CBG MEB

Public Assessment Report

Scientific discussion

Arparial 25 mg/5 mg, 50 mg/5 mg, 25 mg/7.5 mg and 50 mg/7.5 mg, film-coated tablets

(metoprolol tartrate/ivabradine hydrochloride)

NL/H/3038/001-004/DC

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This module reflects the scientific discussion for the approval of Arparial 25 mg/5 mg, 50 mg/5 mg, 25 mg/7.5 mg and 50 mg/7.5 mg, film-coated tablets. The procedure was finalised on 6 May 2015. 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 22.

List of abbreviations

AUC_{last}	Area under the plasma concentration-time curve from time zero to the last measurable concentration
BSE	Bovine Spongiform Encephalopathy
CCS	Canadian Cardiovascular Society
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
Cmax	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
CV	Coefficient of Variation
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
EMA	European Medicines Agency
eMC	Electronic Medicines Compendium
ERA	Environmental Risk Assessment
ESC	European Society of Cardiology
ETT	Exercise Tolerance Test
EU	European Union
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
ICH	International Conference of Harmonisation
IMS	Intercontinental Marketing Service
IV	Intravenous
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
MHRA	Medicines and Healthcare products Regulatory Agency of the UK
NICE	National Institute for Health and Care Excellence
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PL	Package Leaflet
RH	Relative Humidity
QP	Qualified Person
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TED	Total Exercise Duration
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
$t_{½}$	Half-life

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Arparial 25 mg/5 mg, 50 mg/5 mg, 25 mg/7.5 mg and 50 mg/7.5 mg, film-coated tablets from Les Laboratoires Servier.

The product is indicated for the symptomatic treatment of chronic stable angina pectoris as substitution therapy in adult patients with normal sinus rhythm already controlled by metoprolol and ivabradine taken concomitantly at the same dose level.

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. In these kinds of applications the results of new clinical trials relating to that combination are provided. However, it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

The reference products used for this marketing application are Corlentor/Procoralan (ivabradine) and Lopresor (metoprolol). Ivabradine is registered through a centralized procedure (2005) as Procoralan/Corlentor. Lopresor (metoprolol) is the originator product which was first registered in Europe in the 1970's.

The combined use of metoprolol and ivabradine in patients with stable angina pectoris is justified as both drug substances are well established in medical use and co-prescription is common in this indication. The combination of ivabradine with a beta-blocker in the symptomatic treatment of chronic stable angina pectoris 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. This combination is also supported by clinical data.
The proposed metoprolol/ivabradine FDC would allow a simplification of therapy by decreasing the number of individual dose units to be taken by patients and may improve patient compliance to treatment of this chronic disease.

The clinical development programme consisted of two 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 metoprolol/ivabradine FDC and the free combination, i.e. the two tablets administered concomitantly; and one interaction study performed in accordance with "Guideline on the investigation of pharmacokinetic drug interactions" (CPMP/EWP/560/95/Rev. 1 Corr., 2012).

The concerned member states (CMS) involved in this procedure were Czech Republic, France, Germany, Hungary, Italy, Latvia, Poland, Romania and Slovakia.

The marketing authorisation is granted based on article 10b of Directive 2001/83/EC.

A national scientific advice meeting took place with the MEB in May 2013. The rationale of the FDC and the clinical development were discussed.

The proposed metoprolol/ivabradine FDC is intended for treatment of stable angina pectoris as substitution therapy in adult patients. A PIP waiver was granted by the Paediatric Committee on 28 May 2013 for all subsets of the paediatric population (EMEA-001405-PIP01-12).

II. QUALITY ASPECTS

II.1 Introduction

Arparial 25 mg/5 mg is a white, round, film-coated tablet of 7.3 mm diameter engraved with '1' on one face and ☞ on the other. Each film-coated tablet contains 25 mg of metoprolol tartrate and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
Arparial 50 mg/5 mg is a white, round, film-coated tablet of 8.5 mm diameter engraved with '2' on one face and ☞ on the other. Each film-coated tablet contains 50 mg of metoprolol tartrate and 5 mg of ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
Arparial 25 mg/7.5 mg is a white, oblong film-coated tablet of 9.3 mm long and 5.8 mm wide engraved with '3' on one face and ☞ on the other. Each film-coated tablet contains 25 mg of metoprolol tartrate and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).
Arparial 50 mg/7.5 mg is a white, oblong film-coated tablet of 10.8 mm long and 6.7 mm wide, engraved with '4' on one face and ☞ on the other. Each film-coated tablet contains 50 mg of metoprolol tartrate and 7.5 mg of ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).

The film-coated tablets are packed in PVC/PVDC/aluminum blisters or high density polyethylene bottles equipped with a polypropylene stopper, containing a desiccant.

The excipients are:
Core – pregelatinised starch (maize), microcrystalline cellulose, maltodextrin, colloidal anhydrous silica (E551), magnesium stearate (E470b).
Film-coating – glycerol (E422), hypromellose (E464), macrogol 6000, magnesium stearate (E470b), titanium dioxide (E 171).

The formulations are not proportional. The amount of ivabradine is less than 5% of the tablet core weight. The amount of the filler (cellulose) is changed to account for the difference in the amount of ivabradine; the amounts of other core excipients remaining the same for the concerned strengths.

II.2 Drug Substance

The active substances are metoprolol and ivabradine. Metoprolol is an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is a white or almost white crystalline powder or colourless crystals and shows polymorphism. However, the manufacturer always produces the same crystal form. Metoprolol tartrate is very soluble in purified water.

The CEP procedure is used for the active substance metoprolol. 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 European Pharmacopoeia.

Ivabradine is an established active substance not described in any pharmacopoeia, and for which full documentation has been provided in the dossier. It is a white to slightly yellow powder which is freely soluble in water, but partly re-precipitates after 1 h at room temperature. Ivabradine is a chiral compound with one chiral center, it is a single isomer, has the S-configuration, and has a specific optical rotation of +28º, at 20 °C.

Manufacturing process
For metoprolol a CEP has been submitted; therefore no details on the manufacturing process have been included.
Ivabradine hydrochloride is manufactured in a three step process. No class-I solvents are used during the synthesis. Ivabradine hydrochloride has been adequately characterized and acceptable specifications have been adopted for the solvents and reagents. However, during the application procedure, concerns were raised regarding one of the intermediate substances used in the manufacturing process. It was concluded that an audit should be performed at the manufacturing site of this intermediate, and no ivabradine hydrochloride manufactured with this intermediate substance

will be used in the manufacturing of the finished product before the new audit in this site is performed and an updated QP declaration is provided.

Quality control of drug substances

The drug substance specification for metoprolol is in line with the Ph. Eur., the additional requirements of the CEP, and a limit for particle size. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full-scale batches.

The drug substance specification for ivabradine hydrochloride has been established in-house by the MAH. In view of the route of synthesis and the various European guidelines the specification is acceptable. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two pilot-scale and three production-scale batches.

Stability of drug substances

The active substance metoprolol is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Stability data for ivabradine hydrochloride have been provided for two pilot-scale batches and three full-scale batches. The pilot batches and one full-scale batch were stored at 25°C/60% RH (36 months), 30°C/60%RH (12 months), 30°C/70% RH (36 months) and at 40°C/75% RH (6 months). The other two full-scale batches were stored at 25°C/60% RH (36 months), 30°C/75% RH (36 months) and 40°C/75% RH (6 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 re-test period of 3 years is acceptable, based on available completed 36 months long-term stability studies. No specific temperature restrictions are required as the drug substance is found stable when stored at both 25°C/65% RH and 40°C/75% RH.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. Compatibility of the drug substances with each other and with the excipients was demonstrated. A formulation was developed based on the formulation of the ivabradine monoproduct (Procoralan). Wet granulation was selected for the manufacturing process. The pharmaceutical development of the product has been adequately performed.

The test batches used in the bioequivalence study have the same quantitative composition and are manufactured according to the proposed manufacturing process. The batch sizes of the biobatches are acceptable given the proposed batch size of the commercial batches.

Comparative *in vitro* dissolution tests were carried out in order to compare the dissolution profiles of the metoprolol/ivabradine FDC batches with those of metoprolol tartrate and ivabradine used for the bioequivalence study. Dissolution studies on the batches used in the bioequivalence study do not show comparable dissolution except for ivabradine for the 25 mg/7.5 mg strength at all three pH values and metoprolol at pH 4.5 for both strengths, however, bioequivalence was demonstrated *in-vivo*.

The biowaiver of strengths is supported by dissolution studies in which the 25 mg/5 mg strength is compared to the 25 mg/7.5 mg strength and the 50 mg/5 mg strength is compared with the 50 mg/7.5 mg strength. In both cases the dissolution profiles for both drug substances are comparable, at pH 1.2, 4.5 and 6.8. As the dissolution profiles are similar, the biowaiver for the 25 mg/5 mg and 50 mg/5 mg strengths is acceptable. The pharmaceutical development has been described in sufficient detail.

Manufacturing process

The metoprolol tartrate/ivabradine hydrochloride tablets are manufactured by a wet granulation process. The drug substances are mixed with microcrystalline cellulose and pregelatinized starch and granulated with maltodextrin solution, dried and sieved. Then the granulate is mixed, and the lubricated granulate is compressed into tablets. The tablets are film-coated and packed. Validation studies have been performed on three pilot batches per strength (total of 12 batches) at an industrial site.

The manufacturing process has been described in sufficient detail. All in-process controls and relevant process parameters are acceptable. The product is manufactured using conventional manufacturing

techniques. Process validation for full-scale batches will be performed post authorisation, the required process validation scheme has been submitted.

Control of excipients
The excipients comply with the Ph. Eur. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, average mass, identification of drug substances, assay of drug substances, degradation products content, uniformity of dosage units, dissolution and microbiological quality. The product specifications for release and end-of-shelf life for the final products have been provided, these are not identical. The limits for degradation products have been raised at end of shelf life compared to release to cover for degradation that has been observed during stability studies. The specification is acceptable. The analytical methods have been adequately described and validated.
Batch analytical data from the proposed production site have been provided on three pilot-scale batches per strength (total of 12 batches) demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product has been provided on eight pilot-scale batches (two for each strength) stored at 25°C/60% RH (24 months), 30°/65% RH (24 months), 30°/75% RH (24 months), and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PVC/PVDC/Aluminium blister packs or HPDE bottle with desiccant.
The proposed shelf-life of 18 months, without any specified storage conditions, for the tablets packaged in PVC/PVDC blisters and in HDPE bottles can be accepted. During storage an increase in the specified degradation products from ivabradine is observed, under all storage conditions in both packages, and for all strengths, however, all staying within specification up to 18 months under long term conditions. The photostability of the drug product was examined in accordance with the Note for Guidance on Photostability Testing (illumination and UV exposure). As no degradation was observed for any of the batches studied, the drug product can be considered photostable.
In-use stability was tested, however not on a batch towards the end of its shelf life. This will be done post approval. Furthermore, the MAH has justified why no tablets were removed from the bottle during in-use stability. Under the applied conditions (25°C/60%RH or 30°C/75%RH) no deterioration of the drug products was observed.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product. Certificates from the suppliers are provided declaring that the magnesium stearate and the glycerol of the coating system are from vegetable origin, and therefore do not pose a risk of transmitting TSE/BSE.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Arparial film-coated tablets have a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:
- The MAH committed that no batch of ivabradine hydrochloride manufactured with one specified intermediate will be marketed before the new audit in the production site is performed and an updated QP declaration has been submitted to the authorities. The updated QP declaration has been submitted in September 2015.
- The MAH committed to test a batch toward the end of shelf-life in an in-use stability study.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

Metoprolol
Metoprolol is a cardioselective beta-blocker, with greater blocking effect on beta1-receptors than on beta2-receptors. Safety pharmacology studies with metoprolol showed no special hazard for humans.

Ivabradine
Ivabradine is a selective and specific inhibitor of the cardiac *I*f current. Safety pharmacology studies with ivabradine showed no relevant risks for humans. Inhibition in the hERG assay was shown at high concentrations (at least 70-fold the human total C_{max} and 240-fold based on the unbound fraction) and was thus not clinically relevant. No effect on QT was observed in dogs at high doses (C_{max} up to 270-fold human value). 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 of metoprolol and ivabradine
No non-clinical studies were performed with the combination metoprolol/ivabradine. There is no non-clinical proof of concept that combined treatment would be beneficial for this indication. However, this is not needed considering the clinical experience with the combination since metoprolol and ivabradine have already been widely co-prescribed and since ivabradine is approved to be used in combination with beta-blockers in the symptomatic treatment of chronic stable angina pectoris.

III.2 Pharmacokinetics

Metoprolol
Metoprolol is extensively distributed to extravascular tissues. Metoprolol distributes to brain of mouse and rat and to foetuses of mouse. Metoprolol is only about 12% bound to human serum proteins. Metoprolol is eliminated by biotransformation and excreted mainly in the urine. Elimination half-life increases in the order rat, cat, dog and man and is 3.5 hours in man. The main urinary metabolites in man, dog and rat were formed by oxidative deamination, O-dealkylation with subsequent oxidation and by aliphatic hydroxylation. The main metabolite was the zwitterionic phenylacetic acid metabolite in the species studied. One of the metabolites, hydroxylated metoprolol and an intermediate to the main metabolite are beta-blockers with the same pharmacological profile as the parent drug but with lower potency. The acute toxicity in the mouse of the metabolites was lower than for metoprolol.

Ivabradine
Ivabradine is rapidly and almost completely absorbed with a moderate bioavailability of ~40% due to first-pass effect. Plasma protein binding is 60-70%. A gender effect is evidenced in rats, with females being on average 3-fold more exposed than males. Ivabradine and metabolites rapidly equilibrate in most tissues, except in brain and testis where passage is very low. Ivabradine showed reversible binding to melanin and was distributed into amniotic fluid of pregnant rats and was excreted in maternal milk of rats. Ivabradine is metabolised by oxidation via CYP450, mainly CYP3A4 and is neither an inducer, nor an inhibitor of main CYP450 drug-metabolising enzymes. Total plasma clearance at steady state was moderately high in rats (males: 66 to 32 ml/min/kg from 2.3 to 37 mg/kg/d; females: ~40 ml/min/kg) and in dogs (~15 ml/min/kg) and the renal clearance contributed to ~5% of the total plasma clearance. Elimination of ivabradine mainly occurred via hepatic metabolism. In the rat, the main half-life (terminal phase) ranged from 6 h in males to 14 h in females, consistent with a lower total clearance in females, and was not associated with any accumulation in repeat-dose studies. In the dog, the main half-life (first exponential phase) was less than 2 h. Faeces were the major route of excretion of unchanged ivabradine and its metabolites in rats and dogs. In both species, most of radioactivity (85-94%) was eliminated within 48 h. In plasma, faeces, bile and urine, most of the radioactivity (78-100%) comprised metabolites, with only minor amounts of unchanged compound.

Combination of metoprolol and ivabradine
No non-clinical interaction studies with metoprolol/ivabradine were performed. A clinical interaction study regarding the metoprolol/ivabradine combination is available. No additional non-clinical data are needed regarding pharmacokinetic interactions between metoprolol and ivabradine because this combination is already a clinically well-known combination.

III.3 Toxicology

Metoprolol
Acute toxicity was investigated in mice and rats. LD50 in mice was 69 – 80 mg/kg after intravenous administration and 2300-2460 mg/kg after oral administration. In rats, LD50 was 72-74 mg/kg after intravenous administration and 3470-4670 mg/kg after oral administration. Observed symptoms included sedation, irritation, spasm and convulsions before death.

Repeat-dose toxicity studies were performed in rats, up to 26 weeks, and in dogs, up to 52 weeks. In rats, no effects were reported besides a slight increase in haematocrit values and a slight decrease in blood glucose. In dogs, reported effects were disturbance of balance, increased abdominal muscular tone, mydrialysis, hyperaemia, vomiting, tremor, ataxia, prostration, dyspnoea and loss of consciousness. In several studies, a prolonged PR-interval was found; in one study (a 3 month study), also a prolonged QT-interval.

Metoprolol was devoid of mutagenic/genotoxic potential in the bacterial cell system (Ames) test and in *in vivo* assays involving mammalian somatic cells or germinal cells of male mice.

Metoprolol was not reported to be carcinogenic in mice and rats after oral administration of doses up to 800 mg/kg for 21 to 24 months.

Metoprolol did not affect fertility in males. In females, treated from 14 days prior to mating, throughout gestation and throughout lactation, fertility was not affected but a slight reduction of intrauterine growth was observed as well as a higher frequency of stillbirths at high dose. Metoprolol did not cause congenital malformations in rats or rabbits. In rabbits, foetal loss was increased at high dose. In rats treated from day 15 of gestation up to 21 days post partum, no effects were observed.

No new impurities or degradation products are reported for metoprolol.

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 IV; rats: ≥557 mg/kg PO, ≥74 mg/kg IV). In dogs, the observed effects were neurobehavioural changes (maximum tolerated dose: between 11 and 22 mg/kg orally 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 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 atrio-ventricular block and second-degree atrioventricular block. These ECG changes were seen at dose levels associated with mean plasma C_{max} 20-fold above that in humans 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 electroretinographic (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 embryotoxic and teratogenic in rats and rabbits. Embryotoxic 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 neonatally and had septal defects. In a pre- and postnatal development study in rats, increased post-natal mortality was observed.

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.

After in silico analysis (Derek Software: Nexus 2.0.2.) of 36 structures involved in (or observed during) the synthesis of ivabradine, the structures of bromodiox and chloroethane elicited a structural alert for mutagenicity (alkylating agent). During the manufacturing of metoprolol/ivabradine FDC, bromodiox will be maintained below the Threshold of Toxicological Concern. Chloroethane is not used during the synthesis of ivabradine.

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.

Combination of metoprolol and ivabradine
No non-clinical combination studies are available in which the combination metoprolol/ivabradine was tested. This is considered not necessary because clinically this is a well-known combination. Furthermore, there is no shared target organ of toxicity that would warrant further investigation.

III.4 Ecotoxicity/environmental risk assessment (ERA)

No environmental risk assessment was provided. The fixed dose combination of metoprolol and ivabradine is intended for patients who are already controlled by metoprolol 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

Both metoprolol tartrate and ivabradine hydrochloride are well-known active substances with established efficacy and tolerability.

To support the application, the MAH submitted two bioequivalence studies and one interaction study.
A clinical overview has been provided, with clinical data supporting the efficacy of ivabradine combined with a metoprolol. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

The pharmacokinetic studies are specified below.

Bioequivalence studies:

- Bioequivalence study I was designed to compare one tablet of the FDC of metoprolol tartrate 25 mg/ivabradine 7.5 mg and the co-administration of the corresponding monocomponents under fed conditions.
- Bioequivalence study II was designed to compare one tablet of the FDC of metoprolol tartrate 50 mg/ivabradine 7.5 mg and the co-administration of the corresponding monocomponents under fed conditions.

Interaction study:

- A PK interaction study evaluated the interaction between metoprolol tartrate 50 mg and ivabradine 7.5 mg given concomitantly compared to administration of each mono-component alone under fed conditions.

The reference products used were Lopresor mite 50 mg or half a 50 mg tablet, and Procoralan 7.5 mg tablets.

The MAH provided the following rationale to use fed conditions in the studies:

- The absorption of ivabradine is impacted by food. After administration with a standard breakfast or a high fat meal, the peak plasma concentration time (t_{max}) is slowed down from 1 to 2 hours: The peak plasma concentration (C_{max}) and the Area under the Curve (AUC) are also increased (30 to 40%) (EMEA, Procoralan, 2013). The administration of metoprolol with food impacts the bioavailability which is reported to increase by approximately 30 to 40% (MHRA, Metoprolol, 2011).
- The SmPC of both compounds recommend intake during meals. Furthermore, guidelines state: “For products where the SmPC recommends intake of the reference medicinal product only in fed state, the bioequivalence study should generally be conducted under fed conditions”.

The studies are sufficient for this type of application. The rationale for conducting the studies under fed conditions is accepted.

Biowaiver

The MAH identified two subgroups of formulations, based on metoprolol dose:
Subgroup 1: 25/5 mg and 25/7.5 mg
Subgroup 2: 50/5 mg and 50/7.5 mg

In each subgroup, the formulations are not proportional but they comply with the biowaiver criteria as:

i) the amount of ivabradine is less than 5% of the tablet core weight, and
ii) the amount of the filler (cellulose) is changed to account for the change in the amount of ivabradine; the amounts of other core excipients remain the same for the concerned strengths.

Furthermore, the following biowaiver criteria are fulfilled:

- The pharmaceutical products are manufactured by the same manufacturing process
- The qualitative composition of the different strengths is the same
- The dissolution results demonstrate the similarity of metoprolol and ivabradine dissolution profiles between 25/5 mg and 25/7.5 and between 50/5 mg and 50/7.5 mg and support the biowaiver request.
- The pharmacokinetics of both active ingredients is linear between 25 mg and 200 mg for metoprolol and between 0.5 mg and 24 mg for ivabradine.

Based on the above it is acceptable to perform only one biostudy at the highest dosage of ivabradine, 7.5 mg for each sub-group, with 25 and 50 mg of metoprolol in accordance with the criteria defined in the bioequivalence guideline CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, 2010.

Bioequivalence studies

Bioequivalence study I - 25 mg/7.5 mg strength

Design

A randomized, open label, three-period, three-sequence, reference replicated, crossover bioequivalence study was carried out under fed conditions in 54 healthy male and female subjects, aged 18-55 years. In each of the 3 study periods, either the test product (FDC tablet containing 25 mg of metoprolol tartrate and 7.5 mg of ivabradine) or the reference treatment (half a Lopresor mite 50 mg tablet and one Procoralan 7.5 mg tablet given concomitantly) was taken. The products were administered orally as a single dose with 240 mL of water at 30 min after start of a high-fat, high-calorie breakfast. The high-fat, high-calorie breakfast consisted of 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash browns or similar, and 240 mL of whole milk (according to the EMA Guideline). This breakfast was a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. This test meal derived approximately 150, 250, and 500-600 kcal from protein, carbohydrate and fat, respectively.
The 3 periods were separated by a wash-out period of at least 7 days between administrations.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

The wash-out period of at least 7 days between doses is sufficient as the half-life of ivabradine is 11 hours and metoprolol's half life is 3 to 4 hours.
The sampling around the expected t_{max} is sufficient (t_{max} of ivabradine is 1 to 2 hours, t_{max} of metoprolol is 1.5 to 2 hours after oral administration). In general the sampling schedule is sufficient.
The composition of the meal is according to the guideline.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable. The sample size was determined based on historical data. Previous investigations resulted in an intra-individual coefficient of variation (CV%) of up to 40% for C_{max} of ivabradine and up to 33% for AUC_{last} of ivabradine.
Consequently, a replicated design was used in order to assess the intra-individual variability for the reference product and to potentially justify a wider acceptance range for C_{max} of ivabradine.
For AUC_{last} of metoprolol and ivabradine and C_{max} of metoprolol an acceptance range of 80-125% was applied to perform the bioequivalence test. For C_{max} of ivabradine a potentially wider acceptance range could have been applied (up to 69.84 to 143.19%) according to the European Medicine Agency (EMA) Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr, 2010), since an intra-individual CV for C_{max} is shown to be above 30%.

Results

The reference product was administered twice, except for 1 subject who was excluded due to adverse events (AEs: nasopharyngitis and sinusitis) in period 1 (test product) and did not receive the reference product. Therefore, 54 observations for the test treatment and 106 observations for the reference treatment were obtained.

Table 1 Geometric means of pharmacokinetic parameters for metoprolol (25 mg as tartrate) and ivabradine (7.5 mg)

PARAMETER (unit)	TEST PRODUCT Geom. Mean (geom. CV%) N= 54	REFERENCE PRODUCT Geom. Mean (geom. CV%) N= 106
Metoprolol		
AUC_{last} (ng.h/mL)	155.0 (96.2%)	149.3 (92.9%).
C_{max} (ng/mL)	34.1 (72.6%)	31.8 (66.0%)
T_{max} (h) median (range)	1.33 (0.67, 5.0)	1.33 (0.67, 4.5)
$t_{1/2}$ (h)	3.65 (29.5%)	3.62 (28.6%)

Ivabradine		
AUC_{last} (ng.h/mL)	68.1 (46.9%)	66.0 (43.3%)
C_{max} (ng/mL)	19.8 (49.1%)	18.7 (44.1%)
T_{max} (h) median (range)	1.0 (0.33, 4.5)	1.33 (0.33, 5.0)
$t_{1/2}$ (h)	2.45 (33.5%)	2.50 (30.8%)

Table 2 Bioequivalence evaluation of metoprolol (N=53)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0\text{-}last)}$	103.21	98.78; 107.84	17.0
C_{max}	106.05	97.93; 114.84	27.2

[1] Within-subjects CV% estimated from the Residual Mean Squares using only the reference product data.

Table 3 Bioequivalence evaluation of ivabradine (N=53)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0\text{-}last)}$	102.22	97.56; 107.10	14.7
C_{max}	104.78	96.13; 114.22	28.7

[1] Within-subjects CV% estimated from the Residual Mean Squares using only the reference product data.

Bioequivalence study II - 50 mg/7.5 mg strength

Design

A randomized, open label, three-period, three-sequence, reference replicated, crossover bioequivalence study was carried out under fed conditions in 54 healthy male and female subjects, aged 18-55 years. In each of the 3 study periods, either the test product (FDC tablet containing 50 mg of metoprolol tartrate and 7.5 mg of ivabradine) or the reference treatment (one Lopresor mite 50 mg tablet and one Procoralan 7.5 mg tablet given concomitantly) was taken. The products were administered orally as a single dose with 240 mL of water at 30 min after start of a high-fat, high-calorie breakfast. The high-fat, high-calorie breakfast consisted of 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash browns or similar, and 240 mL of whole milk (according to the EMA Guideline). This breakfast was high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. This test meal derived approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively.
The 3 periods were separated by a wash-out period of at least 7 days between administrations.

Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16 and 24 hours after administration of the products.

The wash-out period of at least 7 days between doses is sufficient in view of the half-lives of both active substances. The sampling around the expected t_{max} is sufficient. In general the sampling schedule is sufficient. The composition of the meal is according to the guideline.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable. The sample size was determined based on historical data.
In view of the reported intra-individual coefficient of variation (CV%) of up to 40% for C_{max} of ivabradine and up to 33% for AUC_{last} of ivabradine, a replicated design was used in order to assess the intra-individual variability for the reference product and to potentially justify a wider acceptance range for C_{max} of ivabradine (up to 69.84 to 143.19%).
For AUC_{last} of metoprolol and ivabradine and C_{max} of metoprolol an acceptance range of 80-125% was applied to perform the bioequivalence test.

Results

The reference product was administered twice, except for two subjects who dropped out due to adverse events (headache, nausea and vomiting for one subject, and mild diarrhoea, nausea and

vomiting for the second subject) in period 1 or prior to dosing in period 3, respectively (both subjects received only the reference treatment). Therefore, 52 observations for the test treatment and 107 observations for the reference treatment were obtained.

Table 4 Geometric means of pharmacokinetic parameters for Metoprolol (50 mg as tartrate) and ivabradine (7.5 mg)

PARAMETER (unit)	TEST PRODUCT Geom. Mean (geom. CV%) N=52	REFERENCE PRODUCT Geom. Mean (geom. CV%) N=107
Metoprolol		
AUC_{last} (ng.h/mL)	311.9 (84.1%)	329.6 (79.0%)
C_{max} (ng/mL)	65.8 (71.1%)	71.1 (64.8%)
T_{max} (h) median (range)	2.00 (0.67, 5.0)	1.67 (0.33, 6.0)
$t_{1/2}$ (h)	3.66 (27.4%)	3.69 (28.0%)
Ivabradine		
AUC_{last} (ng.h/mL)	73.1 (51.5)	74.3 (51.8%)
C_{max} (ng/mL)	20.6 (47.3)	21.6 (52.9%)
T_{max} (h) median (range)	1.67 (0.33, 5.0)	1.00 (0.33, 4.5)
$t_{1/2}$ (h)	2.61 (30.9%)	2.65 (34.0%)

[1] Within-subjects CV% estimated from the Residual Mean Squares using only the reference product data.

Table 5 Bioequivalence evaluation of metoprolol (N=52)

Pharmacokinetic parameter	Geometric Mean on Ratio Test/Ref	Confidence Intervals	CV%[1]
AUC(0-last)	97.00	92.70; 101.50	17.4
Cmax	94.57	86.91; 102.90	29.5

[1] Within-subjects CV% estimated from the Residual Mean Squares using only the reference product data.

Table 6 Bioequivalence evaluation of ivabradine (N=52)

Pharmacokinetic parameter	Geometric Mean on Ratio Test/Ref	Confidence Intervals	CV%[1]
AUC(0-last)	98.74	94.12; 103.59	17.2
Cmax	96.00	87.73; 105.05	27.6

[1] Within-subjects CV% estimated from the Residual Mean Squares using only the reference product data.

Conclusion on bioequivalence studies I and II

Bioequivalence was demonstrated in both studies:

- between the fixed dose combination tablet Arparial 25 mg/7.5 mg and half of the marketed tablet of metoprolol tartrate 50 mg (Lopresor mite 50 mg breakable tablets) co-administered with the marketed tablet of ivabradine (Procoralan 7.5 mg tablets). The 90% confidence intervals AUC_{last} and of C_{max} were all fully included within the range of 80% to 125%.
- between the fixed dose combination tablet Arparial 50 mg/7.5 mg and the marketed tablet of metoprolol tartrate 50 mg (Lopresor mite 50 mg tablets) co-administered with the marketed tablet of ivabradine (Procoralan 7.5 mg tablets). The 90% confidence intervals AUC_{last} and of C_{max} were all fully included within the range of 80% to 125%.

Pharmacokinetic interaction study

Design

The interaction study was a randomized, open label, three-period, six-sequence crossover study under fed conditions. It was performed in 96 healthy male and female volunteers aged 18-55 years.

In each of the 3 study periods, the test treatment consisting of the co-administration of the two marketed drugs (one tablet of Lopresor mite 50 mg and one tablet of Procoralan 7.5 mg) and the reference treatment (one tablet of Lopresor mite 50 mg or one tablet of Procoralan 7.5 mg) were

administered orally as a single dose. All treatments were administered 30 minutes after starting a high-fat, high-calorie breakfast, consumed over a maximum period of 30 minutes. The high-fat, high-calorie breakfast consisted of 2 slices of buttered toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash browns or similar, and 240 mL of whole milk (according to the EMA Guideline). This breakfast was high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 kcal) meal. This test meal derived approximately 150, 250, and 500-600 kcal from protein, carbohydrate, and fat, respectively.
The 3 periods were separated by a wash-out period of at least 7 days.

The subjects were randomised just prior to dosing in treatment period 1 (Day 1), into one of the following sequences.

Table 7 Sequences of drug administrations

	Periods		
Number of volunteers	P1	P2	P3
16	Meto 50 mg	Iva 7.5 mg	Meto 50 mg + Iva 7.5 mg
16	Meto 50 mg	Meto 50 mg + Iva 7.5 mg	Iva 7.5 mg
16	Iva 7.5 mg	Meto 50 mg	Meto 50 mg + Iva 7.5 mg
16	Iva 7.5 mg	Meto 50 mg + Iva 7.5 mg	Meto 50 mg
16	Meto 50 mg + Iva 7.5 mg	Meto 50 mg	Iva 7.5 mg
16	Meto 50 mg + Iva 7.5 mg	Iva 7.5 mg	Meto 50 mg

Meto = Metoprolol; Iva = Ivabradine

The design and methods are sufficient. The MAH sufficiently justified the use of fed conditions, as for the two bioequivalence studies. In addition, the blood sampling, the analytes measured, the pharmacokinetic parameters assessed and the primary and additional parameters used were identical to those defined in the bioequivalence studies.

Results
One subject was withdrawn due to adverse events (AEs) after treatment in period 2. Consequently, this subject completed period 1 (metoprolol alone) and period 2 (ivabradine alone) but not period 3 (ivabradine and metoprolol). All other subjects completed the study as planned. The subject who discontinued was excluded from the primary PK analysis set for ivabradine (n=95) as well as from the primary PK analysis set for metoprolol (n=95).

Table 8 Pharmacokinetic data for metoprolol

Pharmacokinetic parameter	Geometric Means (±CV) Test product (N=95)	Reference product (N=95)
$AUC_{(0\text{-last})}$	265.2 (90.8%)	263.3 (89.8%)
C_{max}	52.9 (73.6%)	52.5 (65.2%)
T_{max} [1]	2.5 (0.67, 7.0)	2.5 (0.67, 6.0)

[1] Median (Min, Max)

Table 9 Pharmacokinetic data for ivabradine

Pharmacokinetic parameter	Geometric Means (±CV) Test product (N=95)	Reference product (N=95)
$AUC_{(0\text{-last})}$	77.4 (40.0%)	78.2 (38.3%)
C_{max}	20.4 (49.9%)	20.1 (43.2%)
T_{max} [1]	2.0 (0.33, 4.5)	2.0 (0.33, 4.5)

[1] Median (Min, Max)

Table 10 Interaction evaluation of metoprolol

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0\text{-last})}$	100.22	(97.11; 103.42)	13.11
C_{max}	100.53	(93.87; 107.65)	28.98

[1] Within-subjects CV% estimated from the Residual Mean Squares

Table 11 Interaction evaluation of ivabradine

Pharmacokinetic parameter	Geometric Mean Ratio Test/Ref	Confidence Intervals	CV%[1]
$AUC_{(0\text{-last})}$	99.47	(95.73; 103.36)	16.00
C_{max}	102.55	(96.24, 109.27)	26.80

[1] Within-subjects CV% estimated from the Residual Mean Squares

Conclusion on pharmacokinetic interaction study

Geometric mean ratios of AUC_{last} and C_{max} of ivabradine were near 100% (99.47% for AUC_{last} and 102.55% for C_{max}). The corresponding 90% confidence intervals were all fully included within the range of 80% to 125%. The mean $t_{1/2}$ of ivabradine was nearly equal after administration of ivabradine together with metoprolol or alone (2.45 and 2.41 hours, respectively). For both treatments median t_{max} was equal (2 hours).

Metoprolol PK parameters were unaffected by concomitant administration of ivabradine. Geometric mean ratios of AUC_{last} and C_{max} of metoprolol were near 100% (100.22% for AUC_{last} and 100.53% for C_{max}). The corresponding 90% confidence intervals were all fully within the range of 80% to 125%. The mean $t_{1/2}$ of metoprolol was nearly equal after administration of metoprolol together with ivabradine or alone (3.42 and 3.41 hours, respectively). For both treatments median t_{max} was equal (2.5 hours).

The MEB has been assured that the pharmacokinetic studies have 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.3 Pharmacodynamics

The justification of the combination of metoprolol and ivabradine is based on their heart rate lowering effect through different physiopathologic mechanisms. This leads to a reduction in cardiac workload and myocardial oxygen consumption which is beneficial to patients with stable coronary artery disease and symptoms of angina.

IV.4 Clinical efficacy

The efficacy of ivabradine combined with a beta-blocker in stable angina pectoris was demonstrated during the clinical development of ivabradine. The extension of the indication of ivabradine in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and with a heart rate > 60 bpm was approved by the CHMP (EMEA, EPAR scientific discussion Procoralan/Corlentor, 2010). Further to the referral under Article 20 of Regulation (EC) n° 726/2004, the threshold of resting HR was set-up to ≥ 70 bpm before treatment initiation in angina.
The therapeutic guidelines also recommend ivabradine in combination with a beta-blocker or when a beta-blocker is contra-indicated or not tolerated (NCGC, 2011; Montalescot, 2013). These clinical data supporting the efficacy of ivabradine combined with a beta-blocker, or more specifically with metoprolol, are presented below.

ASSOCIATE study

The ASSOCIATE study was a 4-month, randomized, double blind, placebo-controlled, parallel-group international multicentre study, evaluating the anti-anginal efficacy and safety of oral administration of ivabradine compared to placebo on top of background therapy with atenolol. Atenolol is a selective β1-receptor antagonist, as is metoprolol (Tardif, 2009).

In this study, 889 patients from 20 countries were randomized to either ivabradine (n=449) or placebo (n = 440).
The primary objective of this study was to demonstrate the superior efficacy of ivabradine (5 mg b.i.d. then 7.5 mg b.i.d. given orally for 2 months each) versus 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. 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 (i.e. 12 ± 1 hours and 24 ± 2 hours post-dosing, respectively) on centralised reading values.
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 16.3s 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 heart rate 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 heart rate 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 heart rate was ≤ 65 bpm at baseline, and whose background beta-blocker dose was judged to be maximal, due to a resting heart rate ≤ 60 bpm and/or supine systolic blood pressure ≤ 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 heart rate 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 stable angina pectoris receiving beta-blocker therapy whether their resting heart rate was above or below 65 bpm (Tardif, 2012).

ADDITIONS study
The ADDITIONS study evaluated the efficacy, safety, and tolerability of ivabradine added to beta-blockers, and its effect on angina symptoms and quality of life in routine clinical practice (Werdan, 2012).
This study was conducted in Germany and involved 2,330 patients with chronic stable angina pectoris that were observed by general practitioners, practitioners, internists and cardiologists.
Patients included in the study should have concurrent limitations at normal exercise level (CCS grade 2) and in their quality of life. The treating physician was asked to include patients for whom he had already decided that Procoralan in combination with beta blockers was the appropriate treatment.
Patients were treated with ivabradine twice daily (bid) in flexible doses in combination with beta-blockers (metoprolol 43%, bisoprolol 37%, nebivolol 13%, carvedilol 7%) for 4 months.
Resting heart rate, the number of angina attacks and nitrate consumption were documented. Quality of life was evaluated by the EQ-5D patient questionnaire at each visit. A descriptive statistical analysis was performed. Baseline and last observation values after 4 months were compared (Werdan, 2011).
After 4 months ivabradine (mean dose 12.37 ± 2.95 mg/day) reduced heart rate by 19.4 ± 11.4 to 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 ($p < 0.0001$). After 4 months' treatment with ivabradine, most of the patients classified as Canadian Cardiovascular Society (CCS) grade I (68%) whereas most patients (51%) were CCS grade II at baseline. Moreover, 84.1% of patients did not consume short-acting nitrates in the week prior to the last visit after 4 months, compare to 40.2% at baseline.
The absolute change in quality of life index (EQ-5D) improved by 0.17 ± 0.23 ($p < 0.0001$). The overall efficacy of ivabradine was considered by the physicians as "very good" (61%) or "good" (36%) in most patients (Werdan, 2012).
In daily clinical practice, combining ivabradine with beta-blocker not only reduces heart rate, number of angina attacks, and nitrate consumption, but also improves the quality of life in patients with stable

angina pectoris and in this study 43% of the patients received metoprolol as their beta-blocker (Werdan, 2012).
A sub-analysis of the ADDITIONS study performed on patients taking ivabradine combined with metoprolol confirmed the results of the main study.
After 4 months ivabradine (mean daily dose 12.6 ± 2.89 mg) combined with metoprolol (mean daily dose 102.5 mg ± 49.9 and daily dose range from 0 to 200 mg), reduced heart rate by 19.7 ± 11.2 ($p < 0.0001$). The number of angina attacks was reduced by 1.4 ± 2.0 ($p < 0.0001$), and nitrate consumption by 2.0 ± 2.9 U, as mean value ($p < 0.0001$). After 4 months' treatment with ivabradine, most of the patients were CCS grade I (65.3%). whereas most patients (51%) were CCS grade II at baseline. Moreover, 84.9% of patients did not consume short-acting nitrates in the week prior to the last visit after 4 months, compared to 39.5% at baseline. The EQ-5D index improved by 0.162 ± 0.226 ($p < 0.0001$).

Results of ADDITIONS study

	ADDITIONS Study (beta-blockers + ivabradine)		**Sub-analysis of ADDITIONS Study** (metoprolol + ivabradine)	
	Baseline	after 4 months	Baseline	after 4 months
Mean daily dose of ivabradine	9.55 ± 1.46 mg	12.37 ± 2.95 mg	9.6 ± 1.37 mg	12.6 ± 2.89 mg
Mean daily dose of metoprolol			107.9 mg ± 50.3	102.5 mg ± 49.9
HR (mean value)	85.0 ± 12.3 bpm	65.6 ± 8.2 bpm	84.9 ± 12.0 bpm	65.3 ± 7.9 bpm
Reduction of HR		19.4 ± 11.4		19.7 ± 11.2
Reduction of number of angina attacks by week		1.4 ± 1.9		1.4 ± 2.0
Reduction of nitrate consumption		1.9 ± 2.9°U		2.0 ± 2.9°U°
Percentage of patient not using that short acting nitrate in the week prior to the visit	40.2%	84.1%	39.5%	84.9%
CCS grade				
I	29,0%	67.9%	29.2%	65.3%
II	50.8%	28.8%	50.9%	31.8%
III	19.4%	3.1%	18.5%	2.8%
IV	0.8%	0.3%	1.4%	0.1%
Absolute change in quality of life index (EQ-5D index)		0.17 ± 0.23		0.162 ± 0.226

($p < 0.0001$)

IV.5 Clinical safety

Monocomponents

Metoprolol

The common undesirable effects of metoprolol are: dizziness, headache, sleep disturbances, bradycardia, palpitations, orthostatic hypotension, exertional dyspnoea, nausea and vomiting, abdominal pain, fatigue, cold extremities (eMC, Lopresor, 2010).

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.
Other adverse reactions such as headache, dizziness, bradycardia, uncontrolled blood pressure (EMEA, Procoralan, 2013) including conduction abnormalities occur in < 10% of the cases.
Ivabradine is devoid of intrinsic negative inotropic effects (Diaz, 2006).

Combination

The safety of ivabradine combined with a beta-blocker in stable angina pectoris was evaluated during the clinical development of ivabradine. The extension of the indication of ivabradine in combination

with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and with a heart rate > 60 bpm was approved by the CHMP (EMEA, EPAR scientific discussion Procoralan/Corlentor, 2010). Further to the referral under Article 20 of Regulation (EC) n° 726/2004, the threshold of resting HR was set-up to ≥ 70 bpm before treatment initiation in angina. The therapeutic guidelines also recommend ivabradine in combination with a beta-blocker or when a beta-blocker is contra-indicated or not tolerated (NCGC, 2011; Montalescot, 2013).

ASSOCIATE study
Ivabradine in combination with atenolol was well tolerated in the study. The number of patients withdrawn from treatment owing to emergent adverse events were 13 (2.9%) in the ivabradine group and 4 (0.9%) with placebo (difference not significant). Among these emergent adverse events, there were five serious adverse events 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 emergent adverse events were those related to bradycardia, reported by 19 patients (4.2%) in the ivabradine group (12 patients with ivabradine 5 mg b.i.d. and 7 with ivabradine 7.5 mg b.i.d.) and 2 patients (0.5%) with placebo. Only 1.1% of adverse events 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, 11 – 13 were reported by nine patients (2%) in the ivabradine group and four (0.9%) in the placebo group. There were small, non-significant changes in supine blood pressure from baseline to the last value on treatment (from 127.3 ± 12.0 to 128.3 ± 14.8 mmHg for systolic blood pressure and from 78.6 ± 7.4 to 78.1 ± 8.0 mmHg for diastolic blood pressure 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).

ADDITIONS study
Suspected adverse drug reactions were documented in 14 patients (0.6%): phosphenes occur in 0.13%, dizziness in 0.13%, nausea, palpitation, bradycardia, chest discomfort and flushing in 0.09%; none were severe (Werdan, 2011). A final evaluation of the overall efficacy and tolerance of ivabradine therapy was made using a physician's assessment scale ("very good", "good", "moderate" and "poor"). The tolerability was rated as "very good/good" for 72%/28% of patients respectively (Werdan, 2011).
In the sub-analysis performed on patients taking ivabradine combined with metoprolol, 7 patients (0.71%) reported suspected adverse drug reactions. No severe drug reaction was documented.

BEAUTIFUL study
In a post-hoc subgroup analysis of the randomized controlled BEAUTIFUL trials, in patients with symptomatic angina at randomisation (n=1507), no safety signal was identified regarding cardiovascular death, hospitalization for acute myocardial infarction or heart failure (ivabradine 12.0% versus placebo 15.5%, p=0.05). 90% of patients received concomitantly beta-blockers in the subpopulation with limiting angina, 36% (157/438 patients) received metoprolol tartrate. Serious adverse events were experienced by 135 patients (18%) in the ivabradine group vs. 144 patients in the placebo group (19%), with no significant difference in any case. No safety concern was raised with this subpopulation with limiting angina (Fox, 2009).

Prescription data
According to Intercontinental Marketing Service (IMS) prescription data (March 2012), the most used beta-blockers in stable angina patients in Europe (Belgium, Czech republic, France, Italy, Poland, Portugal, Spain, UK) are the following:

1. Bisoprolol, given once daily: 8.0 million prescriptions, representing 47% of prescribed beta-blockers
2. Atenolol given once daily: 3.7 million prescriptions, representing 20% of prescribed beta-blockers
3. Metoprolol given once or twice daily: 3.1 million prescriptions, representing 17% of prescribed beta-blockers

Therefore, metoprolol is the main beta-blocker that can be administered twice daily. The tartrate salt is the salt used for immediate release formulations, adapted to twice daily dosing.

Metoprolol tartrate and ivabradine are administered at the same dose interval and timing (bid) and the bioavailability of each component increases with simultaneous intake of food.
The combination of the two components is also supported by the therapeutic experience and the co-prescription of ivabradine and metoprolol in medical practice in the stable angina pectoris indication.
Co-prescriptions from theIMS database of metoprolol and ivabradine compared to the number co-prescriptions of ivabradine and any beta-blocker in chronic ischemic heart disease (I20+I25) is shown in the table below. Data is provided from Germany, Italy, France and Slovakia between December 2011 and December 2012.

Number of co-prescriptions from IMS database of metoprolol and ivabradine (December 2011-December 2012)

Country	Number of co-prescriptions Ivabradine + ß-blocker	Number of co-prescriptions Ivabradine + Metoprolol	Ratio (%) Iva + Meto/Iva + ß-blocker
Germany	6835	2541	37%
Italy	105262	15397	15%
France	68536	1810	2.6%
Slovakia	12521	3864	31%
Total	193154	23612	12%

Safety evaluation
Pharmacovigilance data are of interest for a new combination. The MAH has a database for Procoralan (ivabradine) from 25 October 2005 to 25 April 2013 although the data related to the co-prescription of metoprolol with ivabradine are scarce.
From 25 October 2005 to 25 April 2013, 2063 cases-reports were reported with ivabradine. Out of these cases-reports, 124 patients were treated concomitantly with metoprolol. Among them, 64 patients were treated for coronary artery diseases, 10 for heart failure, 3 for coronary artery disease and heart failure and 47 for another or unknown indication.
In the 67 patients treated for coronary artery disease, the most frequently reported reactions are listed events: bradycardia (12 events, 3% of all events) and related symptoms (dizziness (6 events, 2%), fatigue (4 events, 1%), hypotension (2 events, 8%). The other most frequent reactions reported are all listed, and include photopsia (3 events, 4%), pruritus (3 events, 4%), ventricular extrasystoles (2 events, 1%), nausea (2 events, 1%) and diarrhoea (2 events, 1%).
Overall, the majority of the reported events were listed events for ivabradine or metoprolol. As expected considering the heart rate lowering mechanism of action of both drugs, the most frequent adverse drug reaction was bradycardia and bradycardia-related symptoms. No safety signal was detected regarding the unlisted events.
This analysis should be interpreted cautiously taking into account the low number of patients. Nevertheless, knowledge on the safety of combined use with any beta-blocker is much more extensive. Clearly bradycardia is an important adverse effect of combined beta-blocker and ivabradine. This is well addressed in the SmPC, and obviously the intended use of the FDC as a substitution of two monocomponents in patients who are on a stable dose of these products.

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 Arparial.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Bradycardia - Phosphenes and blurred vision - 2nd and 3rd degree atrioventricular blocks - ECG prolonged QT interval - Increase in blood pressure in hypertensive patients - Atrial fibrillation (AF) - Anaphylactic shock - Hypoglycaemia
Important potential risks	- Supraventricular tachyarrhythmia other than atrial fibrillation - Immune system disorders

	- Severe Ventricular arrhythmias - Myocardial infarction
Missing information	- Children and adolescent (< 18 years old) - Pregnant and lactating women - Severe hepatic insufficiency - Severe renal insufficiency - Chronic heart failure patients with intraventricular 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 metoprolol 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 Arparial FDC can be used instead of co-administration of the separate products Lopresor and Procoralan. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Arparial 25 mg/5 mg, 50 mg/5 mg, 25 mg/7.5 mg and 50 mg/7.5 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are considered an approvable fixed dose combination. Both metoprolol 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 Lopresor and Procoralan. The clinical data on concomitant use are considered sufficient to support the FDC combination in patients with stable angina pectoris 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 fixed dose combination is positive, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 6 May 2015.

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

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