.25 mg. The 90% confidence intervals for AUC_{last} and C_{max} of both active substances were fully included within the range of 80-125%.

Bioequivalence study III

Design

This study was a single centre, open-label, randomised, single-dose, two-period, cross-over study in 100 healthy male and female subjects, under fed conditions. The objective of the study was to demonstrate the bioequivalence of ivabradine (7.5 mg) and carvedilol (25 mg) administered in single dose concomitantly as a fixed combination (Carivalan 7.5 mg/25 mg tablet) or as a combination of marketed tablets of the two drugs (Procoralan 7.5 mg and Dilatrend 25 mg).

Results
Ivabradine and carvedilol pharmacokinetic parameters were similar after administration of the fixed combination of ivabradine 7.5 mg and carvedilol 25 mg and concomitant administration of ivabradine 7.5 mg plus carvedilol 25 mg. The 90% confidence intervals for AUC_{last} and C_{max} of both active substances were fully included within the range of 80-125%, see table below:

Table 5 Geometric means of C_{max} and AUC_{last}, Geometric mean ratio of test/reference with 90% CI - carvedilol and ivabradine (N=92)

Analyte	Parameter	Ratio (%)	90% CI (%)	CV (%)
carvedilol	**C_{max}**	1.05	0.96 - 1.15	38.81
	AUC_{last}	0.97	0.93 - 1.01	15.55
ivabradine	**C_{max}**	0.93	0.85 - 1.02	38.47
	AUC_{last}	0.95	0.91 - 1.00	19.10

Conclusion bioequivalence studies
The 90% confidence intervals calculated for AUC_{0-t}, and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted studies it can be concluded that the Carivalan 7.5 mg/12.5 mg tablet, 7.5 mg/6.25 mg and 7.5 mg/25 mg are bioequivalent to the combination of one tablet Procoralan plus one tablet Dilatrend, under fed conditions.

The MEB has been assured that the bioequivalence studies has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.2.2 Interaction study

Design
This study was a single centre, open-label, randomised, single-dose, three-period, six-sequence, cross-over study to evaluate the potential pharmacokinetic interaction between ivabradine (7.5 mg) and carvedilol (12.5 mg) administered in single dose either alone or as a concomitant administration of marketed tablets of the two drugs in healthy male and female subjects under fed conditions. 72 healthy male and female subjects participated in three study periods.

The design and methods are sufficient. Additional parameters (metabolites) were analysed to determine possible interactions. It is acceptable to conduct the interaction study with the 12.5 mg carvedilol strength instead of the 25 mg strength due to safety reasons. The use of Procoralan 7.5 mg tablets (Les Laboratoires Servier, France) and Kredex 12.5 mg tablets (Roche, France) is justified.

Results
Three subjects were withdrawn during the study. Therefore 69 subjects were eligible for pharmacokinetic analysis.

Table 6 Summary of the statistical analysis of ivabradine and carvedilol Interaction study

	ivabradine n=69			carvedilol n=69		
	Treatment A/B			Treatment A/C		
Parameter	**Geometric mean ratio (%)**	**90% Confidence interval (%)**	**CV%***	**Geometric mean ratio (%)**	**90% Confidence interval (%)**	**CV%***
AUC_{last} (h*ng/ml)	1.08	1.03 – 1.13	15.82	0.96	0.92 – 1.01	16.79
C_{max} (ng/ml)	1.05	0.98 – 1.12	23.27	0.95	0.88 – 1.03	27.54

*Intra-individual CV estimated from the residual squares.
Treatment A: ivabradine 7.5 mg (Procoralan) and carvedilol 12.5 mg. (Kredex)
Treatment B: ivabradine 7.5 mg (Procoralan)
Treatment C: carvedilol 12.5 mg. (Kredex)

Conclusion interaction study
Ivabradine and metabolite N-desmethyl-ivabradine pharmacokinetic parameters were unaffected by co-administration of carvedilol. Carvedilol, the R- and S-enantiomer and the main metabolite 4-

hydroxyphenyl-carvedilol pharmacokinetic parameters were also unaffected by co-administration of ivabradine.

Geometric mean ratios of AUC_{last} and C_{max} of carvedilol and ivabradine after administration alone or together with respectively ivabradine and carvedilol were near 100% and the corresponding 90% confidence intervals were fully included within the range of 0.80-1.25%.

IV.2.3 Biowaiver

The Carivalan 6.25 mg/5 mg, 12.5 mg/5 mg and 25 mg/5 mg film-coated tablets formulations are not dose proportional with the higher strengths but still comply with the biowaiver criteria defined in the bioequivalence guideline CPMP/EWP/QWP/1401/98 Rev.1/Corr.2010. The amount of ivabradine is less than 5% of the tablet mass and it is acceptable to compensate the decreased amount of active substance with an inert filler. All biowaiver criteria are considered fulfilled.
The biowaiver claimed for the 5 mg/6.25 mg, 5 mg/12.5 mg and 5 mg/25 mg strengths can be granted.

IV.3 Pharmacodynamics

Carvedilol and ivabradine are well-known active substances with established pharmacodynamics. Both drugs act via different and complementary pathways on the sinus node, since carvedilol is a non-selective beta-blocker/alpha-1 blocker, whereas ivabradine is a pure heart rate lowering agent that selectively inhibits the I_f pace-making current.

IV.4 Clinical efficacy

The efficacy of ivabradine combined with a beta-blocker was demonstrated during the clinical development of ivabradine. The concomitant use of beta blockers and ivabradine is reflected in ivabradine indications in the symptomatic treatment of chronic SAP and in the treatment of CHF (EPAR, Procoralan, 2014). The therapeutic guidelines also recommend ivabradine in combination with a beta-blocker for the management of angina in patients with stable coronary artery disease (CAD) (Montalescot, 2013; NICE 126, 2012), and the management of CHF (McMurray, 2012; NICE 267, 2012).

The section below presents an overview of the use of beta-blockers/ivabradine and of carvedilol/ivabradine in clinical studies on SAP and heart failure (HF).

1. Stable angina pectoris
Clinical studies and sub-analysis supporting the combined use of ivabradine/beta-blocker and carvedilol/ivabradine in SAP are summarised in table 7 and detailed hereafter.

Table 7- Clinical studies supporting the combined use of carvedilol and ivabradine in SAP

Study name	Number of patients	Duration	Design	Treatment groups
ASSOCIATE	889	4 months	RDB	• ivabradine + atenolol • placebo + atenolol
BEAUTIFUL	10,917	3 years	RDB morbi-mortality	• ivabradine • placebo • on top of beta-blocker (90%)
BEAUTIFUL sub-analysis	• 1,507 w angina • 254 w angina and on carvedilol		RDB posthoc morbi-mortality	• ivabradine + carvedilol • Placebo + carvedilol
ADDITIONS	• 2,330 • 901	• 4 months • 1 year	Non interventional Open	• ivabradine + beta-blocker
REDUCTION Sub-analysis	344	4 months	Non interventional Open	• ivabradine + beta-blocker

The ASSOCIATE study
The ASSOCIATE study was a 4 month, randomised, double-blind, placebo-controlled, parallel-group, international, multi-centre study evaluating the antianginal efficacy and safety of oral administration of ivabradine compared to placebo on top of background therapy with atenolol (Tardif, 2009).

The primary objective of this study was to demonstrate the superior efficacy of ivabradine (5 mg bid then 7.5 mg bid given orally for 2 months each) vs placebo, when given in combination with atenolol (50 mg daily), in patients with stable chronic effort angina pectoris who still present a positive exercise tolerance test (ETT), with or without symptomatic angina in everyday life.

Design
A number of 889 patients from 20 countries were randomised to either ivabradine (n=449) or placebo (n=440). The primary efficacy criterion was the improvement between baseline and end of 4 months of treatment (M4) in the total exercise duration (TED) on a treadmill ETT according to the standard Bruce protocol at the trough of ivabradine and atenolol activity (12 ± 1 hrs and 24 ± 2 hrs post-dosing, respectively) on centralised reading values.

Results
The ivabradine group showed a significant improvement in the primary efficacy criterion, TED at 4 months of treatment (24.3 ± 65.3 seconds vs 7.7 ± 63.8 seconds in the ivabradine and placebo groups respectively, $p<0.001$), with an adjusted between-group difference of 16.3 seconds in favour of ivabradine. There were also significant improvements with ivabradine treatment, relative to placebo, in all other ETT criteria at M4 and 2 months of treatment (M2) (Tardif, 2009).
Resting HR reduction with ivabradine administered on top of atenolol was slightly less than observed for the same doses of ivabradine given as monotherapy in previous studies. These results indicate that the combination of ivabradine with a beta-blocker induces a simple additional HR lowering effect without any synergistic effect.
The frequency of angina attacks decreased significantly from baseline to M4 in both treatment groups, from 1.8 + 3.3 to 0.9 + 2.4 attacks/week in the ivabradine group, and from 1.6 + 2.4 to 0.9 + 2.1 attacks/week with placebo (between-group difference not significant) (Tardif, 2009).
Post-hoc complementary analyses of ETT results were performed in the subgroups of patients whose HR was ≤65 bpm at baseline, and whose background beta-blocker dose was judged to be maximal, due to a resting HR ≤60 bpm and/or supine systolic BP ≤100 mmHg and/or mean PR interval ≥200 ms at baseline. Improvements in ETT criteria with ivabradine in both subgroups were similar to those observed in the full analysis set, showing that ivabradine improved exercise capacity in patients whose baseline HR was relatively low, and in patients for whom an increase in beta-blocker dose would have been impossible

Therefore, ivabradine resulted in significant improvements in exercise capacity relative to placebo in patients with SAP receiving beta-blocker (atenolol) therapy whether their resting HR was above or below 65 bpm (Tardif, 2012).

The BEAUTIFUL study

Design

The BEAUTIFUL study was a three-year, randomised, double-blind, placebo-controlled, international, multicentre study, evaluating the effects of lowering HR with ivabradine on CV events in patients with stable CAD and left ventricular systolic dysfunction (LVSD) on top of conventional CV treatment as recommended by ESC guideline on stable CAD (Fox, 2008b).

The primary endpoint was: first event among cardiovascular (CV) death, hospitalisation for acute myocardial infarction (MI), or hospitalisation for new onset or worsening HF.

Results

In this study, 10,917 patients received at baseline either beta-blockers (87%), aspirin (85%), ACE-inhibitors (80%), statins (74%) and/or diuretics excluding anti-aldosterone agents (59%) and were randomised to either ivabradine or placebo.

- In the randomised set (n=10,917), in CAD patients with left ventricular (LV) dysfunction who were receiving appropriate background CV medication, no effect of ivabradine was observed on the primary composite endpoint. In the pre-specified subgroup of high-risk patients (baseline HR ≥70 bpm), there was a trend towards improvement in the ivabradine group vs placebo, which was associated with significant reductions in hospitalisations for MI and hospitalisations for coronary revascularisation.
- In the post-hoc analysis on patients with symptomatic angina at randomisation (n=1,507), the subgroup closest to the population indicated in the European SmPC for ivabradine, ivabradine was combined with beta-blockers in 90% of patients, however not all patients achieved target dose: 48% patients on carvedilol (121/254) received at least half the target dose of 50 mg/day.
  In patients with symptomatic angina, a relative risk reduction (RRR) of 24% (HR 0.76 (95% CI [0.58 - 1.00]) was observed on the primary composite endpoint of CV death of hospitalisation for acute MI or new onset or worsening HF.
- A post-hoc analysis of the BEAUTIFUL study evaluated the effect of a beta-blocker in combination with ivabradine in all randomised patients with symptomatic angina at baseline who received the combination of beta-blocker with the randomised treatment ivabradine or placebo (n=1,350).
  A significant RRR of 40% (HR 0.60 (95% CI [0.41 - 0.87]) on the primary composite endpoint of CV death or hospitalisation for acute MI or new onset or worsening HF was observed.

Overall, in the BEAUTIFUL study, in the subgroup of patients with symptomatic angina, statistically significant improvements in the ivabradine group were observed on the primary composite endpoint of CV death or hospitalisation for acute MI or new onset or worsening HF. This effect was similar to the one observed with the combination beta-blocker and ivabradine.

The BEAUTIFUL sub-analysis

A post-hoc analysis of the BEAUTIFUL study was performed in all randomised patients with symptomatic angina at baseline who received the combination of carvedilol with the randomised treatment ivabradine or placebo (n=254).

Patients prescribed carvedilol associated with ivabradine showed a significant RRR of 60% (HR 0.40 (95% CI [0.19 - 0.83]) on the primary composite endpoint of CV death or hospitalisation for acute MI or new onset or worsening HF.

The favourable effect of carvedilol in combination with ivabradine on the primary composite endpoint of CV death or hospitalisation for acute MI or new onset or worsening HF was similar to the effect observed with beta-blocker in combination with ivabradine in patients with symptomatic angina at baseline.

The ADDITIONS study

The ADDITIONS study evaluated the efficacy, safety, and tolerability of ivabradine added to beta-blocker, and its effect on angina symptoms and quality of life (QoL) in routine clinical practice (Werdan, 2012).

This study included 2,330 patients with chronic SAP and limitations in their QoL. The parameters recorded included HR, number of angina attacks, nitrate consumption, tolerance, and QoL.

- All patients (n=2,330) were treated for 4 months with a flexible dose of ivabradine bid in addition to a beta-blocker (metoprolol 43%, bisoprolol 37%, nebivolol 13%, carvedilol 7%). Beta-blockers were usually prescribed a dosage considered optimal for the individual patient. A quarter of patients (24%) were at target beta-blocker dose, and 78% were at least 50% of the target dose. The target dose for carvedilol was defined as 100 mg/day. Of the 165 patients who were prescribed carvedilol (7%) the mean daily dose at baseline was 29.6 ± 16.6 mg.
  After 4 months, ivabradine (mean dose 12.37 ± 2.95 mg/day) reduced HR by 19.4 ± 11.4 to absolute HR 65.6 ± 8.2 bpm (p<0.0001). The number of angina attacks was reduced by 1.4 ± 1.9 per week (p<0.0001), and nitrate consumption by 1.9 ± 2.9 U per week (p<0.0001). At the end of the observation period, most of the patients were classified as Canadian Cardiovascular Society (CCS) grade I (68%) whereas 51% of patients were CCS grade II at baseline. Moreover, after 4 months, 84.1% of patients did not consume short-acting nitrates in the week prior to the last visit, as compared to 40.2% at baseline. The absolute change in EQ-5D improved by 0.17 ± 0.23 (p<0.0001).
  The ADDITIONS study demonstrated that in daily clinical practice, combining ivabradine with beta-blockers not only reduces HR, number of angina attacks, and nitrate consumption, but also improves the QoL in patients with SAP.
- After a one-year treatment with ivabradine and beta-blockers (n=901), during the ADDITIONS study follow-up, the same parameters were evaluated.
  From the 901 patients with chronic stable angina treated with ivabradine for one year, 53% had undergone a percutaneous coronary intervention or a coronary artery bypass grafting and 35% had a history of MI. All patients received beta-blockers (metoprolol 41%, mean daily dose (mdd) 109.6 mg; bisoprolol 39%, mdd 6.9 mg; nebivolol 13%, mdd 4.9 mg and carvedilol 7%, mdd 28.9 mg) along with concomitant standard therapy.
  At baseline, 49% of patients were classified CCS grade II, mean HR was 86.1 ± 12.6 bpm, a mean of 1.7 ± 2.2 angina attacks per week were reported, consumption of short-acting nitrates was 2.3 ± 3.2 units/week, and the EQ-5D index was 0.66 ± 0.28.
  After one year, ivabradine (mdd 12.53 ± 2.84 mg) had reduced HR to 65.4 ± 8.8 bpm, the number of angina attacks by 1.4 ± 2.5 per week (p<0.0001, Wilcoxon signed rank test), and nitrate consumption by 1.9 ± 3.1 units/week (p<0.0001). EQ-5D index had improved by 0.18 ± 0.27 (p<0.0001) and 61% of patients were classified CCS grade I.
  Moreover, the treatment effect of ivabradine on HR and angina symptoms was independent of background beta-blocker dose.
  Results at one year of the ADDITIONS study are therefore consistent with the favourable results observed at 4 months with the combination of ivabradine and beta-blockers.

The REDUCTION sub-analysis

Design

The REDUCTION study was a multicentre, prospective, open-label, non-interventional study to evaluate the efficacy and safety of ivabradine in everyday routine practice (Koester, 2010).
A number of 4,954 patients treated with ivabradine in sinus rhythm and a need for symptomatic treatment of chronic SAP were included and followed by 1,503 general practitioners, internal medicine physicians and cardiologists in private practices in Germany. Treatment was initiated with ivabradine 5 mg bid and increased after 2-4 weeks up to a target dose of 7.5 mg bid. A lower dose of 2.5 mg bid was suggested in patients ≥75 years, patients with a renal insufficiency having a creatinine clearance <15 ml/min, patients with a HR continuously <50 bpm during treatment, or patients with symptomatic bradycardia

Results

In a sub-analysis of REDUCTION, 344 patients received a beta-blocker in addition to ivabradine. The mean duration of CAD in the group was 6.3 ± 6.2 years and the mean duration of angina pectoris was 4.2 ± 4.6 years.

The most frequently used beta-blockers and average daily doses (add) were metoprolol (41%) add 99.0 mg, bisoprolol (27%) add 5.7 mg, carvedilol (9%) add 22.5 mg and nebivolol (9%) add 5.1 mg. Co-medication beside the beta-blocker and ivabradine treatment during the observation period was given in 330 patients (96%), including acetylsalicylic acid, ACE inhibitor, statins, diuretics, etc.

The efficacy results show that the HR was reduced by 12.4 ± 11.6 bpm from 84.3 ± 14.6 to 72.0 ± 9.9 bpm between baseline evaluation and the second follow-up visit after 4 months (p<0.0001). No

marked changes were seen in the ECG parameters. At the time of follow-up visit 4 months later, the frequency of angina pectoris episodes had been significantly reduced under ivabradine therapy (from 2.8 ± 3.3 to 0.5 ± 1.3 attacks per week, p<0.0001). Efficacy and tolerance were graded as 'very good/good' for 96 and 99% of the patients treated.

In conclusion, ivabradine effectively reduces HR and angina pectoris in combination with beta-blockers and is well tolerated by patients in everyday practice. These results suggest that ivabradine is an effective and safe adjunct to a beta-blocker therapy in symptomatic CAD patients along with their current beta-blocker treatment.

2. Chronic Heart Failure

The efficacy of combining ivabradine with a beta-blocker in CHF was demonstrated during the clinical development of ivabradine.

Clinical studies and sub-analysis supporting the combined use of carvedilol and ivabradine in CHF are summarised in Table 8 and detailed hereafter.

Table 8. Clinical studies supporting the combined use of carvedilol and ivabradine in CHF

Study name	Patient number	Duration	Design	Treatment groups
SHIFT	• 6,505 in FAS	1-4 years	RDB morbi-mortality	• ivabradine • placebo
SHIFT sub analysis	• 4,150 w HR≥75 • 2,596 w carvedilol • 1,318 w carvedilol and HR≥75		RDB posthoc morbi-mortality	• ivabradine+carvedilol • placebo+carvedilol
CARVIVA HF	121	3 months	Randomised Open	• carvedilol • ivabradine • ivabradine+carvedilol
BAGRIY	• 41 • 69	3 months 5 months	Non interventional Open	• carvedilol • ivabradine+carvedilol

The SHIFT study

Design

The SHIFT study was an international, randomised, double-blind, parallel-arm, event-driven morbidity mortality study, designed to assess the benefits of ivabradine in patients with moderate to severe CHF and LVSD and receiving currently recommended therapy for this disease (Swedberg 2010a, Swedberg 2010b, Swedberg 2012; Böhm, 2010, Böhm, 2012; Borer, 2012; Komajda 2013).

The main selection/inclusion criteria included: systolic CHF (all aetiologies of CHF included, except for congenital heart disease, severe aortic or mitral stenosis, severe aortic regurgitation, or severe primary mitral regurgitation), with NYHA class II, III or IV, and in stable clinical condition for ≥4 weeks, with optimal and unchanged CHF medications and dosages for ≥4 weeks, with documented hospital admission for worsening HF within 12 months before selection, in sinus rhythm at selection with resting HR ≥70 bpm (ECG documentation), documented LVSD (LVEF ≤35%) within 3 months before inclusion.

Patients had to be on stable background treatment for ≥4 weeks at entry. Background treatment had been up-titrated as far as contraindications and tolerability would allow, and there was a particular emphasis on optimising beta-blocker dosage as close to target as possible for each patient before initiation of study treatment. Against this background treatment, patients were randomly allocated to receive ivabradine (initiated at 5 mg bid, which could be adjusted up or down to 7.5 mg bid or 2.5 mg bid, according to resting HR and/or symptoms of bradycardia at 14 or 28 days and then at every 4-monthly visit thereafter) or matching placebo.

The primary criteria were the composite endpoint of the time to first event among CV death (including death from unknown cause) or hospitalisation for worsening HF.

Results
In the **randomised set (RS)** (n=6,505), over a mean follow-up duration of 22 months, results demonstrated that oral ivabradine, when added to guideline-recommended treatment, reduces mortality and rehospitalisation associated with CHF in patients with elevated HR (≥70 bpm), as per below Table 9.

Table 9. SHIFT study results in the RS (N=6,505) - Effect of ivabradine on cardiovascular outcomes

	Ivabradine (N=3,241)	Placebo (N=3,264)	HR (95% CI)	P-value
CV death or hospitalisation for worsening HF*	793 (24.5%)	937 (28.7%)	0.82 (0.75 - 0.90)	<0.0001
Hospitalisation for worsening HF	514 (15.9%)	672 (20.6%)	0.74 (0.66 - 0.83)	<0.0001
CV death	449 (13.9%)	491 (15.0%)	0.91 (0.80 - 1.03)	0.128

HR = hazard ratio based on an adjusted Cox's proportional hazards model with prognostic factors as covariates.
CI = confidence interval. n: number of patients reaching the endpoint; %: global incidence rate = (n/N) x 100
*Main analysis: primary Composite endpoint

The mean HR at baseline was around 80 bpm in the RS. During the study, it was decreased by -15.4 ± 10.7 bpm in the ivabradine group, between baseline and day 28, vs -4.6 ± 10.6 bpm in the placebo group, corresponding to a statistically and clinically significant between-group difference of -10.9 bpm (95% CI [-11.4 - -10.4]). This HR lowering effect was sustained during the study as at the last post-randomisation visit. A greater proportion of patients showed an improvement between baseline and last post-randomisation visit in NYHA classification in the ivabradine group than in the placebo group (27.6% vs 24.0%, p=0.0010, complementary test) in the RS. At the last post-randomisation visit, the analyses of patient global assessments consistently showed a greater percentage of patients with improved symptoms in the ivabradine group than in the placebo group (71.8% vs 67.6%, p=0.0005, complementary test).

In the **sub-group of patients with a baseline heart rate ≥75 bpm** (n=4,150) ivabradine significantly improved all outcomes, including CV death as per Table 10. The demographic data and baseline characteristics of this sub-group did not differ substantially from the RS in the majority of criteria and there were no relevant differences between the treatment groups

Table 10. SHIFT sub-study in patients with HR ≥75 bpm (N=4,150) - Effect of ivabradine on cardiovascular outcomes

	Ivabradine (N=2,052)	Placebo (N=2,098)	HR [95 % CI]	p-value
CV death or hospitalisation for worsening HF*	545 (26.6%)	688 (32.8%)	0.76 (0.68 - 0.85)	<0.0001
Hospitalisation for worsening HF	363 (17.7%)	503 (24.0%)	0.70 (0.61 - 0.80)	<0.0001
CV death	304 (14.8%)	364 (17.4%)	0.83 (0.71 - 0.97)	0.0166

HR = hazard ratio based on an adjusted Cox's proportional hazards model with prognostic factors as covariates.
CI = confidence interval.
n: number of patients reaching the endpoint; %: global incidence rate = (n/N) x 100
* Primary Composite endpoint

A **post-hoc analysis of the SHIFT study** evaluated the effect of beta-blocker according to the type of beta-blocker in combination with ivabradine in all randomised patients who received the combination of beta-blocker with ivabradine or placebo at randomisation (n=2,886). Outcomes were explored in 4

subgroups according to the beta-blocker received at baseline: 2,596 patients on carvedilol (45% of all patients receiving beta-blocker), 1,483 patients (26%) on bisoprolol, 1,424 (25%) on metoprolol (tartrate and/or succinate), and 197 (3%) on nebivolol.

The analysis of events was performed exclusively while on the combination (i.e. only on events that occurred between the first and last (+2 days) concomitant intake of beta-blocker and the study treatment).The favourable effect of beta-blocker in combination with ivabradine compared with beta-blocker in combination with placebo on the main composite endpoint of CV death or hospitalisation for worsening HF was consistent whatever the beta-blocker (HRs 0.75–0.89, p for interaction=0.86) (Bocchi, 2015).

Overall, in the SHIFT study, statistically significant improvements in the ivabradine groups were demonstrated for the primary composite endpoint (i.e. hospitalisation for worsening HF and CV death) in the RS and in the subgroup of patients with HR ≥75 bpm at baseline.

In addition, analysis of the SHIFT population shows that the combination of beta-blocker + ivabradine in patients with systolic HF is associated with an improvement in the primary composite endpoint, regardless of the individual beta-blocker co-prescribed with ivabradine.

The SHIFT carvedilol sub-analysis
A post-hoc analysis of the SHIFT study was performed on the 2,596 patients receiving carvedilol, the most frequently used beta-blocker, in combination with ivabradine or placebo. Most also received RAS inhibitors (77% on ACE inhibitor and 15% on ARB), diuretics (87%), and MRA (70%).
Ivabradine + carvedilol significantly reduced, vs placebo + carvedilol, the incidence of the main composite endpoint of CV death or hospitalisation for worsening of HF in patients with stable moderate to severe CHF (NYHA class II, III or IV, resting HR ≥70 bpm and LV systolic dysfunction) receiving other recommended therapies for their disease. The RRR of 20% (HR 0.80 (95% CI [0.68 - 0.94]) was clinically and statistically significant (p=0.008).
The HR lowering effect of ivabradine + carvedilol (-14 bpm after 14 days) was maintained throughout the study.

In the subgroup of patients with HR ≥75 bpm and receiving carvedilol at baseline (n=1,654), the incidence of the primary composite endpoint was significantly lower in the ivabradine + carvedilol group than in the placebo + carvedilol group (23.2% versus 28.1% respectively). The estimate of the hazard ratio was 0.79 (95% CI [0.65 - 0.95]), corresponding to a statistically significant 21% RRR of the primary composite endpoint in the ivabradine + carvedilol group compared to the placebo + carvedilol group (p=0.0139).

In summary, in the SHIFT population, the favourable effect of carvedilol + ivabradine on the primary composite endpoint (CV death or hospitalisation for worsening HF) is similar to the effect observed with beta-blocker + ivabradine. The favourable effect of carvedilol + ivabradine is also observed in patients with HR ≥75 bpm at baseline.

The CARVIVA HF study
Design
The CARVIVA HF study is a randomised, open-label, endpoint study to evaluate the effect of carvedilol, ivabradine and the combination of both on exercise capacity in 121 patients with HF (Volterrani, 2011). At baseline, most patients (n=115, 95%) were on ACE inhibitors. Sixty-six patients (55%) were on beta-blockers (bisoprolol, carvedilol, or metoprolol) but with suboptimal dose of ACE inhibitors at the selection visit. After a run-in phase, patients were randomly allocated to 3 groups, carvedilol up to 25 mg bid (n=38), ivabradine up to 7.5 mg bid (n=41); and carvedilol/ivabradine up to 12.5 mg/7.5 mg bid (n=42).
The primary endpoints were the distance covered in the 6-min walking test and maximal oxygen consumption (MVO2) on the cardiopulmonary exercise test.

Results
The distance walked on the 6-min walking test and the exercise time on MVO2 test significantly improved in the ivabradine and combination groups (both p<0.01 vs baseline), as did peak VO2 and ventilatory anaerobic threshold (VAT) (p<0.01 for ivabradine and p<0.03 for combination vs carvedilol, respectively). No changes in these parameters were found in the group with carvedilol alone. The

maximal dose was more frequently tolerated in patients receiving ivabradine (36/41) than in those receiving carvedilol (18/38) or combination therapy (32/42) (p<0.01 ivabradine vs carvedilol). HR was reduced in all three groups, but to a greater extent by the combination.

In addition, NYHA class improved substantially more in patients on ivabradine and combination therapy compared with those on carvedilol. An improvement in patients receiving ivabradine or the combination (from 4.3 ± 0.5 to 6.7 ± 0.9, p<0.01) vs baseline for ivabradine, and from 4.7 ± 0.8 to 6.1 ± 6, p<0.02 for combination was observed in the assessment of QoL. However no changes were detected in patients receiving carvedilol (from 4.6 ± 0.8 to 4.1 ± 0.6, p=NS).

The physical and social domains of the MacNew Quality of Life after Myocardial Infarction (QLMI) scale improved in patients treated with ivabradine and the combination but not in those on carvedilol (physical domain: 36 ± 11%, 27 ± 9%, and −7 ± 4%, respectively, p<0.01; ivabradine and combination vs carvedilol; social domain: 41 ± 8%, 32 ± 12, and −9 ± 5%, respectively, ivabradine and combination vs carvedilol, p<0.01).

The BAGRIY study
The Bagriy study included for the first 3 months 41 patients in sinus rhythm, with previous MI, CHF (NYHA class II-III) and HR ≥70 bpm who were treated for 3 months with carvedilol (n=21) or carvedilol + ivabradine (n=20) (Bagriy, 2013).
Patients had not been taking beta-blockers for ≥2 months and were ivabradine naïve. In addition, carvedilol 3.125 mg bid was initiated on top of standard therapy, and doubled every 2 weeks until 25 mg bid or maximum tolerated dose was reached. Ivabradine 5 mg bid was prescribed 1-2 days after carvedilol initiation, and up titrated to 7.5 mg, bid, one month later if HR ≥70 bpm.
The addition of ivabradine to carvedilol in CHF patients resulted in a shorter up-titration of the beta-blocker, higher final beta-blocker dose, greater HR reduction and a better exercise capacity as per Table 11.

Table 11. Bagriy study results at 3 months (N=41) - Effect of carvedilol versus carvedilol + ivabradine in CHF patients

Parameter	carvedilol (N=21)	carvedilol + ivabradine (N=20)
Patients at ≥50 % of carvedilol target dose, (N(%))	8 (38%)	16 (80%)*
Duration of carvedilol uptitration (months)	27 ± 0.7	1.9 ± 0.5*
Final dose of carvedilol (mg/day)	29.6 ± 6.2	37.4 ± 8.4*
Δ HR (bpm)	7.2 ± 2.4	12.9 ± 3.5*
Δ distance in the 6-min walking test (m)	32.4 ± 11.7	68.3 ± 12.7*

*p<0.05

The follow-up of Bagriy study at 5 months was performed in 69 patients with CHF: 36 patients receiving carvedilol alone and 33 patients receiving carvedilol/ivabradine. All patients were in sinus rhythm and angina was present in 55 patients.
The mean dosage of ivabradine at 5 months was 12.2 ± 2.1 mg/day. Patients receiving carvedilol/ivabradine achieved higher dosages of carvedilol over the study (37.8 ± 13.9 mg/day) than the group receiving carvedilol alone (30.9 ± 15.3 mg/day) (p=0.049).
Patients receiving carvedilol/ivabradine had lower resting HR at 5 months (61.6 ± 3.1 vs 70.2 ± 4.4 bpm, p<0.05) than those on carvedilol alone. Adding ivabradine to carvedilol in patients with HF was also associated with better exercise capacity, with significant increases in the 6-min walk test. Moreover, addition of ivabradine shortly after initiation of carvedilol significantly improved left ventricular ejection fraction (LVEF) (p<0.05) and improved the up-titration of the beta-blocker.

IV.5 Clinical safety

Monocomponents
Carvedilol
Common adverse reactions are: bronchitis, pneumonia, upper respiratory tract infection, urinary tract infection, anaemia, weight increase, hypercholesterolaemia, impaired blood glucose control (hyperglycaemia, hypoglycaemia) in patients with pre-existing diabetes, depression, depressed mood,

visual impairment, lacrimation decreased (dry eye), eye irritation, bradycardia, oedema, hypervolaemia, fluid overload, as well as orthostatic hypotension, disturbances of peripheral circulation (cold extremities, peripheral vascular disease, exacerbation of intermittent claudication and Reynaud's phenomenon), dyspnoea, pulmonary oedema, asthma in predisposed patients, pain in extremities and pain in administration site conditions. Among gastrointestinal disorders, nausea, diarrhoea, vomiting, dyspepsia and abdominal pain were reported. Renal failure and renal function abnormalities in patients with diffuse vascular disease and/or underlying renal insufficiency, micturition disorders are also seen commonly.

Dizziness, headache, asthenia, cardiac failure, hypotension are reported to be *very common*.

Ivabradine
About 15% of patients experience visual symptoms, a transient, enhanced brightness in a limited area of the visual field known as luminous phenomena or phosphenes (Riccioni, 2009), because the drug also blocks a retinal current with similar characteristics. This side effect is transient and reversible, but in 1% of patients, ivabradine has to be discontinued.

The most *commonly* reported adverse reactions during treatment are: headache, generally during the first month of treatment, dizziness possibly related to bradycardia, blurred vision, bradycardia, AV 1st degree block (ECG prolonged PQ interval), ventricular extra systoles, atrial fibrillation, uncontrolled BP.

In fact, ivabradine has a favourable tolerability profile due to selective interaction with I_f channels (Riccioni, 2012).

Combination
Clinical safety in healthy volunteers
The combined administration of ivabradine and carvedilol was tested in the five pharmacokinetic studies performed for the clinical development of the carvedilol/ivabradine fixed dose combination, including in total 364 healthy volunteers. The results show that the FDC is well tolerated, with no unexpected adverse events as compared to each mono component.

Clinical safety in patients
Safety data regarding the free combination of carvedilol and ivabradine in SAP and CHF patients are available from specific sub-analysis of BEAUTIFUL and SHIFT morbi-mortality trials. They are presented below, as well as safety data supporting the safety of ivabradine combined with a beta-blocker, evaluated during the clinical development of ivabradine.

The BEAUTIFUL angina carvedilol sub study
A post-hoc analysis of the BEAUTIFUL study evaluated the safety of the free combination of carvedilol and ivabradine, among the patients with symptomatic angina at baseline who received carvedilol in combination with ivabradine or placebo.

The Safety Set 1 consisted of 288 patients: 146 patients in the ivabradine + carvedilol group and 142 in the placebo + carvedilol group.

The safety profile of ivabradine combined with carvedilol in SAP remains similar to the known safety profile of ivabradine, and did not raise any new safety concerns as compared to carvedilol alone.
These data on the free combination do not suggest any substantial difference in the safety profile from what is known for both mono components.

The ASSOCIATE study
Ivabradine in combination with atenolol was well tolerated in the ASSOCIATE study. The number of patients withdrawn from treatment owing to EAEs were 13 (2.9%) in the ivabradine group and 4 (0.9%) with placebo (difference not significant). Among these EAEs, there were five SAEs in the ivabradine group (1.1%) and three in the placebo group (0.7%). The most frequent causes of withdrawal related to bradycardia [ivabradine five patients (1.1%), placebo none] and unstable or aggravated angina pectoris [ivabradine three patients (0.7%), placebo one (0.2%)]. The most frequent EAEs were those related to bradycardia, reported by 19 patients (4.2%) in the ivabradine group (12 patients with ivabradine 5 mg bid, 7 patients with ivabradine 7.5 mg bid) and 2 patients (0.5%) with

placebo). Only 1.1% of AEs related to bradycardia were symptomatic. Phosphenes, (luminous phenomena described as increases in brightness in limited areas of the visual field) and blurred vision, which have been associated with ivabradine treatment in previous studies, were reported by 9 patients (2%) in the ivabradine group and four (0.9%) in the placebo group. There were small, non-significant changes in supine BP from baseline to the last value on treatment (from 127.3 ± 12.0 to 128.3 ± 14.8 mmHg for systolic BP and from 78.6 ± 7.4 to 78.1 ± 8.0 mmHg for diastolic BP with ivabradine, and from 127.6 ± 12.6 to 126.1 ± 14.8 and 78.1 ± 7.2 to 78.1 ± 7.5 mmHg, respectively, with placebo). There was one death during the treatment period, a fatal suicide in the ivabradine group and two deaths after the last study drug intake in the placebo group (Tardif, 2009).

The REDUCTION sub-analysis

In the sub-study analysis of the REDUCTION trial, 344 patients received a beta-blocker in addition to ivabradine. Eight suspected ADRs not classified as severe were reported in 5 patients. The most common were nausea and dizziness and 1 patient developed headache. None of the patients complained about luminous phenomena (phosphenes). A cardiac ADR was reported in 1 patient with sinus bradycardia and there were no other cardiac side effects. There were no SAEs and no deaths were reported. After discontinuation of the drug, all side effects were reversible without any clinical sequelae (Koester, 2010).

The ADDITIONS study

In the ADDITIONS study, the subgroup of patients receiving both carvedilol and ivabradine consisted of 165 patients (Werdan, 2012). Suspected ADRs were documented in 14 patients and none were severe. The tolerability was rated as “very good/good” for 72%/28% of patients respectively (Werdan, 2011).

Chronic Heart Failure

The SHIFT carvedilol sub-analysis

In the SHIFT study, 45% of all patients receiving beta-blocker were treated with carvedilol. In a post-hoc analysis of these patients, the Safety Set consisted of 2,744 patients: 1,383 patients in the ivabradine/carvedilol group and 1,361 in the placebo/carvedilol group. In the Safety Set, 1,036/1,383 patients (74.9%) in the ivabradine + carvedilol group and 984/1,361 patients (72.3%) in the placebo + carvedilol group reported at least one EAE.

The safety profile of ivabradine combined to carvedilol in CHF remains similar to the known safety profile of ivabradine, and did not raise any new safety concerns as compared to carvedilol alone.

These data on the free combination do not suggest any substantial difference in the safety profile from what is known for both mono components.

Prescription data

Data regarding the prescriptions of carvedilol in clinical practice are available from the Intercontinental marketing service (IMS) database and from international registries on CHF and SAP patients.

Among all beta-blockers, carvedilol is the second beta-blocker prescribed for SAP in a twice daily administration (2.6 million prescriptions - IMS 2012, 13 countries). In CHF, carvedilol is the most widely used beta-blocker in a twice daily administration (2.2 million prescriptions - IMS 2013, 13 countries).

According to 1-year IMS data collected in September 2014 in 4 EU countries (France, Germany, Italy and Spain) (Table 12), ivabradine and carvedilol co-prescriptions have reached up to 98,278 prescriptions, representing 12.8% of the total prescriptions of ivabradine + a beta-blocker. In these countries, the co-prescriptions reached 51,025 in September 2012 and 93,293 in September 2013, which indicates an increasing tendency to co-prescribe both drugs.

Table 12. Co-prescriptions of ivabradine + beta-blocker & ivabradine + carvedilol; All indications; IMS, in 4 EU Countries

Month/Year	Number of co-prescriptions ivabradine + ß-blocker	Number of co-prescriptions ivabradine + carvedilol
09/2012	406,638	51,025
09/2013	643,360	93,293
09/2014	769,587	98,278

Co-prescriptions per dose of ivabradine + carvedilol are presented in Table 13.

Table 13. Co-prescriptions of ivabradine + carvedilol per rank of prescription of the different dosages of the free combination; All indications; IMS, in 4 EU countries

Dosage of the free combination (carvedilol + ivabradine)	Total (N=98,278)	%
6.25/5	43,182	43.94%
25/5	27,843	28.32%
6.25/7.5	14,593	14.85%
25/7.5	7,988	8.13%
12.5/5	3,245	3.30%
12.5/7.5	675	0.69%
50/5	466	0.47%
3.125/5	381	0.39%
3.125/7.5	-	-
50/7.5	-	-

Safety evaluation
Data from the MAH Pharmacovigilance database on post-marketing experience with Procoralan (ivabradine) from 25 October 2005 (first MA) to 25 October 2014, totalise 6,663 events in 3,033 patients, out of whom, 110 patients treated concomitantly with carvedilol.

The most frequently reported reactions in the 110 patients on carvedilol and ivabradine are the following events, all listed for either ivabradine or carvedilol:
Bradycardia (including PT bradycardia, sinus bradycardia and HR decreased) (10.3% of all events), fatigue/asthenia (5.6%), dizziness (4.7%), hypotension (including PT hypotension, BP decreased and BP systolic decreased) (4.0%), dyspnoea (3.7%), photopsia (3.0%), malaise/presyncope (2.7%) and cardiac failure (including PTs cardiac failure, cardiac failure acute and cardiac failure congestive) (2%).

As expected considering the HR-lowering mechanism of action of both drugs, the most frequent adverse drug reaction (ADR) was bradycardia and related symptoms. No safety signal was detected regarding the unlisted events.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Carivalan.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Bradycardia • Phosphenes/blurred vision • 2nd and 3rd degree atrioventricular blocks (AVB II and III) • ECG prolonged QT interval • Increase in blood pressure in hypertensive patients

	• Atrial fibrillation • Hypoglycaemia • Anaphylactic shock
Important potential risks	• Supraventricular tachyarrhythmia's other than atrial fibrillation • Immune disorders • Severe ventricular arrhythmia • Myocardial infarction
Missing information	• Children and adolescents (<18 years old) • Pregnant and lactating women • Severe hepatic insufficiency • Severe renal impairment • CHF patients with intra-ventricular conduction defects

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.7 Discussion on the clinical aspects

The combined use of carvedilol and ivabradine is well established. The literature data submitted by the MAH support the use of the combination. The pharmacokinetic studies investigating bioequivalence and interaction potential show satisfactory results: a single tablet of the Carivalan FDC can be used instead of co-administration of the separate products Procoralan and Dilatrend. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Carivalan 6.25 mg/5 mg, 6.25 mg/7.5 mg, 12.5 mg/5 mg, 12.5 mg/7.5 mg, 25 mg/5 mg and 25 mg/7.5 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are considered an approvable fixed dose combination. Both carvedilol and ivabradine are well known, established substances, which are used as a combination in clinical practice.

A pharmacokinetic study showed that there is no pharmacokinetic interaction between the individual compounds of this fixed-dose combination product. The proposed combination product was demonstrated to be bioequivalent with co-administration of the separate reference products Dilatrend and Procoralan. The clinical data on concomitant use are considered sufficient to support the FDC combination in patients with SAP or CHF who are on a stable fixed dose regimen with both monocomponents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that the benefit-risk balance for this FDC is positive, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 9 November 2016.

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STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE – SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the name of a marketing authorisation holder in Greece	NL/H/3546/IA/001/G	IA	16-12-2016	16-1-2017	Approval	No
Change in the (invented) name of the medicinal Product in Cyprus, Luxembourg and Slovakia.	NL/H/3546/001-006/IB/002/G	IB	23-2-2017	25-3- 2017	Approval	No