Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Ivabradine

Proprietary Product Name: Coralan

Sponsor: Laboratories (Australia) Pty Ltd

December 2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	3 September 2010
Active ingredient(s):	Ivabradine
Product Name(s):	Coralan
Sponsor's Name and Address:	Servier Laboratories (Australia) Pty Ltd 8 Cato Street Hawthorn Vic 3122
Dose form(s):	Film-coated tablet
Strength(s):	5 mg and 7.5 mg
Container(s):	Calendar packs of aluminium/PVC blister strips packed in cardboard boxes
Pack size(s):	14 or 56
Approved Therapeutic use:	Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm, who are unable to tolerate or have a contraindication to the use of beta blockers, OR in combination with atenolol 50 mg once daily when heart rate is at or above 60 bpm and angina is inadequately controlled.
Route(s) of administration:	Oral
Dosage:	The usual recommended starting dose of ivabradine is 5 mg orally twice daily, i.e. once in the morning and once in the evening during meals. After 3 or 4 weeks of treatment the dose may be increased to 7.5 mg twice daily depending on therapeutic response.
ARTG Number (s)	107297, 107301

Product Background

Coralan (ivabradine) is a heart rate lowering agent, acting by selective inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are relatively specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, myocardial contractility or ventricular repolarisation in humans at the therapeutic dose.

Coralan has been considered previously on one occasion by the Australian Drug Evaluation Committee (ADEC) which has now been succeeded by the Advisory Committee on Prescription Medicines (ACPM). That was at the 247th meeting of the ADEC on 4 August 2006 when a resolution was passed recommending approval for the current indication. The following issues were raised in the ADEC discussion:

- that ivabradine was a weak anti-anginal; 4 pivotal trials had been submitted with the evidence of ivabradine's efficacy as an anti-anginal not being very effective from a statistical point of view; it appeared that the drug had not been tested precisely according to NIH protocol
- the amount of exercise prolongation was only very small, some extra 28 seconds versus placebo
- it was regarded as critically important that the drug only be used for classic or exertional angina

The currently approved indication for ivabradine is:

Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm who are unable to tolerate or have a contraindication to the use of beta-blockers.

This submission by Servier Laboratories (Australia) Pty Ltd requested amendment of the Product Information (PI) to permit the addition of ivabradine to beta-blockers in the treatment of stable angina. As such this implies a widening of the patient population and represents an extension of indication.

The indication which was sought originally is worded as follows (the addition is underlined):

Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm <u>who are already treated with a beta-blocker, or are</u> unable to tolerate or have a contraindication to the use of beta-blockers.

Following receipt of the supplementary clinical evaluation report, the sponsor proposed the following indication:

Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm who are unable to tolerate or have a contraindication to the use of beta-blockers, or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose whose heart rate is > 60 bpm.

For the current indication involving monotherapy, the recommended starting dose of ivabradine is 5 mg twice daily (bd) with an increase to 7.5 mg bd after 3-4 weeks depending on therapeutic response.

For the proposed use in addition to a beta-blocker, the following paragraph in the Dosage and Administration section of the product information (PI) is proposed:

Concomitant use with Beta-Blockers

Ivabradine treatment can be initiated at the usual recommended dose of 5 mg twice daily. The dose may be increased to 7.5 mg twice daily depending on the therapeutic response and heart rate. If during treatment heart rate decreases persistently below 50 bpm at rest, or the patient experiences symptoms related to bradycardia, the dose may be decreased to 2.5 mg twice daily. If heart rate remains below 50 bpm or symptoms of bradycardia persist, treatment with ivabradine should be discontinued.

Regulatory Status

Approval was given in the European Union (EU) on 23 October 2009 to amend the indication for the use of ivabradine in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and with a heart rate > 60 beats per minute (bpm). The full wording of the approved indication in the EU is as follows:

Symptomatic treatment of chronic stable angina pectoris in coronary artery disease patients with normal sinus rhythm. Ivabradine is indicated:

- *in patients unable to tolerate or with a contra-indication to the use of beta-blockers*
- *or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is >60 bpm*

Servier has not submitted an application for marketing authorisation for ivabradine in the USA or New Zealand while in Canada an application for marketing authorisation, including the current application, has been submitted in June 2010. In Switzerland, a similar application to the current Australian submission was submitted in June 2009 and approved on 2 August 2010 with the same indication as in Europe.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

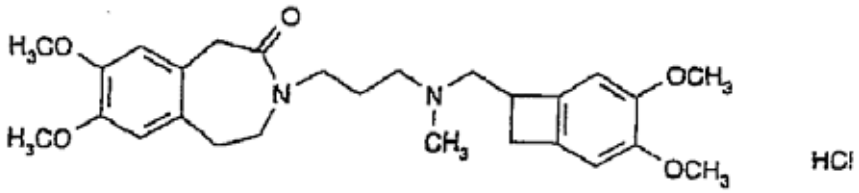
II. Quality Findings

Drug Substance (active ingredient)

The chemical structure of ivabradine contains two rings: one benzazepinone and one benzocyclobutane linked with an azapentane chain. The structural form of ivabradine includes one asymmetric carbon and ivabradine corresponds to the S enantiomer. The hydrochloride salt is a white to slightly yellow hygroscopic powder, soluble in water (50 mg/mL) and in 0.9% saline solution (14 mg/mL). The pH is 5.1 – 5.4 in aqueous solutions at concentration of 10 mg/mL.

Chemical Name: 3-(3-{[((7S)-3,4-Dimethoxybicyclo[4,2,0]octa-1,3,5-trien-7-yl) methyl] methylamino}propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one, hydrochloride. CAS Number (base): 155974-00-8. Molecular formula: C27H36N2O5, HCl; Molecular weight (hydrochloride): 505.06

Chemical Structure:



Drug Product

The excipients included in the Coralan tablets are:

Core- lactose, magnesium stearate, starch maize, maltodextrin and silica (colloidal anhydrous). Film-coating- hypromellose, titanium dioxide (E 171), macrogol 6000, glycerol, magnesium stearate, yellow iron oxide (E 172), red iron oxide (E 172).

Quality Summary and Conclusions

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

Nonclinical Summary and Conclusions

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Initial Submission - Introduction

The current application consisted of one clinical report for the Phase III study CL3-16257-057 evaluating the combination of ivabradine with the beta-blocker, atenolol in 889 patients with stable angina.

Based on results of the above study, the sponsor has applied to vary the conditions for registration of Coralan (ivabradine) with respect to the following:-

The Interactions section in the current PI, which currently reads as follows:

"While, in absence of long term safety and efficacy data, the combination of ivabradine with beta blockers is not recommended, if the combination with beta blockers appears necessary, a starting dose of 2.5 mg twice daily of ivabradine and close monitoring should be considered provided that heart rate is above 60 bpm." to the following:

"Ivabradine can be used in combination with a beta-blocker if resting heart rate is at or above 60 bpm, and heart rate is carefully monitored."

On basis of the results of the randomised controlled trial CL3-16257-057 and to maintain consistency with proposed changes to the Interactions section, the Indications are proposed to be amended to:

"Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm who are already treated with a beta-blocker, or are unable to tolerate or have a contraindication to the use of beta-blockers."

The following information is proposed to be added to the Dosage and Administration section of the proposed PI:

"Concomitant use with beta-blockers: Ivabradine treatment can be initiated at the usual recommended dose of 5 mg twice daily. The dose may be increased to 7.5 mg twice daily depending on the therapeutic response and heart rate. If during treatment, heart rate decreases persistently below 50 bpm at rest, or the patient experiences symptoms related to bradycardia, the dose may be decreased to 2.5 mg twice daily. If heart rate remains below 50 bpm or symptoms of bradycardia persist, treatment with ivabradine should be discontinued."

Initial Submission - Pharmacokinetics

There were no new pharmacokinetics data presented in the submission.

Initial Submission - Pharmacodynamics

There were no new pharmacodynamics data presented in the submission.

Initial Submission - Efficacy

Study design and patient population

CL3-16257-057 was a randomised, double-blind, placebo-controlled, parallel-group, international multicentre study, with a centralised, balanced and non-adaptive randomisation with stratification by centre. The 6 to 8 week, single-blind, run-in period on atenolol (50 mg once daily [od] and placebo (bd) was followed by a 4-month double-blind treatment period divided into two periods of 2 months each.[1] Patients complying with inclusion criteria were randomised to receive either ivabradine (5 mg bd for 2 months followed by forced titration to

[1] It lasted 6 weeks for patients previously treated with atenolol 50 mg daily and 8 weeks for patients previously treated with another beta-blocker at an equivalent dose.

7.5 mg bd for another 2 months unless heart rate (HR) was <50 bpm or placebo, in combination with atenolol (50 mg od). Three exercise tolerance tests (ETTs) were performed during the run-in period (the first two at selection visits and the third one 5 days before inclusion visit) and one ETT at the end of each treatment period (that is, at Month 2 visit [M2] and Month 4 visit [M4]). The study was conducted from 8 June 2005 to 17 October 2007 and involved 219 centres in 20 countries including Argentina (23 sites), Brazil (17), Bulgaria (9), Canada (12), Chile (8), Czech Republic (8), Germany (6), Hungary (20), Italy (7), Norway (6), Poland (20), Romania (8), Russia (31), Slovakia (5), South Africa (7), Spain (7), Sweden (3), Thailand (5), Ukraine (11) and United Kingdom (6). The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki 1964, amended in Edinburgh 2000 and annotated in Washington, 2002. The study protocol was reviewed by independent Ethics Committees in the various countries concerned and the study was initiated only after favourable opinions were obtained and in accordance with the local regulations. The study was conducted in accordance with Good Clinical Practice (GCP). The ivabradine formulation used in this study was the registered formulation of ivabradine.

The study included outpatients, aged between 18 (or the legal age) and 75 years, with a history of stable chronic effort angina pectoris for at least 3 months prior to pre-selection, with no angina at rest and no angina of Class IV (classified by the Canadian Cardiovascular Society),[2] with clinical stability (no significant change in frequency, severity or triggering activity within one month preceding pre-selection and no changes in nitrate consumption), with documented coronary artery disease,[3] and who were treated for at least 3 months preceding pre-selection by atenolol 50 mg daily or by a beta-blocker at an equivalent dose. The heart rate (on supine electrocardiogram [ECG]) at pre-selection and inclusion was to be ≥ 60 bpm on atenolol (50 mg od) or equivalent beta-blocker treatment. Patients were to have three positive exercise tolerance tests during the run-in, with the second and third being stable (defined as values of "time to 1 mm ST segment depression" within ± 20%, or ± 1 minute [min] at the two visits). A positive ETT with the standard Bruce protocol (Table 1) was defined as: occurrence of limiting angina (assessed by investigator and expressed as moderate to severe angina pain that would ordinarily cause the patient to stop his or her exercise during normal daytime activity) and significant ST segment depression, defined as ST segment depression of at least 1 mm, compared to the value at rest, horizontal or down sloping and persisting for at least 80 milliseconds (ms) after J-point, on at least 3 consecutive complexes; both events were to occur between 3 and 12 min following initiation of the ETT. If the ETTs

[2] **Classification of angina by the Canadian Cardiovascular Society**

Class I: Ordinary physical activity, such as walking and climbing stairs, does not cause angina. Angina results from strenuous or rapid or prolonged exertion at work or recreation.

Class II: Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold, in wind, or when under emotional stress, or only during the few hours after awakening. Walking more than 2 blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.

Class III: Marked limitation of ordinary physical activity. Walking one to two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace.

Class IV: Inability to carry on any physical activity without discomfort - anginal syndrome *may be* present at rest.

[3] Documented coronary artery disease (CAD), documented by one of the following: (1) A history of myocardial infarction ≥ 3 months before pre-selection. Diagnosis documented by Q-wave on the ECG and/or significant cardiac enzyme elevation.

were interrupted for any other reason than reaching both above mentioned positivity criteria, then the test was not considered as being positive.

Table 1: ETT Stages of the Bruce Protocol

Stage	Period (min)	Speed (mph)	Incline
1st	0 – 3	1.7	10%
2nd	3 – 6	2.5	12%
3rd	6 – 9	3.4	14%
4th	9 – 12	4.2	16%
5th	12 – 15	5.0	18%
6th	15 – 18	5.5	20%
7th	18 – 21	6.0	22%

The background anti-anginal therapy was prospectively defined and eligible patients were switched to atenolol 50 mg od (if on a different beta-blocker) at the start of the run-in. Short-acting nitrates were permitted throughout the study and their use was reported in a patient diary and analysed as part of the efficacy assessment. In case short-acting nitrates were taken within the 3 hours before the performance of the ETT (or the patient smoked within the last 3 hours), the test had to be postponed by at least 24 hours.

The main exclusion criteria were:

- HR < 60 bpm measured on ECG at rest;
- Recent acute myocardial infarction (less than 3 months before pre-selection), coronary bypass surgery (less than 3 months before pre-selection) or coronary angioplasty (less than 6 months before pre-selection);
- Previous treatment with atenolol at a dosage superior to 50 mg daily or with another beta-blocker at a dosage corresponding to more than 50 mg of atenolol daily;
- Resting angina, unstable angina, Prinzmetal angina or microvascular angina;
- Known high-grade left main coronary artery disease (equal or greater than 50%) that had not been surgically bypassed or mechanically improved;
- Patient who could not perform exercise tests for reasons of incapacitation related to limiting neurological, orthopaedic, or rheumatologic disease or symptomatic peripheral vascular disease of the lower limbs;
- Contraindication to beta-blockers (for example, severe rhythm or conduction disturbances, left ventricle thrombus);
- Clinically significant heart disease other than coronary artery disease (for example, congenital, hypertensive, pericardial, valvular, rheumatic disease, non-ischaemic cardiomyopathy);
- Congestive heart failure Stage III or IV NYHA uncontrolled heart failure;
- Symptomatic hypotension or hypotension defined as blood pressure (BP) < 90/50 mmHg;
- Uncontrolled hypertension (systolic blood pressure at rest > 180 mmHg or diastolic blood pressure at rest > 100 mmHg);
- Permanent atrial fibrillation or paroxysmal atrial fibrillation present at the time of pre-selection, flutter, pacemaker or cardioverter-defibrillator implantation;
- Use of certain concomitant medications which were likely to interact with ivabradine were not allowed.

Efficacy endpoints and statistical considerations

There are two TGA-adopted European guidelines particularly relevant to this submission, besides the general guidelines:

CPMP/EWP/234/95 Rev 1 Guideline on the Clinical Investigation of Anti-Anginal Medicinal Products in Stable Angina Pectoris which replaces:
pp. 289 - 296 of Rules 1998 (3C) - 3CC20a (Adopted by TGA 12 February 2002)
CPMP/EWP/234/95 (Adopted by TGA August 1997)
and pp. 187 - 190 of Rules 1989
Published: TGA Internet site
Effective: 29 September 2006.

pp. 127 - 132 of Rules 1998 (3C) - 3CC6a: *Clinical Investigation of Medicinal Products for Long-Term Use* which replaces:
pp. 163 - 165 of Rules 1989
Effective: 12 February 2002
See also: pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (Adopted by TGA with conditions)

Primary assessment criterion and time of evaluation

The primary efficacy endpoint was the change in the total exercise duration (TED) (using centrally read values and acquired during the treadmill exercise tolerance tests, ETT) from baseline to the end of treatment period (M4) and was compared between the ivabradine and placebo groups. The ETT was performed on a treadmill using the standard Bruce protocol, consisting of a series of graded effort stages of 3 minutes each.

The main efficacy analysis was carried out on the Full Analysis Set-ETT (FAS-E) and confirmed in the Per Protocol Set at 4 months (PPS-E4). For the ETT analysis at trough of drug activity, the Full Analysis Set – ETT (FAS-E) was defined as all patients from the randomised set having documented coronary artery disease, stable effort angina at pre-selection visit, taken at least one dose of study drug post-Month 0 visit, that is, inclusion visit (M0) and at least one post-M0 value of TED (evaluated by central reading) observed during an ETT planned at trough of drug activity. Two Per Protocol Sets (PPS) were defined for the analysis of the ETT data, relating to the 4-month treatment period (PPS-E4) and the 2-month treatment period (PPS-E2) respectively; in addition to the above criteria for FAS-E population, patients had to conform with other criteria to be included in the PPS.[4]

The superiority of ivabradine versus placebo was tested on the change in TED (primary criterion) over the 4-month treatment period using a parametric analysis of covariance adjusted on country factor with baseline as a covariate (the placebo subtracted difference in TED was estimated). Two robustness analyses were performed: a parametric analysis of

[4] A positive ETT at the M0 visit (made before the first study drug intake and at trough of atenolol activity and using the Bruce protocol), that was within the define stability threshold with respect to SEL2 ETT; A central reading value for TED from an M0 ETT; A treatment duration of atenolol (50 mg/day (or less) or with other equivalent beta-blocker) superior or equal to 1.5 months prior to pre-selection visit; Treatment duration of atenolol during run-in period (SEL1 to M0 visits) superior or equal to 35 days for patients already treated with atenolol 50 mg/day and to 42 days for patients already treated with another beta-blocker considered as equivalent to atenolol 50 mg/day; Overall compliance of atenolol observed between SEL1 and M0 visits evaluated between 70% and 130% (inclusive); No treatment interruption duration of atenolol strictly superior to 3 consecutive days between SEL1 and M0 visits; With no documented blind breaking.

variance without adjustment and a non-parametric covariance analysis with adjustment based on the Wilcoxon Rank Norm.

The sample size in the study had 95% power to detect at least a 30 seconds difference between treatment groups (with a standard deviation of 110 seconds).

The analysis of the secondary efficacy criteria was carried out on the other ETT criteria, that is, time to 1 mm ST segment depression (TST), time to angina onset (TAO), time to limiting angina (TLA), total exercise duration (TED), heart rate at rest and at peak of exercise, reason for stopping exercise (TED was directly obtained from the software and TST was assessed by the cardiologist of the Core Reading Centre) over the 4-month treatment period (FAS-E and PPS-E4) using similar analyses as for the primary criteria.

Symptomatology of angina criteria

The mean number of angina attacks, the mean global consumption of short-acting nitrates (SAN) and the mean consumption of SAN for angina attacks per week were studied over the 4-month treatment period and over the 2-month treatment period on the FAS-A, PPS-A4 and PPS-A2 patient populations; the Full Analysis Set – ETT (FAS-E) was defined as all patients from the randomised set having documented coronary artery disease, stable effort angina at pre-selection visit, taken at least one dose of study drug post-M0 and at least one post-M0 evaluation of number of angina attacks for angina attacks observed over a period of at least 7 days. Changes over the 4-month treatment period and over the 2-month treatment period were estimated between ivabradine and placebo and within each treatment group using a two-sided 95% confidence interval calculated with parametric and non-parametric approaches without adjustment (based on the Hodges-Lehmann estimator for independent samples). The same analyses were performed in patients with at least one attack at baseline and in patients with at least SAN intake at baseline.

Protocol deviations, Baseline demographics and disease characteristics

A total of 2681 patients were screened, 2622 were pre-selected and entered the single-blind atenolol run-in phase. Of these, 1792 were not included (84.2% or 1508/1792 patients were not included due to lack of positive or stable ETT), but analysed for demographics and baseline characteristics (Non Included Set). A total of 889 patients were included in the study and randomised to treatment with ivabradine (n=449) or placebo (n=440).

As a high rate of screened patients were not pre-selected, not selected (at SEL1 or at SEL2) or not included in this study, a Non-Included Set was defined in order to describe the main characteristics of these patients (demography, history of coronary artery disease and previous drug treatments for angina pectoris) and the reasons for their non-inclusion were given. It appears that a highly selected group of patients was included in this study as 1792 of 2622 patients were not eligible for the study.

The number and type of protocol deviations occurring before or at inclusion were evenly distributed between the 2 groups. Furthermore, the number and type of protocol deviations occurring during the study were fairly evenly distributed between the 2 groups. Slight differences of note that may have affected the ETT assessment were use of wrong ETT protocol and the use of unauthorised treatment, both of which had a slightly higher incidence in the ivabradine group compared with placebo.

The Full Analysis Set ETT (FAS-E) consisted of 875 patients (98.4% of the Randomised Set) and 14 patients in the Randomised Set were excluded from the FAS-E, due to missing post M0 evaluation of TED [8 patients in the ivabradine group (1.8%) and 6 in the placebo group (1.4%)]. The Per Protocol Set ETT at 4 months (PPS-E4) consisted of 796 patients (89.5% of

the Randomised Set and 91.0% of the FAS-E and 79 patients of the FAS-E dataset were excluded (46 patients in the ivabradine group and 33 in the placebo group); the main reasons for exclusion from the PPS-E4 were inadequate treatment exposure (insufficient or excessive exposure of study drug/atenolol)(n=30), visit not done (and therefore ETT not done) (n=20), inadequate time between ETT and last study drug/atenolol intake, non-positivity or stability, wrong ETT protocol, ETT not at trough (n=25). The Per Protocol Set ETT at 2 months (PPS-E2) consisted of 824 patients (92.7% of the Randomised Set and 94.2% of the FAS-E) with similar reasons for exclusion (inadequate treatment exposure and wrong ETT assessment).

The Full Analysis Set Angina Symptomatology (FAS-A) consisted of 885 patients (99.6% of the Randomised Set) and 4 patients of the Randomised Set were excluded from the FAS-A; 2 patients each in the ivabradine group (0.4%; one for no documentation of the CAD and one for having no evaluation of angina symptomatology≥ 7 days post inclusion visit) and placebo group (0.5%, both for having no evaluation of angina symptomatology≥ 7 days post - inclusion visit). The Per Protocol Set Angina Symptomatology at 4 months (PPS-A4) consisted of 777 patients (87.4% of the Randomised Set and 87.8% of the FAS-A). Overall 112 patients of the Randomised Set were excluded from the PPS-A4 (57 patients in the ivabradine group and 55 in the placebo group) and the main reasons for exclusion were inadequate treatment exposure (n=51), non- stable consumption of SAN for prophylaxis between M0 and M4 (n=21), Visit and ETT not done (n=20) and clinical deterioration or improvement of angina symptomatology (change of ≥ 5 in the number of angina attacks per week between visits) during run-in period (n=14). The Per Protocol Set Angina Symptomatology at 2 months (PPS-A2) consisted of 813 patients (91.5% of the randomised Set and 91.9% of the FAS-A) with similar reasons for exclusion.

Baseline characteristics were comparable between the ivabradine and placebo treatment groups. A majority of patients were male (84.4%) and were <65 years old (68.8%) with a mean age of 59.8 ± 7.8 years. They had been diagnosed with angina pectoris with a mean duration (± SD [standard deviation]) of 70.5 ± 68.8 months (5.9 years) and had angina pain of grade I (19.5%), grade II (68.6%), or grade III (11.9%) (Canadian Classification). All had received previous pharmacological treatment for angina, without any clinically relevant difference between treatment groups and almost all (99.9%) were receiving selective beta-blocking agents at selection with atenolol being the most common beta-blocker. Most patients had concurrent medical conditions, mainly vascular disorders (78.2%), metabolism and nutrition disorders (72.4%), cardiac disorders (27.2%) and gastrointestinal disorders (23.8%). The main non-specific concomitant treatments received during the treatment period were anti-thrombotic agents (94.5%), serum-lipid reducing agents (78.4%), cardiac therapy (70.3%) and agents acting on the renin-angiotensin system (67.3%) with no major differences between groups. Furthermore, there were no significant differences between treatment groups in baseline vital signs, ECG and baseline efficacy endpoints. The selected patient population in this study appeared to reflect the patient population for the sought indication.

Overall, 870 patients (97.9%) were treated for at least 3 months and mean (± SD) study drug treatment duration was 3.8 ± 0.5 months for ivabradine and 3.8 ± 0.4 months for placebo. Overall study drug compliance was good with 886/887 evaluable patients achieving compliance between 70-130%. The overall mean compliance was 99.1 ± 4.2%. At M2, 93.7% of overall patients were eligible for up-titration (that is, patients with HR ≥ 50 bpm at M2) and 90.0% in the ivabradine group were actually up-titrated to 7.5 mg bd The FAS-E consisted of 875 patients (98.4% of RS) and the FAS-A consisted of 885 patients (99.6% of RS) and patients in these datasets showed similar baseline demographics and disease characteristics to those described above in the RS with no significant differences between the ivabradine and placebo treatment groups.

Efficacy results

Primary efficacy results

Over the 4-month treatment period, patients treated with ivabradine showed greater increase in mean total exercise duration (TED) compared with placebo-treated patients in the FAS-E dataset (mean ± SD 24.3 ± 65.3 seconds (s) and 7.7 ± 63.8 s in the ivabradine and placebo groups, respectively; difference= 16.3 s (95% confidence intervals [CI] [7.9 ; 24.7], $p < 0.001$; t test on parametric approach adjusted on country and baseline) (Table 2). There was a diversity of results in the difference countries. In Romania and Slovakia, countries which had about 20 participants in each arm, the placebo group fared better. In Brazil, with about 30 in each arm, the placebo-subtracted difference was only 2.1 s in favour of ivabradine (9.3 vs 7.2). In Russia with the largest number of participants, about 120 in each arm, the difference was 5.1 s. Of the remaining countries which showed a positive difference in favour of ivabradine and which had reasonable numbers of at least 8-10 in each arm, there were six countries (Argentina, Canada, Norway, Poland, South Africa and Spain) which had negative mean changes on placebo while there were five countries (Bulgaria, Chile, Czech Republic, Hungary and the Ukraine) which had positive mean changes on placebo. At the very least, this suggests something different about the make-up of the populations in that subset of six countries versus that subset of five countries. It also means that the contribution to the overall results from the group of six countries is one which appears in part to be driven by worsening on placebo, not from a positive attribute of ivabradine. The results observed in the FAS-E population were confirmed in the PPS-E4 analysis (treatment difference=17 + 4.4, 95% CI=8.3, 25.7, $p<0.001$) (Table 3). The study had 95% power to detect at least 30 second difference between ivabradine and placebo groups however, the difference between the treatment groups in this study was only 16 seconds and hence it had considerably less power to detect these small changes. Furthermore the clinical relevance of this small improvement in TED over placebo does not appear to be meaningful.

Table 2: TED – Superiority of ivabradine versus placebo in the change from baseline to last value over the 4-month treatment period in the FAS-E

Time (s)		Ivabradine (N = 441)	Placebo (N = 434)
	n	441	434
Baseline	Mean ± SD	445.6 ± 105.6	450.7 ± 107.5
	Median	434	432
	Min - Max	224 - 716	221 - 720
End	Mean ± SD	469.9 ± 119.2	458.4 ± 111.1
	Median	459	447
	Min - Max	165 - 864	190 - 765
End - Baseline	Mean ± SD	24.3 ± 65.3	7.7 ± 63.8
	Median	28	8
	Min - Max	-209 - 247	-265 - 211
Superiority analysis of ivabradine *versus* placebo			
Parametric approach with adjustment	E (SE)[1]	16.3 (4.3)	
	95% CI[2]	[7.9 ; 24.7]	
	p-value[3]	p < 0.001	
Parametric approach without adjustment	E (SE)[4]	16.6 (4.4)	
	95% CI[2]	[8.1 ; 25.2]	
	p-value[5]	p < 0.001	
Non-parametric approach with adjustment	E (SE)[6]	18.9 (3.9)	
	95% CI[2]	[11.2 ; 26.5]	
	p-value[7]	p < 0.001	

N: total number of patients in the treatment group n: number of fully documented patients
1: Estimate (Standard Error) of ivabradine minus placebo effect: difference between group means adjusted on baseline and country factors (main analysis)
2: 95% Confidence Interval of the estimate (two-sided)
3: Student t test based on the overall general linear model (least-squares norm) with baseline as a covariate and country as a random factor
4: Estimate (Standard Error) of ivabradine minus placebo effect: difference between group means
5: Student t test based on the overall general linear model (least-squares norm)
6: Estimate (Standard Error) of ivabradine minus placebo effect: difference between Wilcoxon means adjusted on baseline and country factors
7: Wald test based on the overall general linear model (Wilcoxon norm) with baseline as a covariate and country as a fixed factor

Table 3: TED – Superiority of ivabradine versus placebo in the change from baseline to last value over the 4-month treatment period in the PPS-E4

Time (s)		Ivabradine (N = 395)	Placebo (N = 401)
	n	395	401
Baseline	Mean ± SD	447.5 ± 104.5	449.9 ± 106.6
	Median	437	432
	Min - Max	224 - 716	221 - 720
End	Mean ± SD	471.9 ± 119.4	457.0 ± 109.8
	Median	461	445
	Min - Max	165 - 864	190 - 756
End - baseline	Mean ± SD	24.4 ± 63.6	7.1 ± 64.3
	Median	28	6
	Min - Max	-209 - 247	-265 - 211
Superiority analysis of ivabradine *versus* placebo			
Parametric approach with adjustment	E (SE)[1]	17.0 (4.4)	
	95% CI[2]	[8.3 ; 25.7]	
	p-value[3]	p < 0.001	
Parametric approach without adjustment	E (SE)[4]	17.3 (4.5)	
	95% CI[2]	[8.4 ; 26.2]	
	p-value[5]	p < 0.001	
Non-parametric approach with adjustment	E (SE)[6]	19.7 (4.0)	
	95% CI[2]	[11.8 ; 27.5]	
	p-value[7]	p < 0.001	

N: total number of patients in the treatment group n: number of fully documented patients
1: Estimate (Standard Error) of ivabradine minus placebo effect: difference between group means adjusted on baseline and country factors (main analysis)
2: 95% Confidence Interval of the estimate (two-sided)
3: Student t test based on the overall general linear model (least-squares norm) with baseline as a covariate and country as a random factor
4: Estimate (Standard Error) of ivabradine minus placebo effect: difference between group means
5: Student t test based on the overall general linear model (least-squares norm)
6: Estimate (Standard Error) of ivabradine minus placebo effect: difference between Wilcoxon means adjusted on baseline and country factors
7: Wald test based on the overall general linear model (Wilcoxon norm) with baseline as a covariate and country as a fixed factor

In the FAS-E dataset, patients treated with ivabradine (5 mg bd) showed greater increase in mean total exercise duration (TED) compared with placebo-treated patients over the initial 2-month treatment period, (15.5 ± 60 s and 6.8 ± 56.5 s in the ivabradine and placebo groups, respectively; difference= 8.2 + 3.9 s (95% CI [0.6, 15.7], $p < 0.017$; t test on parametric approach adjusted on country and baseline), although this difference was slightly smaller than that observed after 4 months treatment (Table 4). Comparable results were observed in the PPS-E2 over the 2-month treatment period (between-group difference 7.3 s (95% CI: -0.5, 15.2; $p = 0.033$).

Table 4: TED – Superiority of ivabradine versus placebo in the change from baseline to last value over the 2-month treatment period in the FAS-E

Time (s)		Ivabradine (N = 441)	Placebo (N = 434)
Baseline	n	441	434
	Mean ± SD	445.6 ± 105.6	450.7 ± 107.5
	Median	434	432
	Min - Max	224 - 716	221 - 720
End	Mean ± SD	461.1 ± 116.8	457.4 ± 112.3
	Median	450	436
	Min - Max	106 - 900	192 - 786
End - baseline	Mean ± SD	15.5 ± 60.0	6.8 ± 56.5
	Median	13	5
	Min - Max	-310 - 213	-241 - 226
Within-group changes			
Parametric approach without adjustment	E (SE)[1]	15.5 (2.8)	6.7 (2.8)
	95% CI[2]	[10.1 ; 21.0]	[1.3 ; 12.2]
Non-parametric approach without adjustment	E[3]	15.0	7.0
	95% CI[4]	[9.5; 20.0]	[2.5; 12.0]
Superiority analysis of ivabradine *versus* placebo			
Parametric approach with adjustment	E (SE)[5]	8.2 (3.9)	
	95% CI[6]	[0.6 ; 15.7]	
	p-value[7]	p = 0.017	
Parametric approach without adjustment	E (SE)[8]	8.8 (3.9)	
	95% CI[6]	[1.0 ; 16.5]	
	p-value[9]	p = 0.013	
Non-parametric approach with adjustment	E[10]	7.9 (3.5)	
	95% CI[6]	[1.1 ; 14.7]	
	p-value[11]	p = 0.011	

N: total number of patients in the treatment group n: number of fully documented patients
1: Estimate (Standard Error) of the difference END – Baseline: mean of the differences within group
2: 95% Confidence Interval of the estimate (two-sided) based on the overall general linear model (least-squares norm)
3: Estimate of the difference END – Baseline: Hodges-Lehmann estimator within group
4: 95% Confidence Interval of the estimate (two-sided) based on Walsh averages
5: Estimate (Standard Error) of ivabradine minus placebo effect: difference between group means adjusted on baseline and country factors
6: 95% Confidence Interval of the estimate (two-sided)
7: Student t test based on the overall general linear model (least-squares norm) with baseline as a covariate and country as a random factor
8: Estimate (Standard Error) of ivabradine minus placebo effect: difference between group means
9: Student t test based on the overall general linear model (least-squares norm)
10: Estimate (Standard Error) of ivabradine minus placebo effect: difference between Wilcoxon means adjusted on baseline and country factors
11: Wald test based on the overall general linear model (Wilcoxon norm) with baseline as a covariate and country as a fixed factor

Secondary efficacy results (based on ETT)

The mean time to 1 mm ST segment depression (TST) showed significantly greater increase between baseline and last value over the 4-month treatment period in the ivabradine group compared to the placebo group (45.7 ± 93.0 s and 15.4 ± 86.6 s, respectively; difference= 28.5 s, 95% CI: 16.8 ; 40.3, p<0.001 adjusted on baseline and country factors). This result was supported by the parametric analysis without adjustment and the nonparametric analysis, as well as by the analyses of the PPS-E4, where the estimate of the between-group difference was 33.4 s (95% CI: 21.2, 45.7; p < 0.001). The significant difference between treatment groups were observed even over the 2-month treatment period in the FAS-E: (35.0 ± 84.1 s and 7.8 ± 82.6 s with ivabradine and placebo, respectively; difference= 25.3 s, 95% CI: 14.4, 36.3, p < 0.001).

In general, the time to onset of angina pain closely followed the time to 1 mm ST segment depression, both at baseline and at the end of the 4-month treatment period. Over the 4-month treatment period, time to onset of angina pain (in the FAS-E) showed significantly greater increase in the ivabradine group (+ 49.1 ± 83.3 s) compared with placebo (+22.7 ± 79.1 s) with a between-group difference of 25.5 s (95% CI: 15.0, 36.0, p < 0.001). This result was supported by the parametric analysis without adjustment and the non-parametric analysis, as well as by the analyses of the PPS-E4 (difference=29.0 s, 95% CI: 18.2, 39.8; p < 0.001). These results were also favourably supported by the change over the 2-month treatment period in the FAS-E (30.2 ± 72.2 s and 17.2 ± 72.3 s with ivabradine and placebo, respectively; difference= 12.3 s, 95% CI: 2.9, 21.7; p = 0.005), although the difference was smaller than that observed at 4 months.

The time to limiting angina pain shortly (less than 5 s) preceded the time of TED, both at baseline and at the end of the 4-month treatment period. The values showed significantly greater increase in the ivabradine group compared with placebo (26.0 ± 65.7 s and 9.4 ± 63.8 s, respectively; between-group difference in change of 16.3 s, 95% CI: 7.9, 24.7, p < 0.001) in the FAS-E adjusted on baseline and country factors. This result was supported by the parametric analysis without adjustment and the non-parametric analysis, as well as by the analyses of the PPS-E4, with an estimate of the between-group difference of 17.4 s (95% CI: [8.7 ; 26.1]; p < 0.001). Significant difference between treatment groups was also observed over the 2-month treatment period in the FAS-E (17.0 ± 60.7 s and 8.2 ± 56.8 s with ivabradine and placebo, respectively; difference in change of 8.2 s, 95% CI: 0.6, 15.8; p = 0.018), although the difference was almost half of that observed at 4 months.

The mean resting HR (in the standing position just before commencing ETT and at the trough of drug activity) showed statistically significantly greater decrease over the 4-month treatment period in the ivabradine group compared with placebo in the FAS-E (by 10.8 ± 10.8 bpm and 2.2 ± 10.1 bpm, respectively; difference between groups= -8.8 bpm, 95% CI: -10.0, -7.6,). One third of patients in the FAS-E ivabradine group (153/441; 34.7%) experienced a drop in HR of between 0 and 10 bpm, 28.6% of patients (126/441) experienced a drop of between 10 and 20 bpm and 20.2% (89/441) experienced a drop of more than 20 bpm. However, the > 20 bpm drop was mainly experienced by patients having higher resting HR at baseline (mainly patients with HR > 70 bpm at baseline). The reduction in mean resting HR was also seen over the 2-month treatment period (9.7 ± 10.5 bpm in the ivabradine group and by 2.2 ± 10.6 bpm in the placebo group).

The mean HR at peak of exercise also showed greater decrease between baseline and last value over 4 months (in the FAS-E) in the ivabradine group (by 11.3 ± 13.2 bpm) compared with the placebo group (by 0.9 ± 12.3 bpm), with a between-group difference in change of –10.8 bpm (95% CI =-12.4 ; -9.1). Mean HR at peak of exercise over the 2-month treatment

period decreased by 8.9 ± 11.7 bpm in the ivabradine group and by 0.1 ± 11.0 bpm in the placebo group in the FAS-E (between group difference was -9.2 bpm, 95% CI: -10.7, -7.8).

In the ivabradine group, rate pressure product (RPP) showed a greater decrease over the 4-month treatment period in the ivabradine group compared to placebo, both at rest (by 1269 ± 1655 units and 360 ± 1622 units in ivabradine and placebo groups, respectively) and at peak of exercise (by 1630 ± 3474 units and 66 ± 3447 units, respectively). Results were similar over the 2-month treatment period in the FAS-E.

All patients stopped the ETT for the reason of limiting angina at baseline, while at M4, 76.7% of the patients in the ivabradine group have stopped for this reason compared with 85.2% in the placebo group.

Symptomatology of angina

During the run-in period, (when patients in both groups received only atenolol background treatment) relatively few angina attacks were experienced, (mean 1.8 ± 3.3 attacks/week in ivabradine group and 1.6 ± 2.4 in placebo group). Only a slight non-significant decrease of the number of angina attacks/week was observed in both groups after 4 months (-0.9 ± 2.6 and -0.7 ± 1.8 attacks/week in ivabradine and placebo group, respectively). In patients with at least one angina attack during the run-in (N = 625), the relative number of angina attacks/week was decreased after 4 months by 52.4% ± 76.3 (median = 70.3%) in the ivabradine group and by 45.6% ± 66.8 (median = 64.6%) in the placebo group with no significant difference between treatment groups.

During the run-in period (when patients in both groups received only atenolol background treatment) there was relatively low SAN global consumption, that is, consumption of SAN for angina attacks and for prophylaxis (1.0 ± 2.1 and 1.2 ± 2.9 intake/week in ivabradine and placebo groups, respectively). Half of the patients in the FAS-A (485/885 patients [54.8%]) did not take any SAN during the run-in period. There was only a slight decrease in the mean number of SAN intake/week in both groups after 4 months (-0.3 ± 1.3 and -0.5 ± 1.7 intake/week, respectively) and 2 months with no significant difference between treatment groups. In patients with at least one SAN intake during the run-in period (of the FAS-A, n= 400), the relative number of intakes/week was decreased by 37.5% ± 88.7 (median = 63.4%) in the ivabradine group and by 42.1% ± 72.5 (median = 66.7%) in the placebo group, over the 4-month treatment period, with no significant difference between groups.

Results for consumption of SAN for angina attacks only followed the same trend as for global consumption.

Summary of efficacy

Compared with placebo, ivabradine treatment (5 mg bd for 2 months followed by 7.5 mg bd for another 2 months) showed statistically significant improvements in total exercise duration, time to 1 mm ST segment depression and time to onset of angina in 889 patients with chronic stable angina (with normal sinus rhythm), who were receiving atenolol (50 mg od). Statistically significant improvements over placebo were observed at both 2 months and 4 months, suggesting that 5 mg bd was also associated with significant improvement. However, the clinical relevance of these results is not clear as the difference between ivabradine and placebo groups in mean increase (in TED) was only 7 seconds following 2 months treatment with ivabradine 5 mg and 16 seconds following additional 2 months treatment with ivabradine 7.5 mg. Furthermore, there was no significant improvement in number of angina attacks or consumption of short-acting nitrates, although interpretation of results was limited by low incidence of angina in patients being treated with the beta-blocker.

Significant improvements in exercise tolerance were associated with the expected reduction in HR (both resting and at peak exercise) and rate pressure product.

Initial Submission - Safety

Overview

Adverse events, vital signs at rest (blood pressure, HR), ETT safety parameters (blood pressure at rest and at peak of exercise), 12-lead ECG parameters (central reading) and biological parameters were evaluated; 24-hour Holter ECG parameters (central reading) were measured on a sub-group of 180 patients (90 patients in each treatment group). The Safety Set consisted of all 889 randomised patients, 449 in the ivabradine group and 440 in the placebo group. No patients were excluded from the Safety Set. The Safety Set Holter (SSH) consisted of 180 patients, 90 in the ivabradine group and 90 in the placebo group, recruited in selected centres involved in the Holter sub-study. Patients treated with ivabradine had slightly higher incidence of treatment-emergent adverse events (AEs), treatment-related AEs and discontinuations due to AEs compared with placebo-treated patients. However, the incidence of non-fatal serious adverse events (SAEs) and deaths was low and similar in both treatment groups (Table 5).

Table 5: Overall summary of safety results after randomisation – Safety Set

		Ivabradine (N = 449)	Placebo (N = 440)
Patients having reported			
at least one emergent adverse event	n (%)	130 (29.0)	92 (20.9)
at least one treatment-related emergent adverse event	n (%)	41 (9.1)	12 (2.7)
heart rate decrease / sinus bradycardia / bradycardia	n (%)	19 (4.2)	2 (0.5)
visual adverse event	n (%)	9 (2.0)	4 (0.9)
Patients who died	n (%)	1 (0.2)*	2 (0.5)**
Patients having experienced at least one emergent non-fatal SAE	n (%)	13 (2.9)	8 (1.8)
Patients withdrawn			
due to an adverse event (excluding suicide)	n (%)	12 (2.7)	3 (0.7)
due to heart rate decreased / sinus bradycardia / bradycardia	n (%)	5 (1.1)	-
due to a serious adverse event	n (%)	5 (1.1)	3 (0.7)
due to a treatment-related adverse event	n (%)	5 (1.1)	-
due to a treatment-related serious adverse event (bradycardia)	n (%)	1 (0.2)	-

** Suicide; ** After last study drug intake*

Adverse Effects

In the Safety Set (N = 889), the incidence of patients with at least one emergent adverse event was higher in the ivabradine group (29%, 130/449) compared with the placebo group (20.9%, 92/440). The incidence of treatment-related AEs was also higher in the ivabradine group (ivabradine versus (vs) placebo: 9.1% vs 2.7%), mainly bradycardia (asymptomatic or symptomatic, 4.2% vs 0.5%) and visual adverse events (2.0% vs 0.9%). The *System Organ Classes* (SOCs) showing greater (≥ 1%) event incidence in the ivabradine group compared with the placebo group were *Cardiac Disorders* (6.7% vs 2.5%), *Investigations* (6.0% vs 2.0%), *Vascular Disorders* (3.8% vs 1.6%), *Metabolism and Nutrition Disorders* (2.4% vs 0.9%) and *Blood and Lymphatic System Disorders* (1.1% vs none). The most commonly reported emergent adverse events that were also more frequently (≥ 1%) reported in the ivabradine group were asymptomatic bradycardia (3.1% vs 0.5%), inadequately controlled blood pressure (2.4% vs 0.5%), angina pectoris (1.3% vs 0%), ventricular extrasystoles (1.3% vs 0.2%) and symptomatic bradycardia (1.1% vs 0%) (Table 6).

Table 6: Most frequently reported emergent adverse events (in at least 0.5% of the patients in either group) in the Safety Set

Adverse event (Preferred term)	Ivabradine (N = 449)			Placebo (N = 440)		
	NEAE	n	%	NEAE	n	%
Heart rate decreased*	15	14	3.1	2	2	0.5
Blood pressure inadequately controlled	14	11	2.4	2	2	0.5
Angina pectoris	8	6	1.3	-	-	-
Ventricular extrasystoles	7	6	1.3	1	1	0.2
Dizziness	6	5	1.1	2	2	0.5
Phosphenes	5	5	1.1	3	3	0.7
Headache	5	5	1.1	2	2	0.5
Sinus bradycardia / Bradycardia**	5	5	1.1	-	-	-
Back pain	7	4	0.9	6	5	1.1
Nasopharyngitis	4	4	0.9	6	6	1.4
Influenza	4	4	0.9	2	2	0.5
Hypotension	3	3	0.7	3	3	0.7
Anaemia	3	3	0.7	-	-	-
Gastritis	2	2	0.4	5	5	1.1
Diarrhoea	2	2	0.4	5	3	0.7
Arteriogram coronary	2	2	0.4	2	2	0.5
Asthenia	2	2	0.4	4	2	0.5
Transaminases increased	2	2	0.4	2	2	0.5
ALL	**215**	**130**	**29.0**	**138**	**92**	**20.9**

** The preferred term "heart rate decreased" was used to code asymptomatic bradycardia*
*** The preferred terms "sinus bradycardia" and "bradycardia" were used to code symptomatic bradycardia and are grouped together in this table*
NEAE: number of emergent adverse events
N: total number of exposed patients in the considered treatment group
n: number of affected patients
% = (n/N) x 100

Most of the treatment-related AEs concerned adverse reactions already described in the European Summary of Product Characteristics (SPC) for ivabradine as very common (phosphenes)[5], common (blurred vision, HR decreased/bradycardia, headache, dizziness), or uncommon (diarrhoea, muscle cramp) (Table 7). All cases of emergent decreased heart rate, sinus bradycardia/bradycardia and phosphenes/blurred vision observed during the study were considered by the investigator as related to the study treatment. However, inadequately controlled blood pressure, ventricular extrasystoles, and angina pectoris were not considered as being related to the study treatment. Of the 50 treatment-related emergent adverse events observed in the ivabradine group, six led to treatment discontinuation: five cases of bradycardia (one asymptomatic HR decrease, three sinusal and one non-specified bradycardia) and one case of dizziness. There were no treatment-related emergent adverse events leading to treatment discontinuation in the placebo group.

[5] A phosphene is an entoptic phenomenon characterized by the experience of seeing light without light actually entering the eye.

Table 7: Treatment-related emergent adverse events in the Safety Set

Preferred term	Ivabradine (N = 449)			Placebo (N = 440)		
	NEAE	n	%	NEAE	n	%
Heart rate decreased*	15	14	3.1	2	2	0.5
Sinus bradycardia / Bradycardia**	5	5	1.1	-	-	-
Phosphenes	5	5	1.1	3	3	0.7
Dizziness	4	3	0.7	-	-	-
Palpitations	2	2	0.4	-	-	-
Asthenia	1	1	0.2	3	1	0.2
Visual disturbance	1	1	0.2	1	1	0.2
Gastritis	1	1	0.2	1	1	0.2
Anaemia	1	1	0.2	-	-	-
Blood uric acid increased	1	1	0.2	-	-	-
Bundle branch block right	1	1	0.2	-	-	-
Diarrhoea	1	1	0.2	-	-	-
Diplopia	1	1	0.2	-	-	-
Dry mouth	1	1	0.2	-	-	-
Dyspepsia	1	1	0.2	-	-	-
Electrocardiogram QT prolonged	1	1	0.2	-	-	-
Headache	1	1	0.2	-	-	-
Hyperhidrosis	1	1	0.2	-	-	-
Muscle cramp	1	1	0.2	-	-	-
Nasopharyngitis	1	1	0.2	-	-	-
Photophobia	1	1	0.2	-	-	-
Photopsia	1	1	0.2	-	-	-
Transaminases increased	1	1	0.2	-	-	-
Vision blurred	1	1	0.2	-	-	-
Conjunctivitis	-	-	-	1	1	0.2
Arrhythmia	-	-	-	1	1	0.2
Fatigue	-	-	-	1	1	0.2
Gastroenteritis	-	-	-	1	1	0.2
Rash papular	-	-	-	1	1	0.2
Libido decreased	-	-	-	1	1	0.2
ALL	**50**	**41**	**9.1**	**16**	**12**	**2.7**

NEAE: number of treatment-related emergent adverse events
N: number of exposed patients in the considered treatment group
n: number of patients affected
% = (n/N) x 100
** The preferred term HR decreased was used to code asymptomatic bradycardia*
*** The preferred terms sinus bradycardia and bradycardia were used to code symptomatic bradycardia and are grouped together in this table.*

Adverse Effects of Special Interest

Bradycardia

In the ivabradine group, bradycardia led to treatment withdrawal in five patients, to temporary interruption in one patient, and to reduction of the dose in one patient. In all patients, the episodes of bradycardia were of mild (13/19) or moderate (6/19) intensity, with

no case reported as severe. One case of bradycardia was reported as serious and required hospitalisation. Most patients (15/19) recovered and four were not recovered according to last information available. In the placebo group, both cases were not recovered. Among the 19 cases of HR decrease/bradycardia in the ivabradine group, 11 occurred between M0 and M2 (when the patients were treated with 5 mg dose). Eight cases appeared after M2, seven of them under the 7.5 mg dose.

Inadequately controlled blood pressure

An unexpected finding was the higher incidence of inadequately controlled BP in the ivabradine group compared with placebo (2.4% vs 0.5%). Out of the 11 patients in the ivabradine group with "inadequately controlled blood pressure", only one was at a resting supine measurement. The event occurred under ivabradine 5 mg treatment in eight out the 11 patients. It should be noted that all patients with this adverse event had a medical history of hypertension. None of the occurrences were considered as related to the study treatment by the investigator, none were severe or led to treatment discontinuation, and all recovered. An added therapy was started in 10/11 patients in the ivabradine group compared with 2/2 in the placebo group. After added therapy blood pressure was controlled in all patients at the following visit.

Emergent angina

Another unexpected finding was the slightly higher incidence of emergent angina in ivabradine-treated patients compared with placebo (1.3% vs 0%). The six cases of an emergent event of angina pectoris in the ivabradine group were all considered as being unrelated to study treatment by the investigator and appeared to be due to the progression of the disease as four of these patients had history of myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA) and/or coronary artery bypass graft (CABG). In four patients, the event occurred between M0 and M2 (that is, on the 5 mg dose), one was on the day of the M2 visit and one was strictly after M2 on the 7.5 mg dose (having being up-titrated following an HR measurement of 52 bpm at the M2 visit).

Other cardiac adverse events

Emergent events of ventricular extrasystoles were more frequent in the ivabradine group (6 patients; 1.3%) than in the placebo group (1 patient; 0.2%). All but one (ivabradine group) spontaneously recovered. Emergent ventricular tachycardia was reported by three patients: two patients in the ivabradine group had ventricular tachycardia of moderate intensity during the M2 ETT; the first patient had non-sustained supraventricular tachycardia at SEL1, SEL2 and M0 ETTs according to the Core Reading Centre. The second patient, had ventricular tachycardia (moderate intensity) reported by the investigator during the M4 ETT. However, for this last patient, the presence of ventricular tachycardia was not confirmed by ETT central reading. One patient in the placebo group had ventricular tachycardia of severe intensity during M4 the ETT. All were non-sustained ventricular tachycardia and none appeared to be related to the study treatment according to the investigator.

Visual AEs

Overall, nine patients (2.0%) in the ivabradine group and four (0.9%) in the placebo group had visual adverse events. Phosphenes, which are commonly reported with ivabradine, were observed in five patients (1.1%) in the ivabradine group versus three (0.7%) in the placebo group. In both groups, all cases of visual adverse events were considered as treatment-related by the investigator and recovered spontaneously. None led to treatment discontinuation. No severe case was reported and no patients were withdrawn for a visual AE.

Deaths, SAEs and Discontinuations due to AEs

There was one death (suicide; ivabradine) during the randomised study period. Two patients in the placebo group died after last study drug intake, one from myocardial infarction, and the other from sudden death. Overall, none of these deaths appeared to be related to study medication.

In the Included Set (N = 889), 21 patients (2.4%) experienced an emergent non-fatal serious adverse event during the double-blind treatment period: 13 in the ivabradine group (2.9%) and 8 in the placebo group (1.8%).These concerned mostly cardiac disorders, in relation with the disease, including five patients (1.1%) in the ivabradine group and two (0.5%) in the placebo group. Other serious adverse events concerned various system organ classes with no particular relationship with the disease or study treatment. The majority of the patients with non-fatal SAEs appeared to recover.

Of the 13 ivabradine-treated patients withdrawn from the study, one was due to suicide, five were due to SAEs and seven were due to non-serious AEs. In all, 4 patients were withdrawn due to symptomatic bradycardia, including one with associated angina pectoris, and one each of asymptomatic bradycardia, angina pectoris, unstable angina, cardiac failure, dizziness, gastric ulcer haemorrhage, suicide, coronary anteriogram and foot fracture. Only the events linked to HR reduction and dizziness were considered by the investigators to be related to the study drug. Except for the patient who committed suicide, all patients recovered after treatment discontinuation (with sequelae for the case of cardiac failure). Of the three placebo-treated patients withdrawn from the study (during the period M0-M4), all were due to SAEs.

Laboratory Parameters, Vital Signs

Emergent high out-of-reference range values of creatinine were more frequent in the ivabradine group (8.4%) than in the placebo group (3.5%), as already observed in previous clinical studies. However, no emergent potentially clinically significant abnormal (PCSA) value (that is, > 180 μmol/L) was observed and only two patients in the ivabradine group had an abnormal value considered as clinically significant at M4 under treatment (with adverse event reported), *versus* none in the placebo group. Emergent high out-of-reference range values of transaminases were also slightly more frequent in the ivabradine group than in the placebo group. For only 2 patients in each group these emergent values of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were considered as clinically significant by the investigator and were reported as adverse events (with a relationship to the study drug for one case in the ivabradine group). One more patient in the ivabradine group had an elevated ALT value at baseline (44 IU/L) which increased to 167 IU/L under treatment. In the placebo group one other patient had abnormal values of AST and ALT at baseline which increased further under treatment and were reported as an adverse event, and another had an ALT value within the reference range at baseline (17 IU/L) and a PCSA value on treatment (130 IU/L), but no adverse event was reported.

In contrast, fewer emergent high values of uric acid and CPK were observed in the ivabradine group than in the placebo group. A total of 25 patients had an emergent low platelet values during the 4-month treatment period (2.8% and 3.1% in ivabradine and placebo groups, respectively). Furthermore, two more patients showed abnormal low platelet values at baseline which worsened and became inferior to the lower limit of PCSA values, or were considered as clinically significant on treatment by the investigator. An adverse event of thrombocytopenia with no relationship to the study drug was reported, and the patient had not recovered at the end of the study. In the placebo group, one patient had PCSA low platelet count (104 at M0 ; 82 at M4). High emergent platelet counts were reported in one patient on ivabradine and two on placebo.

No relevant change in systolic and diastolic blood pressure at rest and at peak of exercise was observed in either group from baseline to last value over the 4-month or 2-month treatment period. No cases of ventricular fibrillation and sustained ventricular tachycardia were observed during ETT in the study. One patient (0.2%) in the ivabradine group at M2, and three patients (0.7%) in the placebo group (1 at M2 and 2 at M4) had emergent non-sustained ventricular tachycardia. No patient in the ivabradine group had ST segment depression > 4 mm during the study. In the placebo group, three patients (0.7%) at M2 and one patient (0.2%) at M4 had ST segment depression > 4 mm not present at baseline.

There were no significant changes in mean BP or weight at rest, while HR was decreased in the ivabradine group as expected.

ECG and 24-Holter Analysis

ECG abnormalities

Only assessable ECGs in sinus rhythm were taken into account in the analyses presented. Absence of sinus rhythm was observed in five patients (2 in the ivabradine group and 3 in the placebo group) at M0, five patients (3 and 2 respectively) at M2, and seven patients (3 and 4 respectively) at M4. Compared with placebo, a statistically significant and clinically relevant decrease in HR was observed in the ivabradine group at M2, confirmed at M4. The RR interval was markedly increased in the ivabradine group from baseline to last value over the 4-month treatment period by 149.6 ± 162.1 ms, whereas only a slight increase by 34.3 ± 138.0 ms, with no clinical relevance, was seen in the placebo group. No relevant change was observed in any group for PR interval and QRS duration. In accordance with the observed decrease in HR, the uncorrected QT interval was increased by (mean$\pm$SD) 22.7 ± 24.7 ms in the ivabradine group compared with no relevant change in the placebo group. However, the corrected QT intervals (QTc) showed no relevant increase in ivabradine or placebo groups. No patient showed QTc above 500 ms, neither at baseline nor on treatment, with either correction.

At baseline, patients with ECG abnormalities were slightly more numerous in the ivabradine group (85.6%, 380/444) than in the placebo group (80.9%, 348/ 440 patients with analysable ECG in sinus rhythm). During the treatment period, the percentage of patients with at least one ECG abnormality was comparable to that observed at baseline in both groups at M2: (85.5 and 81.7% in the ivabradine and placebo groups, respectively) and at M4 (85.9% and 82.7%, respectively). At all visits, the most frequent reported ECG abnormality was ischaemia, in relation with the ongoing disease. At M0, ischaemia was more frequent in the ivabradine group (52.0% of patients with analysable ECG) than in the placebo group (45.1%). At the end of the treatment period (M4 visit), the percentage of patients with ischaemia was similar to baseline in the ivabradine group (51.8%) whereas it increased to 49.6% in the placebo group.

Of note, first degree atrioventricular (AV) block was more frequent in the ivabradine group at M2 (8.3%) and M4 (10.7%) than at M0 (6.8%) while it remained stable in the placebo group: 5.3% at M0, 6.5% at M2 and at M4. At last assessment under treatment in fully documented patients, the incidence of emergent first degree AV block in the ivabradine group was twice that observed in the placebo group (4.9% vs 2.6%). However, this abnormality has been already reported with ivabradine treatment as mentioned in the European SPC for ivabradine.

Prolonged QT interval was also more frequently reported as an abnormality (defined as value of QT and/or QTc was > 450 ms in men and > 470 ms in women) in the ivabradine group at M2 (7.8%) and M4 (8.6%) than at M0 (3.8%). In the placebo group, the number of cases of prolonged QT interval was also more frequent at M4 (4.6%) than at M0 (2.8%).Other

abnormalities were reported in similar proportions at M0, M2, and M4 in both groups, with no relevant differences between them.

24-hour Holter monitoring results

24-hour Holter monitoring was performed in patients of selected centres at M0, M2, and M4 visits, and sent to the Core Reading Centre for central reading of HR and abnormalities. A total of 180 patients were included in the Safety Set Holter (SSH), that is, patients having performed at least one Holter analysable by central reader. Ninety patients in each group were included in the analysis. Lowest, highest and mean HR were measured for each patient over the total 24-hour period, the awake time, sleep time, diurnal, and nocturnal periods. Mean, lowest and highest HRs was averaged on 6-RR intervals. As expected, clinically relevant decreases of mean HR were observed in the ivabradine group (around -8 bpm from baseline to M2 and -10 bpm from baseline to end of treatment period at any time of the day) compared to no change in the placebo group. During the awake period at the M4 visit (or last value over study period), the mean HR was 58.9 ± 8.2 bpm on ivabradine vs 68.5 ± 7.7 bpm on placebo whereas during the sleep period, mean HR was 52.3 ± 6.6 vs 59.5 ± 8.2 bpm, respectively.

The lowest mean value of HR over the 24-hour period in ivabradine group was 45 bpm at the end of the treatment period compared with 48 bpm in placebo group. In the ivabradine group 72.0% of patients had a HR < 60 bpm over the 24-hour period (26.8% at baseline), whereas in the placebo group 18.6% of patients had a HR < 60 bpm (24.4% at baseline). The analysis of lowest HRs revealed a mean change over the 4-month period for the ivabradine group of -6.9 ± 5.5 bpm during the awake and -6.7 ± 5.0 bpm during the sleep period. The changes in the placebo group were negligible. Patients with HR values < 40 bpm at the end of the treatment period were also more numerous in the ivabradine group than in the placebo group during all periods.

Highest HR was changed from a mean (± SD) of 110.6 ± 14.6 bpm at baseline to 96.3 ± 15.4 bpm at end of the treatment period in the ivabradine group (mean change of -14.3 ± 16.6 bpm), and from 109.7 ± 15.4 bpm to 106.8 ± 14.1 bpm in the placebo group (mean change of -3.0 ± 14.3 bpm).

The incidence of bradycardia over the 24-hour period (defined as HR < 40 bpm averaged over at least 3-RR intervals, excluding compensatory pauses) was higher in the ivabradine group compared with placebo at both M2 (18.2% vs none) and at the last assessment under treatment [29.3% (24 patients in the ivabradine group, including 15 during awake with 5 patients with bradycardia lasting more than 15 minutes)] compared with 1.2% [1 patient in the placebo group, during awake)]. None were reported as symptomatic adverse event by investigators. The maximum number of episodes of bradycardia (≥ 3) was 876 with a total duration of 159 minutes in a patient in the ivabradine group at M4; in the placebo group a patient had 713 episodes with a total duration of 146 minutes at M2. No bradycardia during sleep (HR < 30 bpm) was observed during the study.

The incidence of pauses was comparable in the two treatment groups. No patient had any pauses during sleep (RR interval > 3.0 s). No junctional rhythm disturbance was observed during the study.

One patient in the ivabradine group had an emergent second degree AV block, at M2, all during sleep (he presented at M0 with an intermittent first degree AV block). No third degree AV block was observed during the study.

One patient (1.2%) in each group had an emergent atrial fibrillation under treatment. Ventricular premature depolarisations (VPDs) were common at baseline, present in 82.9% of

patients in the ivabradine group and 87.2% in the placebo group. At the end of the treatment period, VPDs were present in 84.1% in the ivabradine group and 86.0% in the placebo group. Emergent VPDs were more frequent in the ivabradine group than in the placebo group, as already observed in previous clinical studies. Overall, an average of 2.5 patients in the ivabradine group had > 5 VPD per hour at ≥ one visit compared with 3 in the placebo group.

Accelerated idioventricular rhythm (AIVR; that is, a run of ≥ 3 consecutive VPD with HR 60 - 100 bpm) was observed at baseline in one patient (1.2%) in the ivabradine group and three (3.5%) in the placebo group. No relevant difference between groups was observed in emergent ventricular tachycardia, (that is, a run of ≥ 3 consecutive VPD with HR ≥ 100 bpm), observed in seven patients in each group. Supraventricular premature depolarisation (SVPD) was common at baseline, present in 97.6% of ivabradine patients and 97.7% of placebo patients. On treatment, emergent doublets were more frequent in the ivabradine group than in the placebo group at both visits. Emergent supraventricular tachycardia (SVT; that is, run of ≥ 3 consecutive SVPD with regular HR ≥ 120 bpm), were more frequent in the ivabradine group than in the placebo group at M2 (14 patients (18.2%) versus 6 (7.6%)) and at last assessment under treatment (10 patients (12.2%) versus 4 (4.7%). Supraventricular extrasystoles are already notified in the European SPC and the current Australian PI for ivabradine as adverse effect.

No torsades de pointes were observed during the study.

Summary of safety

Relatively unexpected was the higher incidence in the ivabradine group of emergent angina pectoris [ivabradine vs placebo: 6 patients (1.3%) vs 0 (0%)] and "inadequately controlled blood pressure" [11 patients (2.4%) vs 2 (0.5%) on placebo]; however, most of these cases appear to be due to the natural progression of the angina in a small number of patients in the ivabradine group, and the incidence of where it was noted that all concerned patients had a medical history of hypertension and that none of the occurrences were considered as being related to the study drug by investigators. There were no clinically relevant changes observed in the Safety Set in biochemical parameters or in vital signs.

Ivabradine-treated patients showed higher incidence of AV-blocks, bradycardia, SVPDs and visual adverse events but the incidence of deaths and non-fatal SAEs was low and similar in both ivabradine and placebo groups.

Initial Submission - Limitations of data

Compared with placebo, ivabradine was associated with greater increase in the total exercise duration following 2 months treatment with 5 mg od and additional 2-month treatment with 7.5 mg od. However, the clinical evaluator concluded in June 2009 that the statistical significance and clinical relevance of the difference between ivabradine and placebo groups (7 to 16 seconds only) did not appear to be meaningful. The patients included in the study appeared to be a highly selected population and results were not consistent across different countries. It appeared that the relative improvement in TED in ivabradine-treated patients may be driven by worsening in some placebo-treated patients. Analysis of proportion of patients who made no improvement or got worse on either ivabradine or placebo treatment may have helped with interpretation of results, but such analysis was not done in the study. Furthermore, there was no significant improvement in number of angina attacks or consumption of short-acting nitrates, although interpretation of results was limited by low incidence of angina in patients being treated with the beta-blocker.

Long term safety and efficacy of ivabradine (beyond 4 months) was not evaluated in this patient population (stable angina on beta-blockers).

Some of the other beta-blockers approved for angina are metoprolol (50-100 mg twice or thrice daily), propranolol (120-320 mg/day) and oxprenolol (20-40 mg three times daily up to maximum daily dose of 320 mg). However, some of these doses are not equivalent to the dose of atenolol 50mg od used in the submitted study. Hence, the safety and efficacy of ivabradine when used with all beta-blockers (at their proposed doses for treatment/prophylaxis of angina) has not been established.

Initial Submission - Clinical Summary and Conclusions

Although ivabradine treatment (5 to 7.5 mg bd) given in combination with atenolol (50 mg od) in patients with stable angina pectoris appeared to show slight improvements in exercise capacity (total exercise duration, time to limiting angina, time to angina onset and time to 1 mm ST segment depression) compared with placebo, the statistical significance and clinical relevance of these improvements did not appear to be meaningful due to limitations of the data (as discussed above).

The safety profile of ivabradine was comparable to that observed in the original Product Information and no unexpected safety concerns were identified. However, the incidence of AEs and discontinuations due to AEs was higher in ivabradine-treated patients compared with placebo, especially that of bradycardia and visual AEs, as expected by the mechanism of action of ivabradine.

Safety and efficacy of concomitant administration of ivabradine with beta-blockers was tested using atenolol 50 mg od only; safety and efficacy of ivabradine when used with other beta-blockers (at their proposed doses for treatment/ prophylaxis of angina) has not been established and the risks of increased AEs following concomitant use of ivabradine with some of these beta-blockers has not been adequately evaluated.

Evaluator's Recommendations in the initial Clinical Evaluation Report

The evaluator recommended in June 2009 that overall, the risk-benefit profile of concomitant administration of ivabradine with beta-blockers does not appear to be favourable and the application for changes to the current Coralan PI should be rejected at this stage.

Supplementary Submission - Introduction

The supplementary submission consisted of two volumes comprising the sponsor's response to the clinical evaluation report and volume 1 (of 442) of the clinical study report (CL3-056; BEAUTIFUL study) as supporting documentation for long-term safety.

Supplementary Submission - Sponsor's Response to the Clinical Evaluation Report

In this section, issues raised in the initial clinical evaluation report are numbered followed by the sponsor's response *(in italics)* and then the evaluator's comments on the sponsor's response, provided to the sponsor in February 2010.

The sponsor subsequently responded to the evaluator's commentary on the Supplementary Submission, in March 2010. Where appropriate, these responses are in brackets and follow the evaluator's comments.

1. Population selection: "It appears that a highly selected group of patients was included in this study as 1792 of 2622 patients were not eligible for the study."

Of the 2622 screened patients, 1792 did not meet either pre-selection, selection or inclusion criteria. The sponsor clarified that the majority of the ineligible patients (1508/ 1792, 84.2%) were excluded due to negative ETT at first pre-selection visit or inability to meet ETT stability criteria (defined as values of time to 1 mm ST segment depression was not within

±20% or ±1 min at the 2 subsequent pre-selection visits). The other common reasons for exclusion from the study were withdrawn consent (100 patients, 5.6%), other non-selection exclusion criteria (72 patients, 4%), withdrawn for HR<60 bpm at rest (62 patients, 3.5%) or withdrawn due to an AE or poor tolerance to atenolol (50 patients, 2.8 %). The sponsor concluded that the exclusions from the study are therefore in the majority of cases a direct result of complying with the TGA-adopted guideline.

The evaluators agreed that the majority of the exclusions were due to following the TGA guideline of recruiting patients with stable angina (defined as at least 2 standardised tests performed at start of the study where the difference between the tests should not exceed 20% in order to facilitate the assessment of a pure treatment effect).

2. Results across different countries: "At the very least, this suggests something different about the make-up of the populations in that subset of 6 countries vs that subset of 5 countries. It also means that the contribution to the overall results from the group of 6 countries is one which appears in part to be driven by worsening on placebo, not from a positive attribute of ivabradine."

The sponsor cited that significant variability is inherent in employing ETT as the primary outcome measure as required by the TGA-adopted guidelines. This inherent variability is reflected in the current analysis and is an expected finding.

While the evaluators acknowledge that ETT does have significant variability, they also suggested that analysis of the proportion of patients who made no improvement or got worse on ivabradine or placebo treatment may have helped interpretation of results, but such an analysis was not provided. The proportion of patients with no improvement or worsening would provide a more relevant understanding about the effects of ivabradine. This remains a significant limitation of the study.

3. Primary efficacy results: "The study had 95% power to detect at least 30 second difference between ivabradine and placebo groups."

"However, clinical relevance of these results is not clear as the difference between ivabradine and placebo groups in mean increase in TED was only 7 seconds following 2 months treatment with ivabradine 5 mg and 16 seconds following additional 2 months treatment with ivabradine 7.5 mg."

"Although ivabradine (5 mg and 7.5 mg bd) given in combination with atenolol (50 mg od) in patients with stable angina pectoris appeared to show slight improvements in exercise capacity/ TED, time to limiting angina, time to onset of angina and time to 1mm ST segment depression) compared with placebo, the statistical significance and clinical relevance of these improvements do not appear to be meaningful due to limitations of data."

The sponsor noted that ivabradine was associated with a statistically significant improvement over placebo and that these results support the proposed indication. Furthermore, they state that the TGA does not specify the level of efficacy or improvement over placebo that a drug is required to achieve to demonstrate that safety and efficacy is "satisfactorily established"; they also stated that there is no definition in the TGA Act that include a test of "clinical superior efficacy".

Furthermore, the sponsor cited the following to support the statistically significant positive results:-

> *-The 16 seconds improvement in TED observed during the third Stage of the Bruce protocol (which represents a substantial workload with treadmill speed of 5.5 km/h and gradient of 14%) translated to a clinically meaningful improvement when it is*

considered that it was observed during a period of high metabolic energy expenditure and at trough of drug effect. In Stage 3 of the Bruce protocol, where most patients in study CL3-057 had their improvement in TED, the functional capacity of an individual is approximately 9 METS corresponding to activities considered to be of high intensity, that is, bicycling at 25 km/h, jogging at 9 km/h or cross country skiing at 8 km/h (Jette, et al, 1990).[6]

The TGA guidelines clearly state that translation of exercise variables into METs (metabolic equivalent of the task) provides a standard measure of performance regardless of the type of exercise test or protocol used and does not pose major problems when interpreting the clinical relevance of the observed effect. Therefore it is expected that, as the main outcome measure, total exercise capacity is expressed in METS change from baseline. The sponsor has provided change in TED in terms of METS which was not done in the earlier submission and this helps to understand the clinical relevance of the 16 seconds difference in TED between ivabradine and placebo groups.

Based on literature review, study CL3-057 with ivabradine represents the single most compelling demonstration of the benefit of any combination of anti-anginal drugs to date. Most published studies of combination anti-anginal therapy have shown only small and statistically insignificant benefits of the combination on ETT criteria at the trough of drug activity. In a meta-analysis (Klein, 2002), the difference in TED observed at trough of drug activity, between combination of calcium channel antagonists and beta-blockers and beta-blockers as monotherapy was only 4 seconds and not statistically significant.[7] *Furthermore, in this study CL3-057, the improvement in TED was in accordance with improvements in time to limiting angina (TLA), time to angina onset (TAO) and time to 1 mm ST segment depression (TST); improvements in TAO and TST (which is an objective criteria of ischaemia) were 25 seconds and 28 seconds, respectively ($p<0.001$ for both vs placebo) and were relevant considering the workload at this stage of the exercise. Furthermore, the sponsor has clarified that 70% of the ivabradine patients improved their TED and 49% improved their TED by more than 30 seconds.*

In this response by the sponsor, it has provided information on the proportion of ivabradine-treated patients with improved TED and also those with improved TED >30 seconds. Overall, 70% of ivabradine-treated patients show an improvement in TED and approximately, half of the patients (49%) treated with ivabradine showed an improvement (change from baseline) in TED >30 seconds. However, the proportion of placebo-treated patients with improved TED was not provided and hence no comparisons could be made with placebo for this parameter.

The addition of ivabradine to atenolol 50mg/day appeared to be at least as efficacious as increasing the atenolol dose from 50 to 100 mg/day. The sponsor quoted results from a study CL3-017 submitted previously which evaluated the effect of increasing the atenolol dose from 50 to 100 mg/day on ETT parameters in stable angina patients. The study submitted in the recent dossier evaluated effect of adding ivabradine (5 mg to 7.5 mg bd) on atenolol 50 mg/day in stable angina patients. However, the sponsor pointed out that one difference between these 2 studies was the fact that the less strenuous modified Bruce protocol was used in study CL3-017 while the more strenuous standard Bruce protocol was used in study CL3-

[6] Jette M, Sydney K, Blumchem G. Metabolic Equivalents (METS) in Exercise testing, exercise prescription and evaluation of functional capacity. Clin Cardiol 1990; 13: 555-565.

[7] Klein W, Jackson G, Tavazzi L. Efficacy of monotherapy compared with combined antianginal drugs in the treatment of chronic stable angina pectoris: a metanalysis. Coronary Artery Disease 2002; 13: 427-436.

057 implying that the improvements seen following ivabradine plus atenolol 50 mg were observed at a higher workload than those observed following increasing dose of atenolol from 50 to 100 mg/day.

The sponsor has compared results from 2 studies from an earlier submission which used different exercise protocols. This comparison was not pre-specified and was most probably a post-hoc analysis limiting interpretation. Furthermore, the TGA guidelines clearly state that translation of exercise variables into METs (metabolic equivalent of the task) provides a standard measure of performance regardless of the type of exercise test or protocol used and does not pose major problems when interpreting the clinical relevance of the observed effect. Therefore it is expected that, as the main outcome measure, total exercise capacity is expressed in METS change from baseline. However, the results were not expressed in terms of METS and it is difficult to justify the claim that the addition of ivabradine to atenolol 50 mg/day appeared to be at least as efficacious as increasing the atenolol dose from 50 to 100 mg/day.

[The sponsor subsequently provided the results from two studies, in METs, explaining that the METs-based analysis showed that the total gain in work capacity compared favourably for Ivabradine 7.5mg added to atenolol 50 mg compared to uptitration of atenolol 50 mg to 100 mg.]

Ivabradine also shows anti-anginal efficacy in patients who are maximally beta-blocked. In study CL3-057, patients must have received beta-blocker therapy with atenolol 50 mg od or an equivalent dose of another beta-blocker during the 3 months or longer before being selected for the study and still presented with a positive ETT or symptomatic angina in daily life for selection. Furthermore, the sponsor specified that patients who were on atenolol 100 mg od or equivalent beta-blockade were not eligible for the trial.

The exclusion of patients who were on atenolol 100 mg od or equivalent beta-blockade as stated above implies that efficacy of ivabradine in combination with beta-blockade at these dose levels was not evaluated although it is possible that this dose may have been used in patients with chronic stable angina. Whether ivabradine would be effective in symptomatic patients on these doses of beta-blockers (atenolol 100 mg od or equivalent beta-blockade) was not evaluated.

[The sponsor proposed to align the proposed Product Information document with the EU SPC by amending the Clinical Trials section to include a description of study CL3-057, stipulating that the efficacy data available is in patients treated with atenolol 50 mg od]

The sponsor identified a subgroup of patients in study CL3-057 in whom the level of beta-blockade at baseline could be judged as maximal if they had a resting HR of ≤60 bpm and/ or supine SBP<100 mmHg and/ or mean PR interval >200 ms at baseline and a further increase in dose in beta-blocker dose would be inappropriate in these patients. This included only 144 patients representing 16.5% of the full analysis set. This would imply that the beta-blocker dose was sub-optimal in other 83.5% of the patients, but the sponsor mentioned that their dose may have been limited by AEs or other tolerability issues, which were more difficult to quantify and identify objectively. Furthermore, the sponsor stated that efficacy in this subgroup of patients receiving maximal dose of beta-blockers was similar to that observed in the overall population.

As mentioned in the earlier evaluation, in study CL3-057, the treatment difference (between ivabradine and placebo) in the primary efficacy endpoint of total exercise duration in the subgroup of patients receiving maximal dose of beta-blockers was quantitatively similar to that observed in the overall analysis. However, the difference from placebo was not

statistically significant in this subgroup of patients receiving maximal beta-blockers and the 95% CI were wide and included zero (treatment difference= 16.6, p=0.066, 95% CI: -5.04, 37.7), although this analysis may have been limited by small sample size. Furthermore, there was no comparison of efficacy in subgroups of patients who received maximal dose of beta-blockers with those who received sub-maximal doses of beta-blockers.

4. Symptomatology of angina

"There was only a slight decrease in the mean number of SAN intake/week in both groups after 4 months (-0.3 ± 1.3 and -0.5 ± 1.7 intake/week, respectively) and 2 months with no significant difference between treatment groups. In patients with at least one SAN intake during the run-in period (of the FAS-A, n= 400), the relative number of intakes/week was decreased by 37.5 ± 88.7% (median = 63.4%) in the ivabradine group and by 42.1 ± 72.5% (median = 66.7%) in the placebo group, over the 4-month treatment period, with no significant difference between groups. Results for consumption of SAN for angina attacks only followed the same trend as for global consumption.

There was no significant improvement in number of angina attacks or consumption of SAN, although interpretation of results was limited by low incidence of angina in patients being treated with the beta-blocker."

The sponsor mentioned that consumption of nitrates and incidence of angina attacks per week are just secondary efficacy criteria according to the TGA guidelines.

Furthermore, it stated that the decrease in mean number of angina attacks per week (AA/w) was greater in the more symptomatic patients (those with 1, 2 or 3 AA/w).

However, it is important to note that the placebo response was equally good in these symptomatic patients and there was only a slight difference between ivabradine and placebo even in the most symptomatic patients; mean change from baseline in AA/w was -3.3±5.5 vs -2.4±3.7 AA/w in ivabradine and placebo groups, respectively. The evaluators accepted that consumption of nitrates and incidence of angina attacks per week only help to provide supportive evidence of efficacy and are secondary endpoints only.

Furthermore, the sponsor has provided subgroup efficacy analysis in 247 patients with refractory angina (122 and 125 patients in ivabradine and placebo groups, respectively). In this subgroup, there were no statistically significant differences between ivabradine and placebo groups in baseline characteristics. Ivabradine treatment produced statistically significant greater improvements in TED and TST compared with placebo in patients with refractory angina. Similar results were observed in patients without refractory angina.

Although, not statistically significant, there were some differences in baseline characteristics between 2 groups which may have had an impact on the interpretation of results in this subgroup. There were more females in ivabradine group (ivabradine vs placebo: 22.1% vs 13.6%), but more patients with CCS-III angina in the placebo group (9% vs 16%) and mean time since angina diagnosis was also longer in placebo group (66 vs 73 months); furthermore, history of heart failure was also greater in the placebo group (13.1% vs 24.8%). Both groups were similar in terms of history of CABG, PTCA and extent of coronary disease. However, overall patients in the placebo group seemed to be worse off clinically than those in the ivabradine group. The wide confidence intervals in the subgroup of patients with refractory angina along with differences in baseline disease characteristics make interpretation of efficacy in this subgroup difficult.

5. Long term safety and efficacy: "Long term safety and efficacy of ivabradine (beyond 4 months) was not evaluated in this patient population (stable angina on beta-blockers)."

Since registration, a morbidity-mortality study has been completed: The BEAUTIFUL study (CL3-056) was an international, multi-centre, randomised, parallel-group, double-blind, placebo-controlled trial to evaluate the effect of ivabradine on mortality and the incidence of cardiovascular events in patients with coronary artery disease (CAD) and left ventricular dysfunction (LVD). It involved 10907 patients and the majority of the patients enrolled in this study differed from the scope of the current submission for ivabradine. The subgroup of patients with limiting angina at baseline is the closest to the population indicated in the current PI for ivabradine and was defined as follows:-presence of symptoms limiting physical activity and whether they were related to limiting angina or due to heart failure symptoms (fatigue, palpitations or dyspnoea). Patients with limiting symptoms of angina were in NYHA Classes II or III (slight and marked limitation, respectively, of physical activity due to angina pectoris) which is equivalent to CCS Classes II or III. Overall, a subgroup of 1507 patients (13.8% of randomised patients) was identified as having limitation of activity mainly related to angina and not to heart failure symptoms; the median duration of treatment in this subgroup was 18 months in the ivabradine and placebo treatment groups. In this subgroup, no safety signal was identified regarding cardiovascular death, hospitalization for acute MI or heart failure (ivabradine vs placebo: 12% vs 15.5%, p=0.05).

The majority (n=9487) of the patients also took beta-blockers and safety results in these patients were relevant to the use of ivabradine in combination with beta-blockers in patients with stable angina. The most frequently prescribed beta-blockers in this study were carvedilol, followed by metoprolol and bisoprolol. Overall, 95% were taking medications for heart failure (HF) symptoms and 64% were taking medications for angina symptoms.

Of the patients with limiting angina, 1351 (89.7%) were taking beta-blockers (654 and 697 patients in ivabradine and placebo groups, respectively). In this subgroup, AE incidence was slightly higher in the ivabradine group (ivabradine vs placebo: 52.3% vs 50.8%), although the rate of serious AEs was slightly lower in the ivabradine group (15.3% vs 17.4%). The overall rate of cardiac AEs was slightly lower in the ivabradine group (12.7% s 15.0%) despite the higher incidence of bradycardia in the ivabradine group (3.1% vs 1.2%). The lower rate of cardiac AEs in ivabradine group was largely due to lower rates of atrial fibrillation (2.2% vs 4.0%) and ventricular extrasystoles (1.6% vs 3.5%) compared to placebo. The incidence of angina as an AE was slightly less in the ivabradine group compared with placebo in the full study population (2.5% vs 3%); however, in the subgroup of patients with stable angina taking beta-blockers, ivabradine treatment was associated with an even lesser incidence of angina pectoris compared with placebo (3.1% vs 4.7%), although the difference in the incidence of serious angina was less (1.2% vs 1.9%). As expected, the incidence of bradycardia was higher in the ivabradine group in the overall study population (3.8% vs 1.0%); however, the difference was not increased in the anginal beta blocker subgroup (2.4% vs 1.1%).

Overall, this additional subgroup analysis in patients with baseline limiting angina taking beta-blockers provides important and reassuring information on the safety of ivabradine in a large group of patients with a long follow-up as compared with placebo. This subgroup is the closest to the requested variation of indication for use of ivabradine with beta-blockers.

Overall, this subgroup analysis does provide some long-term safety information for ivabradine in patients with limiting angina on beta-blockers. In study CL3-056, the criteria for identifying this subgroup were only based on questions (to the patient) on symptoms and investigator assessment of whether symptoms limiting physical activity were mainly related to angina or heart failure. Overall, the study included patients with varying severity of

coronary artery disease/ LVD and it was not specified if the patients in the subgroup had stable angina (which is the target patient population for ivabradine in this submission).

6. "Some of the other beta-blockers approved for angina are metoprolol (50-100 mg twice or thrice daily), propranolol (120-320 mg/day) and oxprenolol (20-40 mg three times daily up to a maximum daily dose of 320mg). However, some of these doses are not equivalent to the dose of atenolol 50 mg od used in the submitted study. Hence, safety and efficacy of ivabradine when used with all beta-blockers (at their proposed doses for treatment/ prophylaxis of angina) has not been established."

In order to ensure stability of the patients in study CL3-057, it was required that they receive the same beta-blocker at the same dosage for at least 3 months before selection. To maximise the potential recruitment, the patients could receive another beta-blocker than atenolol within the 3 months before the study provided that this dosage was equivalent to atenolol 50 mg od. Overall, 58% of the patients involved in the study received atenolol 50 mg od within the 3 months before the study and 42% received another beta-blocker with comparable percentages in the ivabradine and placebo groups. Heart rate on ECG at rest is a strong clinical way to assess the extent of beta-blockade. HR on ECG at rest was measured at pre-selection visit when the patients received their pre-selection beta-blocker (atenolol 50 mg od or other equivalent beta-blocker) and at inclusion when all patients received atenolol 50 mg od during the run-in period. Overall, HR was stable at both visits irrespective of whether patients received pre-selection atenolol or other beta-blocker suggesting that there was no modification of beta-blockade in patients switched. The sponsor provided references to suggest that atenolol 'is the most commonly prescribed beta-blocker, for the treatment of ischaemic heart disease in Australia[8] and was one of the most frequently prescribed products at the initiation of study CL3-057 and thus the chosen beta-blocker therapy. Based on literature reviews, the 50 mg/day atenolol dose chosen for background therapy in Study CL3-057 is representative of current general clinical practice. The median dose of atenolol used in a recent population study of beta-blocker use in 55 000 patients after myocardial infarction was 50 mg/day[9]. Similarly, in a recent report from the European Heart Survey, the mean daily dose of atenolol in patients with stable angina after assessment by a cardiologist was 55 mg/day[10],

The sponsor also provided references to suggest that the use of this dose with another new anti-anginal, ranolazine supported the proposed indication for ivabradine. Ranolazine is indicated as add-on therapy for the symptomatic treatment of patients with angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies (such as beta-blockers and/or calcium channel blockers).

[The sponsor responded further by citing the EPAR and a recent report (Setakis et al., 2008[11]) from the UK General Practice Research Database of the UK Medicines and Healthcare Products Regulatory Agency. Only 4.6% of angina patients taking beta-blockers in clinical practice (N = 12 493) received the target dose (100 mg/day for atenolol), 57.2%

[8] IMS, Australia Medical Index Data, December 2008.

9 Gislason, G.H et al. Long-term compliance with beta-blockers, angiotensin-converting enzyme inhibitors, and statins after acute myocardial infarction. European Heart Journal 2006; 27, 1153–1158.

[10] Daly, C. et al. Inadequate control of heart rate in patients with stable angina: results from the European Heart Survey. Eur Heart J 2008 ; 29 (Suppl 1) :204-205 (P1354) ESC Congress 2008, Munich, Germany, 30 August - 3 September 2008.

[11] Setakis E, Williams T, van Staa TP; GPRD Group, Medicines and Healthcare Products Regulatory Agency. Use of beta-blockers in UK clinical practice. London, United Kingdom, 2008.

received < 50% of the target dose, and the mean dose of atenolol was approximately 40 mg/day.[12]]

Although, the evaluators agreed that the degree of beta-blockade may not have changed in patients who were switched to atenolol 50 mg od from other beta-blockers, it is not clear if the patients did receive the optimal beta-blockade dose before ivabradine was added for management of stable angina. Furthermore, data regarding the new anti-anginal, ranolazine is not really relevant for the proposed indication for ivabradine in this submission. Ranolazine is a metabolically acting agent which protects from ischaemia by increasing glucose metabolism relative to that of fatty acids and can be used in combination with haemodynamically acting agents, as their primary effect is not through reduction in heart rate or blood pressure.

[The sponsor explained that in referring to ranolazine the sponsor was not making a pharmacological argument. The ranolazine EU precedent was raised to demonstrate that the EMA approved the indication for its use on top of beta-blockers on the basis of a clinical trial that was similar to study CL3-057. The example simply served to demonstrate that the rationale for selecting atenolol 50 mg od in the ranolazine study was the same as that for selecting atenolol 50 mg od in study CL3-057.]

The sponsor is claiming efficacy of ivabradine with beta-blockers even when the optimal dose of beta-blockade may not have been used and since ivabradine also acts by reducing heart rate while ranolazine does not, it is not appropriate to extrapolate results of ranolazine to this ivabradine submission.

Finally, anti-anginal drug treatment should be tailored to the needs of the individual patient, and should be monitored individually.

7. Safety data: "The incidence of AEs and discontinuations due to AEs was higher in ivabradine-treated patients compared with placebo, especially that of bradycardia and visual AEs. The most commonly reported emergent adverse events that were also more frequently (≥ 1%) reported in the ivabradine group were asymptomatic bradycardia (3.1% vs 0.5%), inadequately controlled blood pressure (2.4% vs 0.5%), angina pectoris (1.3% vs 0%), ventricular extrasystoles (1.3% vs 0.2%) and symptomatic bradycardia (1.1% vs 0%)."

The safety profile of ivabradine in study CL3-057 was comparable to that observed in the current approved PI and no new safety concerns were identified. Furthermore, the safety profile of ivabradine in combination with atenolol in study CL3-057 compared very favourably with its safety when given as monotherapy and in combination with amlodipine in the previous Phase III efficacy studies.

However, it is important to note that the dose of ivabradine used in the previous studies was 7.5 mg bid, while the dose in study CL3-057 was 5 mg bd for first 2 months with up-titration based on heart rate to 7.5 mg bd for another 2 months.

Rates of symptomatic and asymptomatic bradycardia were also evaluated in a complementary analysis in the subgroup of patients with heart rate ≤65 bpm at baseline (n=436), who could be at greater risk of bradycardia. As expected, the incidence of asymptomatic bradycardia in ivabradine-treated patients was higher in this subgroup (4.8%) than in the overall safety set (3.1%), although it was similar to rates seen with ivabradine monotherapy in previous studies. Symptomatic bradycardia was not more frequent in ivabradine-treated patients in this subgroup (2 patients, 0.9%, both recovered without

[12] EMEA, European Public Assessment Report, Scientific discussion for Procoralan. 23 October 2009, Doc. Ref: EMA/CHMP/816960/2009. p.28

sequelae) than in the overall safety set (5 patients, 1.1%) or in patients with baseline HR >65 bpm (3 patients, 1.4%).

In study CL3-056, the mean HR decrease in patients receiving ivabradine was 7.2±11.4 bpm in the population receiving beta-blockers, compared with 8.6±11.8 bpm in patients without beta-blockers. In the population with low HR at baseline (≤65 bpm), the HR reduction was 4.2±6 bpm in patients receiving beta-blockers and 3.2±5.7 bpm without beta-blockers.

Overall, the above results suggest that combination therapy with ivabradine and beta-blockers is not associated with significantly increased risk of bradycardia although the incidence was slightly higher.

The issues regarding higher incidence of inadequately controlled blood pressure in the ivabradine group (in study CL3-057) have been addressed adequately as of the 11 patients, added therapy was started in 10 patients in the ivabradine group and BP was subsequently controlled in these patients.

8. Angina

In 6 patients in the ivabradine group (1.3%) angina pectoris was reported as an AE, compared with none in the placebo group. All cases were judged as unrelated to study medication; for 5 of these patients, these events were reported during first part of the study and none of these patients complained of angina again when they were up-titrated from 5 mg bd to 7.5 mg bd. Furthermore, data from the long-term study CL3-056 did not suggest any increased risk of angina in patients on ivabradine with beta-blockers.

Although the sponsor has clarified about no angina at higher ivabradine dose, all patients may not be able to up-titrate to this dose and this remains a concern, especially in those with reduced HR precluding dosing with ivabradine 7.5 mg bd.

[The sponsor responded by clarifying that there were no AE reports of angina pectoris during treatment with ivabradine 7.5 mg, and that AE reports of angina at the lower ivabradine dose of 5 mg were not considered to be treatment related (and therefore not dose related) by the study Investigators.

The sponsor maintained that the notion that all patients may not be able to up-titrate to the 7.5 mg is not supported by the data and, that notwithstanding the fact that there is no *pharmacological rationale* for AE reports of angina at 5 mg and not 7.5 mg ivabradine doses, the lack of angina reports at the 7.5 mg dose only provides further evidence that the incidence of this AE was not dose-related in clinical-trials.]

9. Ventricular extrasystoles

In study CL3-057, 6 cases (1.3%) of VES were reported in ivabradine group compared to 1 case (0.2%) in placebo group. Among these 6 cases, 4 were reported during an ETT and none of them were as severe, serious or led to discontinuation or more complex ventricular arrhythmias.

Furthermore, long-term data from study CL3-056 did not show any increased risk of VES in ivabradine-treated patients with beta-blockers.

The issues regarding VES have been adequately addressed.

Supplementary Submission – Conclusions and Recommendation of the Clinical Evaluator in February 2010

The supplementary data, volume 1 (of 442) of the clinical study report (CL3-056; BEAUTIFUL study), provided in this submission provided long-term (up to 3 years) safety and efficacy data from the double-blind, placebo-controlled study involving 10917 patients with stable CAD and LVD treated with ivabradine (5 mg bd or 7.5 mg bd). Angina or HF symptoms should have been stable for >3 months and patients were receiving optimal conventional cardiovascular medication on appropriate stable doses for at least 1 month. Another important inclusion criteria was a resting HR of >60 bpm. Most patients had only slight limitation to their physical activity, with 61.4% having NYHA Class II. The most frequent limiting factor for physical activity was fatigue, palpitation or dyspnoea in 70.8% of patients and 13.8% of patients had anginal pain. Hence, this study population appeared to have more symptoms of HF and only a very small proportion of the total study population was representative of the target patient population for ivabradine (patients with chronic stable angina). Approximately 87% of the patients in this study were on concomitant beta-blockers, although, only 46% of the patients in the overall population (45.7% and 47.4% in ivabradine and placebo groups, respectively) were receiving >50% of the recommended (target) dose. It appears that a significant proportion of patients may not have received the optimal dose of beta-blockers. However, the study report does not provide adequate information to enable interpretation regarding whether this population did or did not receive the optimal dose of beta-blockers, especially in patients with anginal pain at baseline (which was closest to the target patient population for proposed indication of ivabradine).

Ivabradine was not associated with statistically significant reduction in the primary composite endpoint [CV death, including sudden death, hospitalisation for acute MI (fatal or not) or hospitalisation for new onset or worsening HF (fatal or not)] in the randomised population. Although, the main point being made by the sponsor in this submission is the significant improvement in subgroup of patients with baseline HR>70 bpm compared to those with baseline HR<70 bpm, it is interesting to note that ivabradine failed to show significant benefit over placebo in the primary composite endpoint in the pre-defined subgroup of patients with baseline HR>70 bpm (RSHR70). Although the significant reduction in hospitalisations for acute MI in the RSHR70 subgroup appeared to be significant, these secondary efficacy endpoint results can only be considered exploratory.

A post-hoc analysis in the subgroup of 1507 patients with anginal pain at baseline (which was closest to the target patient population for the proposed indication in this submission) showed reduction in composite endpoint which almost reached statistical significance (11.99% vs 15.52%, hazard ratio= 0.76, 95% CI: 0.58, 1.00, p=0.050) and was mainly driven by a 42% relative risk reduction for hospitalisation for acute MI with non-significant 12-16% reduction in CV death and hospitalisation for new onset or worsening heart failure. However, the wide confidence limits and inclusion of unity in the 95% CI precluded definite conclusions. Hence,

results which failed to show statistical significance for the primary endpoint in a post-hoc subgroup analysis cannot be considered as adequate evidence for the proposed indication of ivabradine in this submission.

In the study CL3-057 involving only patients with chronic stable angina (the target patient population) submitted earlier, analysis in a small subgroup of patients receiving maximal dose of beta-blockers did not show any statistically significant benefit over placebo in the primary endpoint of total exercise duration. In the new study (CL3-056), the majority of the patients did not represent the target patient population and post-hoc, subgroup analysis in the target patient population (with chronic stable angina) also failed to show statistically significant efficacy results. Furthermore, the study report did not provide any data to enable interpretation regarding whether the patients in this subgroup did or did not receive the optimal dose of beta-blockers. Hence, based on the data submitted it was not clear if ivabradine did provide any benefits when added to optimal dose of beta-blocker therapy.

The safety data from the new study showed a safety profile for ivabradine that was similar to that in the approved PI. The incidence of asymptomatic and symptomatic bradycardia was higher in the ivabradine group compared with placebo and also led to more withdrawals in the ivabradine group. However, the majority of AEs of symptomatic bradycardia were mild to moderate (97%) and was not significantly altered by background beta-blocker intake, gender, baseline LVEF, NYHA Class; however, the incidence of symptomatic bradycardia was higher in patients with baseline HR<70 bpm and those aged >75 years.

Overall, results from the new study CL3-056 failed to address the concerns raised in the initial evaluation and the risk-benefit profile for use of ivabradine in combination with beta-blockers for treatment of chronic stable angina did not appear to be favourable, at this stage of the evaluation process.

Recommendation

It was recommended that the application to register ivabradine (5 mg bd up to maximum dose of 7.5 mg bd) for the treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm who are already treated with a beta-blocker, or are unable to tolerate or have a contraindication to the use of beta-blockers be rejected.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluation consisted of a primary evaluation phase involving assessment of the pivotal Phase III study CL3-16257-057 and a supplementary evaluation phase comprising the sponsor's response to the first clinical evaluation report together with data from the

supportive study, CL3-056, the BEAUTIFUL study. The clinical evaluator recommended rejection in both the primary evaluation report and in the supplementary evaluation report.

Primary Evaluation - Efficacy

CL3-16257-057 (sometimes referred to as CL3-057) was a randomised, double-blind, placebo-controlled, parallel-group, international multicentre study. The 6 to 8 week, single-blind, run-in period on atenolol 50 mg once daily and placebo bd was followed by a 4-month double-blind treatment period divided into 2 periods of 2 months each. Patients were randomised to receive either ivabradine 5 mg bd for 2 months followed by forced titration to 7.5 mg bd for another 2 months + atenolol 50 mg od or placebo + atenolol 50 mg once daily unless heart rate was < 50 bpm.

The primary efficacy endpoint was the change in the total exercise duration (TED) from baseline to the end of the treatment period (4 months) and was compared between the ivabradine and placebo groups. The main efficacy analysis was carried out on the Full Analysis Set-ETT (FAS-E). The sample size in the study had 95% power to detect at least a 30 second difference between treatment groups (with an SD of 110 seconds). Two Per Protocol Sets (PPS) were defined for the analysis of the ETT data, the first for the 4-month treatment period (PPS-E4) and the second for the 2-month treatment period (PPS-E2). There were a number of other secondary endpoints.

Over the 4-month treatment period, patients treated with ivabradine showed greater increase in mean total exercise duration (TED) compared with placebo-treated patients in the FAS-E dataset (change in mean ± SD: 24.3 ± 65.3 s and 7.7 ± 63.8 s in the ivabradine and placebo groups, respectively with a placebo-subtracted difference = 16.3 s, 95% CI [7.9, 24.7], $p < 0.001$) (Table 2).

The Delegate expressed a number of concerns about these data. There was a huge diversity of results amongst the different countries participating and this has been commented on in detail by the evaluator. For example, in Romania and Slovakia, with about 20 participants in each arm, the placebo group fared better while in Russia and Brazil with a total of about 150 in each arm, the differences were minimal. Also as noted earlier, the sample size in the study had 95% power to detect at least a 30 second difference between treatment groups (with an SD of 110 seconds), yet the actual observed difference, 16.3 s, was only about half that size. The standard deviations in each group for the principal parameter of interest were around 65 s, much larger than the actual means themselves. This fact again points up the great diversity of results in what was a highly selected group of patients. Finally, the treatment difference when compared with the baseline TED values, gives a ratio of about 16.3/450 or approximately 3.6%. It was considered questionable whether such a result is clinically significant. However, the sponsor has submitted important clarifying data in this regard.

The results observed in the FAS-E population were confirmed in the PPS-E4 analysis with a treatment difference of 17.0 s, 95% CI [8.3, 25.7], $p < 0.001$. In the FAS-E dataset, an analysis at the end of the first 2 months, while patients were still being treated with ivabradine 5 mg bd, showed a greater increase in mean TED in those patients on ivabradine compared with placebo-treated patients: 15.5 ± 60.0 s in the ivabradine group versus 6.8 ± 56.5 s in the placebo group, with a difference of 8.2 s, 95% CI [0.6, 15.7], $p = 0.017$, with the difference being about half that observed at study end at 4 months.

The secondary efficacy results were, for the most part, consistent with the primary results:

- change in mean time to 1mm ST segment depression: ivabradine group 45.7 ± 93.0 s versus placebo group 15.4 ± 86.6 s with difference = 28.5 s, 95% CI [16.8, 40.3], $p < 0.001$

- change in mean time to onset of angina pain: ivabradine group 49.1 s ± 83.3 s versus placebo group 22.7 ± 79.1 s with difference = 25.5 s, 95% CI [15.0, 36.0], p < 0.001
- change in mean time to limiting angina: ivabradine group 26.0 ± 65.7 s versus placebo group versus 9.4 ± 63.8 s with difference = 16.3 s, 95% CI [7.9, 24.7], p < 0.001
- change in mean resting HR: ivabradine group -10.8 ± 10.8 bpm versus placebo group -2.2 ± 10.2 s with difference = -8.8 s, 95% CI [10.0, -7.6]. In the FAS-E ivabradine group, 20.2% (89/441) of patients experienced a drop in HR of > 20 bpm although such drops were mainly experienced by people with higher baseline resting HRs
- change in mean HR at peak of exercise: ivabradine group -11.3 ± 13.2 s versus placebo group -0.9 ± 12.3 s with difference = -10.8 s, 95% CI [-12.4, -9.1]
- change in mean rate pressure product, that is, HR x BP, at rest: ivabradine group -1269 ± 1655 bpm x mmHg versus placebo group -360 ± 1622 bpm x mmHg with difference = -920 bpm x mmHg, 95% CI [-1115, -725]
- change in mean rate pressure product, that is, HR x BP, at peak of exercise: ivabradine group - 1630 ± 3474 bpm x mmHg versus placebo group -66 ± 3447 bpm x mmHg with difference = -1612 bpm x mmHg, 95% CI [-2041, -1183]
- at end of study, 76.7% patients in the ivabradine group and 85.2% patients in the placebo group stopped the ETT because of limiting angina
- change in the mean number of angina attacks per week over the 4 months of the study: ivabradine group -0.9 ± 2.6 versus placebo group -0.7 ± 1.8, with difference = -0.2, 95% CI [-0.5, 0.1], not significant; similarly there was no significant change in the mean number of angina attacks per week in those patients with at least one angina attack in the run-in period.
- change in the mean number of intakes/week of short acting nitrates over the 4 months of the study: ivabradine group -0.3 ± 1.3 versus placebo group -0.5 ± 1.7 with difference = 0.3, 95% CI [0.1, 0.5]; based on the 95% CI, this result is statistically significant in favour of placebo at least by the parametric approach; certainly the trend is in favour of the placebo group.
- change in the mean number of intakes/week of short acting nitrates over the 4 months of the study in patients with at least one intake during the run-in: ivabradine group -0.7 ± 1.9 versus placebo group -1.2 ± 2.4 with difference = 0.5, 95% CI [0.1, 0.9]; again, based on the 95% CI, this result is statistically significant in favour of placebo at least by the parametric approach and once again the trend is in favour of the placebo group.

Primary Evaluation - Safety

In the Safety Set (N = 889), the incidence of patients with at least one emergent AE was higher in the ivabradine group (29%, 130/449) compared with the placebo group (20.9%, 92/440). The incidence of treatment-related AEs was also higher in the ivabradine group, 9.1%, compared with the placebo group, 2.7%. These were made up principally of bradycardia (either asymptomatic or symptomatic) with 4.2% ivabradine vs 0.5% placebo and visual AEs with 2.0% vs 0.9%, as expected. Most of the treatment-related AEs are already described in the PI.

AEs of special interest

- Bradycardia – in the ivabradine group, bradycardia led to treatment withdrawal in 5 patients, to temporary interruption in 1 patient and to reduction of dose in 1 patient;

episodes were either mild (13/19) or moderate (6/19). There was one serious case involving hospitalisation.

- Inadequately controlled BP – unexpected finding, ivabradine group 2.4% vs placebo 0.5%; all patients with this AE had a history of hypertension, none considered related to treatment or severe or led to treatment discontinuation and all patients recovered.
- Emergent angina – another unexpected finding, ivabradine group 1.3% vs placebo 0%; all cases considered as unrelated to study treatment and due to progression of disease
- Ventricular extrasystoles, ivabradine group, 6/449, 1.3% vs placebo 1/440, 0.2%
- Visual AEs, mainly phosphenes, ivabradine 5/449, 1.1% vs placebo 3/440, 0.7%

Deaths, SAEs and discontinuations due to AEs

There was one death (suicide) in the ivabradine group during the randomized study period. Two patients in the placebo group died after the last study drug intake, one from MI and the other from sudden death. No death was judged to be related to the study medication. A total of 21 patients (2.4%) experienced a non-fatal SAE, ivabradine 13/449 or 2.9% vs placebo 8/440 or 1.8%. These involved mostly cardiac disorders. There were 13 ivabradine-treated patients withdrawn from the study, 8 of them for cardiac-related events such as bradycardia, angina etc. and there were 3-placebo treated patients withdrawn.

Laboratory parameters, vital signs

Emergent high out-of-reference range values of creatinine were more frequent in the ivabradine group (8.4%) than in the placebo group (3.5%), as already observed in previous clinical studies. There were no clinically relevant changes in vital signs.

ECG abnormalities

Compared with placebo, a statistically significant and clinically relevant decrease in HR was observed in the ivabradine group at Month 2 and was confirmed at Month 4. The RR interval was markedly increased in the ivabradine group from baseline to Month 4 by 149.6 ± 162.1 ms versus 34.3 ± 138.0 ms, but there were no clinically relevant changes as a result. There were no significant changes in either PR or QRS duration. In accordance with the observed decrease in HR, uncorrected QT increased but QT_c did not increase in either group. There were no cases of torsades de pointes. The rate of first degree AV block in the ivabradine group, 4.9% was almost twice that in the placebo group, 2.6%. This is not a new finding.

Limitations of the Dataset as Summarized by the Evaluator in the initial Clinical Evaluation Report (June 2009)

Compared with placebo, ivabradine was associated with a greater increase in TED of 7 s following 2 months' treatment 5 mg bd and 16.3 s following an additional 2 months' treatment with 7.5 mg bd. While the results were statistically significant, the evaluator questioned their clinical significance. Furthermore the patients were very highly selected and the results were not consistent across all the countries. Some of the apparent benefit ascribed to ivabradine may be due to worsening in some placebo-treated patients. There was no analysis of the proportions of patients on either treatment who made no improvement or got worse. There was no significant difference in either the number of angina attacks or the consumption of short acting nitrates although the trend for the latter was in favour of placebo.

Long-term safety and efficacy of ivabradine beyond 4 months was not evaluated.

Safety and efficacy of ivabradine when used with all beta blockers was not satisfactorily established because some of the approved doses for angina of other beta-blockers are not equivalent to the dose of atenolol 50 mg once daily used in the study

As a consequence, the evaluator was of the opinion that the risk-benefit profile of concomitant administration of ivabradine with beta-blockers did not appear to be favourable and so the application should be rejected.

Supplementary Data

The sponsor then submitted supplementary data which was evaluated by the clinical evaluator and which consisted of 2 volumes comprising the sponsor's response to the initial clinical evaluation report in one volume together with Volume 1 of the report of the Study CL3-056, the BEAUTIFUL study.

Comments by the Clinical Evaluator on the Sponsor's Response to the initial Clinical Evaluation Report

Highly-selected population

The sponsor clarified that the majority of the ineligible patients (1508/1792, 84.2%) were excluded due to negative ETT at first pre-selection visit or inability to meet ETT stability criteria. The clinical evaluator agreed that the majority of the exclusions were in accordance with the TGA-adopted guideline of recruiting patients with stable angina (at least two standardised tests should be performed at the start of the study and the difference between the two tests should not exceed 20%).

Results across different countries

With regard to the different results across different countries, the sponsor replied that such significant variability is inherent in employing ETT for the primary outcome measure. The clinical evaluator reiterated that analysis of the proportion of patients who made no improvement or got worse on ivabradine would have been helpful but was not provided. As noted by the clinical evaluator this remained a significant limitation of the study.

Statistical vs clinical significance

The sponsor contended that the TGA does not specify the level of efficacy or improvement over placebo required of a drug in order to demonstrate that safety and efficacy have been "satisfactorily established". It is true that the TGA does not set out in detail the necessary or sufficient conditions or thresholds which are the tests of safety and efficacy. As the sponsor says, the latter have to be "satisfactorily established". However, the TGA is expected to test the clinical meaningfulness of efficacy outcomes and not merely examine whether or not an outcome had achieved statistical significance. In terms of clinical significance of outcomes it was helpful and relevant of the sponsor to point out that the 16.3 s of improvement in TED occurred in the higher stages of the Bruce protocol. Most patients in the study had improvement in Stage 3 of the Bruce protocol at which point the functional capacity of the individual was 9 METs, corresponding to activities of high intensity. These METs correlations had not been provided in the original submission.

Previous published results of combination anti-anginal therapy

The sponsor claimed that most published studies of combination anti-anginal therapy have shown only small and statistically significant benefits with respect to ETT criteria at trough of drug activity. The sponsor referred to a meta-analysis by Klein, 2002, comparing the combination of calcium channel blockers and beta-blockers on the one hand with beta-blockers as monotherapy on the other.[7] The difference in TED was only 4 s and not

statistically significant. The Delegate agreed that this does give some context when examining the size of the clinical benefit. Also in this section the sponsor provided information on the proportion of ivabradine-treated patients with improved TED and also those with an improvement in TED of more than 30 s. Overall, 70% of ivabradine-treated patients showed an improvement in TED and 49% of patients treated with ivabradine showed an improvement in TED of more than 30 s. However, as noted by the evaluator, the proportion of placebo-treated patients with improved TED was not provided and hence no valid comparisons with placebo could be made for this parameter.

Comparison of primary efficacy results in pivotal study with previously evaluated results

The sponsor compared the results of the pivotal study, CL3-057, with those from another study, CL3-017, previously evaluated by the TGA. The latter study examined the effect of increasing the dose of atenolol from 50 to 100 mg on ETT parameters in stable angina patients, parameters based on the less strenuous modified Bruce protocol. As pointed out by the clinical evaluator the difficulty of comparing two studies *post hoc* was only compounded by the fact that there was no translation of exercise variables into METs. The latter is the standard validated measure which enables such comparisons to be made.

Maximal beta-blockade

The sponsor contended that ivabradine demonstrated anti-anginal efficacy in patients who are maximally beta-blocked. As noted by the evaluator, the specific exclusion of patients who were on atenolol 100 mg once daily or equivalent meant that any claim that ivabradine would be effective in such doses of beta-blockers was not actually put to the test in the trial.

The sponsor identified a sub-group of patients in study CL3-057 in whom the level of beta-blockade at baseline could be judged to be maximal if they had a strong resting HR of ≤ 60 bpm and/or supine SBP ≤ 100 mmHg and/or PR interval ≥ 200 ms. Clearly, in such patients any further increase in beta-blocker dose would have been inappropriate. There were 144 such patients in the pivotal study, that is, 16.5% of the study population (FAS-E). In this group of patients the placebo-subtracted difference in the gain in mean TED was similar to that observed in the overall population (16.6 s, 95% CI[-5.04, 37.7], p = 0.066). There are a number of comments which can be made regarding this finding. Firstly, this result was not significant with the small sample size no doubt contributing to the wide confidence interval. Secondly, if 16.5% of patients were maximally beta-blocked, then it follows that 83.5% of the study population were on sub-optimal doses of beta-blocker. Finally, there was no comparison of efficacy in the sub-group on maximal beta-blockade with those who received sub-maximal beta-blocker doses.

Symptomatology of angina

There was no significant difference between groups in either the change in mean number of angina attacks per week or in the change in mean number of intakes/week of short acting nitrates. The sponsor's main reply to these findings was that the latter were only secondary efficacy criteria. However, the Delegate argued that they give valuable insights into the actual clinical meaningfulness of the results, in terms of their impact on patients. Furthermore, it is inescapable that the trends (and arguably the statistical significance) for the parameters involving short acting nitrates were in favour of placebo. The low frequency of angina attacks per week could partly explain the lack of a significant treatment effect in that parameter.

Patients with refractory angina

The sponsor provided a sub-group analysis of efficacy in 247 patients with refractory angina (122 on ivabradine vs 125 on placebo) in which ivabradine produced statistically significantly greater improvements in TED. However, importantly, at baseline patients in the placebo group appeared worse off clinically than those in the ivabradine group, that is, the placebo group had more patients with CCS-III angina, had more patients with a history of heart failure and comprised patients whose mean time since angina diagnosis was longer. There was also a greater proportion of females in the ivabradine group.

Long-term efficacy and safety

With regard to the issue of long-term efficacy and safety, data from the mortality-morbidity study, the BEAUTIFUL study, was discussed. This was a study which involved 10,907 patients the majority of whom had baseline characteristics which differed from those enrolled in the pivotal study, CL3-057. The sponsor did identify a sub-group of patients in the BEAUTIFUL study with limiting angina at baseline as the closest to the population targeted by the indication sought in this submission. The major question which the clinical evaluator had about this sub-group of patients with limiting angina was that it was not specified if patients in this sub-group had stable angina which is of course the actual target patient population for ivabradine in this submission.

Degree of beta-blockade in those patients switching from beta-blockers other than atenolol

The evaluator agreed with the sponsor that the degree of beta-blockade may not have changed in patients who were switched to atenolol 50 mg once daily from other beta-blockers (as shown by stability of resting HR between the visit when patients were on their pre-selection beta-blocker, that is, atenolol or other and the time of inclusion when all patients were placed on atenolol). However, as noted by the evaluator, what was not clear was whether all patients were on an optimal dose of beta-blocker before the addition of ivabradine.

Ranolazine[13]

The sponsor also provided references relating to the combined use of atenolol with the new anti-anginal medicine ranolazine and claimed that such evidence supported the proposed indication for ivabradine. Such references were judged as inappropriate by the evaluator because ranolazine acts by a completely different mechanism from that by which ivabradine acts. Ivabradine also acts by reducing HR while ranolazine does not.

Safety data

The sponsor contended that the safety profile of ivabradine in study CL3-057 was comparable to that observed in the current approved PI and no new safety concerns were identified. The evaluator thought it important to note that the dose of ivabradine used in the previous studies was 7.5 mg bd while the dose in the pivotal study CL3-057 was 5 mg bd for the first 2 months with up-titration based on heart rate to 7.5 mg bd for another 2 months. The evaluator agreed that the results suggest that combination therapy of ivabradine and beta-blockers was not associated with a significantly increased risk of bradycardia although the incidence was higher in the combination group. The evaluator also agreed that the issues

[13] Ranolazine (trade name Ranexa in the EU) is an anti-anginal drug whose mechanism of action is largely unknown. It may have some anti-anginal effect by inhibition of the late sodium current in cardiac cells with consequent reduction in intracellular sodium accumulation and a decrease in intracellular calcium overload. It is indicated in the EU as add-on therapy for the symptotmatic treatment of patients with stable angina pectoris who are inadequately controlled or intolerant to first-line anti-anginal therapies (such as beta-blockers and/or calcium antagonists)

regarding the higher incidence of inadequately controlled BP in the ivabradine group in study CL3-057 and those regarding the rate of ventricular extrasystoles were resolved.

Angina as an AE

The evaluator agreed that the sponsor had clarified that, in those patients who had reported angina as an AE in the first 2 months of the study, none had reported it when up-titrated to 7.5 mg bd. However, the evaluator was still concerned for those patients who may not be able to up-titrate (for example, because of reduced HR).

Study CL3-056, the BEAUTIFUL study - Evaluator's Comments

This was a Phase III, randomised, double-blind, placebo-controlled, multicentre, international, morbidity-mortality study with 2 parallel and balanced treatment arms to evaluate the effects of ivabradine on cardiovascular events in 10,917 patients with stable coronary artery disease (CAD) and left ventricular dysfunction (LVD). It included patients > 55 years if no history of diabetes or > 18 years if history of diabetes, with a documented history of CAD associated with LV systolic dysfunction (LV ejection fraction < 39%), LV dilation and in sinus rhythm with resting HR > 60 bpm. Angina or HF symptoms should have been stable for more than 3 months and patients should have been receiving optimal conventional cardiovascular medication on appropriate stable doses for at least one month.

The primary efficacy criterion was the composite endpoint of first event among CV death (including sudden death of unknown cause), hospitalization for acute MI (fatal or not) or hospitalization for new onset or worsening heart failure (fatal or not). The time to occurrence of the primary composite endpoint was compared between treatment groups and Kaplan-Meier survival curves estimated.

The incidence of the primary composite endpoint showed no significant difference between the ivabradine and placebo groups (15.4% vs 15.30%, hazard ratio 1.00, 95% CI [0.91, 1.10], p = 0.945. Also, each of the components of the composite endpoint showed similar incidence rates between the ivabradine and placebo groups (Table 8).

Analysis in a sub-group of patients reporting anginal pain at baseline – A *post hoc* analysis in a sub-group of 1,507 patients (ivabradine 734, placebo 773) who reported anginal pain at baseline also showed a reduction in the primary composite endpoint with ivabradine treatment compared with placebo which almost reached statistical significance (11.99% vs 15.52%, hazard ratio 0.76, 95% CI [0.58, 1.00], p = 0.050 (Table 8). It also must be remembered that there was a failure of the primary endpoint in the BEAUTIFUL study which means that all other endpoints become hypothesis-generating only and not conclusive. Nonetheless, there can be no doubt that this result has relevance for the claimed extension of indication.

Table 8: BEAUTIFUL study - incidence of the primary composite endpoint and selected secondary endpoints in the subgroup of patients with anginal pain at baseline

	Ivabradine (N = 734) NPY = 1140.59 n (%) [%PY]	Placebo (N = 773) NPY = 1173.08 n (%) [%PY]	Hazard ratio E [95% CI]	p-value
Primary composite endpoint	**88 (11.99) [7.72]**	**120 (15.52) [10.23]**	**0.76 [0.58 ; 1.00]**	**0.050**
Secondary endpoints:				
- Cardiovascular death	54 (7.36) [4.59]	64 (8.28) [5.22]	0.88 [0.62 ; 1.27]	0.511
- Hospitalisation for acute MI	28 (3.81) [2.43]	50 (6.47) [4.19]	0.58 [0.37 ; 0.92]	**0.021**
- Hospitalisation for new onset or worsening heart failure	33 (4.50) [2.85]	41 (5.30) [3.43]	0.84 [0.53 ; 1.33]	0.454

E [95% CI]: Estimate of the hazard ratio between treatment groups [two-sided 95% confidence interval of estimate] based on an adjusted Cox proportional hazards model with beta-blocker intake as a covariate
p-value: Log-rank test stratified on beta-blocker intake factor
N: Number of patients in considered treatment group *NPY: Number of patient-years at risk for the primary composite endpoint*
n: Number of patients reaching endpoint *% = (n / N) x 100*
%PY = (n / number of patient years at risk in treatment group) x 100

The overall incidence of AEs was similar in the ivabradine and placebo groups (55.65% vs 55.54%). However, the incidence rates of eye disorders (mainly phosphenes), cardiac disorders (mainly bradycardia), vascular disorders (mainly inadequately controlled BP) and renal/urinary disorders (mainly due to renal failure/impairment) were higher in the ivabradine group.

Overall, the incidence of drug withdrawals due to asymptomatic bradycardia was much higher in the ivabradine (10.2%) group compared with the placebo group (0.85%). The overall incidence of emergent symptomatic bradycardia was also higher in the ivabradine group (3.76%) compared with placebo (1.03%). The incidence of emergent symptomatic bradycardia was higher in patients with baseline HR < 70 bpm and those aged > 75 years.

The overall incidence of visual AEs was more common in the ivabradine group (4.78%) compared with placebo (1.4%).

Emergent cases of atrial fibrillation (AF) were observed at a constant rate during the study in both treatment groups (ivabradine 5.22% vs placebo 4.86%). AF led to withdrawal of study drug in 2.14% and 1.90% of patients in the ivabradine and placebo groups, respectively with most cases mild to moderate.

Overall, there were 1,123 deaths during the study with a slightly higher incidence in the ivabradine group (10.5%) compared with placebo (10.09%). The incidence rates of various cardiac causes leading to death were similar in both groups. Overall, the incidence of serious AEs was slightly lower in the ivabradine group (18.81%) compared with placebo (20.92%). The overall incidence of withdrawals due to AEs was much higher in the ivabradine group (12.18%) compared with placebo (7.40%) with the most common AEs leading to withdrawal being symptomatic bradycardia (2.68% vs 0.63%), HR decreased (2.08'% vs 0.26%), AF (2.14% vs 1.90%) and phosphenes (0.40% vs 0.09%). The incidence rates of hospitalizations during the study were similar in the ivabradine (29.87%) and placebo (30.76%) groups.

Response by the sponsor to evaluation of the supplementary data

The sponsor submitted a response to the evaluation of the supplementary data. The core of that response addressed what the sponsor saw as the major points of contention arising from the evaluation. It was accompanied by two appendices, the first an updated proposed Australian Coralan PI and the second a copy of the European Public Assessment Report (EPAR), Scientific Discussion for Procoralan (the trade name for ivabradine in the EU)

issued on 23 October 2009 and assessing the evidence for the proposed extension of indication.[14]

Relevance or otherwise of the BEAUTIFUL study to the current application

The major point expounded by the sponsor was that the application to amend the indication was not based on the BEAUTIFUL study. In accordance with the TGA-adopted EMA guidelines, the application was based on Study CL3-057 and the company's responses regarding efficacy and the BEAUTIFUL study for long-term safety. While a large number of patients in the BEAUTIFUL study had angina, typical measurements of angina outcomes like symptom relief and exercise tolerance were not taken. The BEAUTIFUL study was submitted by the sponsor as part of the supplementary data only to address the safety questions which were raised in the earlier evaluation report. It further maintained that the TGA agreed that the BEAUTIFUL data would be considered as "supportive" data only and believed that any discussion about the efficacy results from BEAUTIFUL should have been included, at most, as an appendix to the supplementary clinical evaluation report and that its inclusion in the main body of the report distorts the evaluation and leads to inappropriate conclusions. However, it should be noted that supportive data is still evaluable data and therefore needs to be commented on in the evaluation report.

Furthermore, in the EPAR the EU evaluators, while accepting that the BEAUTIFUL study was markedly different in design and patient population from the Phase III studies in the initial submission, went into considerable detail in the main body of that report, analysing both the efficacy and safety results from the BEAUTIFUL study. In fact those same evaluators stated that some of the results, particularly from sub-group analyses, are directly relevant to the approved indication in patients with chronic stable angina pectoris. For example they point out that a substantial number of patients had their physical activity limited by anginal pain at baseline (n = 1,507) and that the efficacy and safety of ivabradine in this sub-group, which was larger than the number enrolled in the pivotal study, was "*of obvious relevance for the claimed indication*".

The EMA's evaluation of the *complete* BEAUTIFUL study report, that is, all 442 volumes, resulted in a more detailed description of the supportive study, compared to the description of CL3-057 (the pivotal study) being included in the approved EU SPC.

Comparison of efficacy data (work capacity) from previously evaluated data with that from the pivotal study for this submission

Some useful information was provided by the sponsor about the comparison of efficacy data from study CL3-017 (previously evaluated by the TGA) and the pivotal study for this submission, CL3-057. It demonstrated that the total gain in work capacity compared favourably for ivabradine 7.5 mg bd added to atenolol 50 mg once daily as in the pivotal study compared with up-titration of atenolol from 50 mg to 100 mg once daily, as in the previously evaluated study (Table 9). However, it must be remembered that the comparison of the two up-titration regimens, one with ivabradine added on and one with the atenolol dose increased, was not direct but indirect.

Table 9: Gain in work capacity in the Exercise Tolerance Test (ETT) obtained with atenolol 50 mg once daily + ivabradine 7.5 mg bd (Study CL3-057, the pivotal study) vs atenolol up-titrated from 50 mg to 100 mg once daily (Study CL3-017, previously evaluated), compared to baseline

[14] EMEA. EPAR Procoralan. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000597/WC500043587.pdf

	Ivabradine 7.5 mg + atenolol 50 mg (study 057)	atenolol 50 mg uptitrated to atenolol 100 mg (study 017)
Time gain in TED compared to baseline	24.3 s	18.8 s
Stage of ETT Protocol at which most patients finished	3*	4**
Workload Equivalent in METs	9	7
Physical activity equivalent[4]	Very heavy- Bicycling at 25km/h	Heavy- Carpentry work
Estimated gain in work capacity (kJ) for a 70 kg man	3.83 kJ	2.30 kJ

* Standard Bruce protocol (speed 5.5km/h, gradient 14%)
**Modified Bruce Protocol (Stage3: speed 2.7km/h, gradient 10%; Stage4: speed 4.4km/h, gradient 12%)

Gain in work capacity on ivabradine compared with that on ranolazine

The sponsor also presented data to indicate that the total gain in work capacity in METs with ivabradine compared favourably to the gain obtained with ranolazine and elsewhere in its response stated that it was not making a pharmacological argument and that therefore the difference in mechanism in action between ivabradine and ranolazine had no bearing on its response. While the Delegate accepted that the sponsor raised the subject of the ranolazine EU precedent to demonstrate that the EMA approved the indication for its use in addition to beta-blockers on the basis of a clinical trial that was similar to CL3-057, the importance of the EU precedent is largely a matter for the Committee for Medicinal Products for Human Use (CHMP). In fact, it is evident from reading the EPAR for ivabradine that the EU evaluators go into considerable detail comparing ivabradine with ranolazine. It is also evident that the fact that the CHMP considered the ivabradine data set to be in line with the previous conclusion of the CHMP concerning ranolazine was an important fact in swaying the decision of the EU evaluators in favour of ivabradine. However, ranolazine has not been approved for use in Australia and the TGA has not had the opportunity of fully evaluating data for ranolazine.

Optimal beta-blockade

It was also pointed out by the sponsor that the EMA agreed in the EPAR that, "*like most patients in clinical practice, patients in Study CL3-057 were treated with the dose of beta-blocker considered to be optimal for them by the treating physician*". However, what is optimal beta-blockade for an individual as considered by the treating physician may not represent what can be actually called optimal beta-blockade.

Long-term efficacy data

The Delegate accepted the sponsor's point that long-term efficacy data is not specifically required in the adopted guideline. However, the TGA cannot ignore any long-term efficacy data which may be available, such as that from the BEAUTIFUL study.

European Public Assessment Report (EPAR)

This was included with the sponsor's response to the supplementary clinical evaluation report and numerous and detailed references were made in that report to the EPAR. There are several useful analyses and tables in the EPAR which the Delegate found helpful.

CL3-056 (BEAUTIFUL)

All patients in the BEAUTIFUL study had CAD and LVD (ejection fraction < 40%). Angina was the main limiting factor in 1,507 patients. The sub-group of patients with anginal symptoms at baseline, and particularly those receiving concomitant beta-blockers, was of particular interest because this was the sub-group of the greatest relevance to the present indication of ivabradine in stable angina and to the requested variation of indication to use ivabradine in combination with beta-blockers. In the EPAR, the following aspects were discussed:

- adjudicated efficacy endpoints and adjudicated endpoints with an outcome of death
- investigator assigned AEs with an outcome of death
- AEs related to cardiac arrhythmias
- bradycardia
- angina pectoris as an AE

Adjudicated efficacy endpoints and adjudicated endpoints with an outcome of death

Patients with stable angina (actually those with angina at baseline)

In patients with stable angina (n = 1,507), there was a reduction of 24% in the primary composite endpoint (hazard ratio 0.76, p = 0.05) and a 42% reduction in hospitalisation for MI (hazard ratio 0.58, p = 0.022) (Table 8).

Patients with stable angina taking beta-blockers

Results for patients taking beta-blockers (n = 1,351) were comparable to those in the full stable angina sub-group, with reductions in the incidence rates of the primary composite endpoint and in secondary endpoints (Table 10). Analyses of adjudicated causes of death did not show any evidence of a signal of increased risk of arrhythmic or sudden death with ivabradine. Both death from presumed arrhythmia and sudden death of unknown cause were also lower with ivabradine than with placebo. There was an increased risk of stroke on ivabradine but the numbers of events are small (Table 11). Thus, cause-specific mortality results in this subgroup did not show any pro-arrhythmic effect of ivabradine in stable angina patients.

Table 10: BEAUTIFUL study - primary and selected secondary endpoints in the sub-group of patients with angina taking beta-blockers (n = 1,351)

	Ivabradine (% PY)	Placebo (%PY)	Hazard ratio [95% CI]	p-value
Taking beta-blockers	**n = 654**	**n = 697**		
Primary composite outcome	80 (7.94)	110 (10.47)	0.76 [0.57;1.01]	0.062
Mortality endpoints:				
All-cause mortality	58 (5.59)	70 (6.38)	0.88 [0.62; 1.24]	0.457
Cardiovascular death	50 (4.82)	60 (5.46)	0.88 [0.61; 1.28]	0.509
CAD death	9 (0.87)	15 (1.37)	0.63 [0.28; 1.45]	0.277
Heart failure endpoint				
Hospitalisation for HF	29 (2.84)	39 (3.65)	0.78 [0.48; 1.26]	0.314
Coronary endpoints				
Hospitalisation for MI	25 (2.46)	44 (4.11)	0.60 [0.37; 0.98]	0.039
Coronary revascularisation	18 (1.76)	33 (3.09)	0.57 [0.32; 1.02]	0.053

CAD: coronary artery disease; HF: heart failure; MI: myocardial infarction; %PY: number per 100 patient-years

Table 11: BEAUTIFUL study - CV mortality in patients with stable angina taking beta-blockers (n = 1,351)

	Ivabradine (%)	Placebo (%)
Taking beta-blockers	**n = 654**	**n = 697**
All cardiovascular death	50 (7.65)	60 (8.61)
Heart failure	5 (0.76)	5 (0.72)
Acute myocardial infarction	2 (0.31)	8 (1.15)
Presumed arrhythmia	11 (1.68)	13 (1.87)
Sudden death of unknown cause	24 (3.67)	30 (4.30)
Stroke	6 (0.92)	1 (0.14)
Other	0	1 (0.14)
Cardiac procedures	2 (0.31)	2 (0.29)

Investigator assigned AEs with an outcome of death

All patients

As noted previously, in the full study population of CL3-056, the overall incidence of all AEs with an outcome of death was slightly higher in the ivabradine group (575 patients, 10.5%) than with placebo (548 patients, 10.1%) and the between-group difference was not significant. The incidence of death and sudden death was also numerically higher in the ivabradine group (306 patients, 5.6%) than with placebo (264 patients, 4.9%) and the between-group difference was again not significant.

Patients with stable angina

In this group, the overall incidence of all AEs with an outcome of death was slightly lower in the ivabradine group (64 patients, 8.7%) than with placebo (77 patients, 10.0%). The incidence of death and sudden death was similar in both groups (ivabradine 39 patients, 5.3% and placebo 39 patients, 5.1%). The incidence of deaths related to cardiac disorders was lower in the ivabradine group (12 patients, 1.6%) than with placebo (21 patients, 2.7%). The incidence of deaths related to cardiac arrhythmias was low and similar in both groups (2 patients in each).

Patients with stable angina taking beta-blockers

As with the previous sub-group, there was no evidence of an increased risk of death or any pro-arrhythmic effect of ivabradine in patients with stable angina taking beta-blockers (Table 12).

Table 12: BEAUTIFUL study - AEs with an outcome of death in the SOCs, General Disorders and Administration Site Conditions & Cardiac Disorders, in the sub-group of patients with stable angina taking beta-blockers (n = 1,350)

	Ivabradine (N = 654)		Placebo (N = 696)		P-value
	n	%	n	%	
All	**58**	**8.9**	**70**	**10.1**	**0.455**
General disorders and administration site conditions	36	5.5	37	5.3	0.973
Fatal outcomes	36	5.5	37	5.3	0.973
Death and sudden death	36	5.5	37	5.3	0.973
Sudden death	28	4.3	33	4.7	0.784
Death	8	1.2	4	0.6	0.328
General system disorders NEC	0	0	0	0	-
Cardiac disorders	11	1.7	19	2.7	0.262
Coronary artery disorders	5	0.8	12	1.7	0.179
Ischaemic coronary artery disorders	5	0.8	9	1.3	0.493
Acute myocardial infarction	2	0.3	5	0.7	0.505
Myocardial infarction	2	0.3	3	0.4	1.000
Angina unstable	1	0.2	1	0.1	1.000
Acute coronary syndrome	0	0	0	0	-
Coronary artery disorders NEC	0	0	3	0.4	0.273
Coronary artery insufficiency	0	0	2	0.3	0.531
Coronary artery disease	0	0	1	0.1	1.000
Heart failures	4	0.6	5	0.7	1.000
Heart failures NEC	4	0.6	4	0.6	1.000
Cardiac failure	4	0.6	3	0.4	0.932
Cardiogenic shock	0	0	1	0.1	1.000
Left ventricular failures	0	0	1	0.1	1.000
Acute left ventricular failure	0	0	1	0.1	1.000
Cardiac arrhythmias	2	0.3	2	0.3	1.000
Ventricular arrhythmias and cardiac arrest	2	0.3	1	0.1	0.962
Ventricular fibrillation	2	0.3	1	0.1	0.962
Cardiac conduction disorders	0	0	1	0.1	1.0000
AV block complete	1	0.1	1	0.1	1.000

AV: atrioventricular

AEs related to cardiac arrhythmias

All patients

There was no evidence of a pro-arrhythmic effect of ivabradine. The incidence rates of AEs and serious AEs related to supraventricular arrhythmias and the incidence of AEs related to ventricular arrhythmias were similar in the two groups. Serious AEs were less frequent with

ivabradine than with placebo, largely due to a much lower incidence of serious AEs of ventricular tachycardia (ivabradine 28 patients, 0.5% vs, placebo 53 patients, 1.0%).

Patients with stable angina

There was no indication of any pro-arrhythmic effect of ivabradine in stable angina patients.

Patients with stable angina taking beta-blockers

There was no evidence of a pro-arrhythmic effect of ivabradine in the sub-group of patients with stable angina who were taking beta-blockers. The incidence rates of supraventricular arrhythmias are shown in Table 13 while those related to ventricular arrhythmias are shown in Table 14.

Table 13: BEAUTIFUL study - Incidence rates of supraventricular arrhythmias in patients with stable angina taking beta-blockers (n = 1,350)

	Ivabradine (N = 654)		Placebo (N = 696)		P-value
EAE	**n**	**%**	**n**	**%**	
All supraventricular arrhythmias	27	4.1	46	6.6	0.057
Atrial fibrillation	15	2.3	28	4.0	0.097
Atrial flutter	5	0.8	2	0.3	0.402
Supraventricular extrasystoles	5	0.8	5	0.7	1.000
Sinus tachycardia	0	0	7	1.0	0.019
Supraventricular tachycardia	1	0.2	4	0.6	0.414
Serious EAE					
All supraventricular arrhythmias	11	1.7	20	2.9	0.200
Atrial fibrillation	7	1.1	18	2.6	0.060
Atrial flutter	4	0.6	2	0.3	0.629

EAE: emergent adverse event

Table 14: BEAUTIFUL study - Incidence rates of ventricular arrhythmias in patients with stable angina taking beta-blockers (n = 1,350)

	Ivabradine (N = 654)		Placebo (N = 696)		P-value
EAE	**n**	**%**	**n**	**%**	
All ventricular arrhythmias	22	3.4	29	4.2	0.529
Ventricular tachycardia	6	0.9	5	0.7	0.916
Ventricular fibrillation	2	0.3	0	0	0.469
Ventricular extrasystoles	12	1.8	25	3.6	0.068
Ventricular arrhythmia	2	0.3	0	0	0.469
Serious EAE					
All ventricular arrhythmias	6	0.9	4	0.6	0.677
Ventricular tachycardia	3	0.5	2	0.3	0.942
Ventricular fibrillation	2	0.3	0	0	0.469
Ventricular extrasystoles	0	0	2	0.3	0.531
Ventricular arrhythmia	1	0.2	0	0	0.969

EAE: emergent adverse event

Bradycardia

As expected in the full study population, the incidence of the AE bradycardia was significantly higher in the ivabradine group (206 patients, 3.8%) than with placebo (56 patients, 1.0%). Among ivabradine-treated patients, the incidence of bradycardia was lower

in the stable angina patients (3.1%) and still lower in stable angina patients taking beta-blockers (2.4%), while the incidence rates for the corresponding placebo groups were relatively unchanged (Table 15).

Table 15: BEAUTIFUL study - incidence of bradycardia as an AE and serious AE in the full study population and in the sub-groups of patients with stable angina & of patients with stable angina taking beta-blockers

	Ivabradine		Placebo		P-value
Bradycardia	**n**	**%**	**n**	**%**	
EAE					
Full study population	206	3.8	56	1.0	<0.001
Stable angina patients	23	3.1	9	1.2	0.013
Stable angina taking beta-blockers	16	2.4	8	1.1	0.109
LVEF ≥ 35%	7	2.1	3	0.8	-
LVEF < 35%	9	2.8	5	1.6	-
NYHA Class II	13	2.6	8	1.5	-
NYHA Class III	3	2.5	0	0	-
Serious EAE					
Full study population	22	0.4	6	0.1	0.004
Stable angina patients	1	0.1	0	0	0.975
Stable angina taking beta-blockers	1	0.2	0	0	0.969
LVEF ≥ 35%	0	0	0	0	-
LVEF < 35%	1	0.3	0	0	-
NYHA Class II	1	0.2	0	0	-
NYHA Class III	0	0	0	0	-

Angina pectoris as an adverse event

The incidence of the AE angina pectoris in the full study population was slightly lower in the ivabradine group (136 patients, 2.5%) than with placebo (175 patients, 3.0%). In the sub-group of patients with stable angina and also taking beta-blockers, the benefit of ivabradine treatment was more marked, with an incidence of angina pectoris of 20 patients (3.1%) in the ivabradine group compared with 33 patients (4.7%) in the placebo group. The same was true for angina pectoris as a serious AE (Table 16).

Table 16: BEAUTIFUL study - incidence of angina pectoris as an EAE and serious AE in the full study population and in the sub-groups of patients with stable angina & of patients with stable angina taking beta-blockers

	Ivabradine			Placebo		
Angina pectoris	**n**	**%**	**%PY**	**n**	**%**	**%PY**
EAE						
Full study population	136	2.5	1.9	162	3.0	2.0
All stable angina patients	23	3.1	2.3	37	4.8	3.2
All stable angina taking beta-blocker	20	3.1	2.3	33	4.7	3.2
LVEF ≥ 35%	10	3.0	2.2	17	4.4	2.9
LVEF < 35%	9	2.8	2.2	16	5.1	3.6
NYHA Class II	16	3.2	2.4	25	4.6	3.2
NYHA Class III	4	2.5	1.9	8	4.5	3.3
Serious EAE						
Full study population	37	0.7	0.5	66	1.2	0.8
All stable angina patients	8	1.1	0.8	17	2.2	1.5
All stable angina taking beta-blocker	8	1.2	0.9	13	1.9	1.3
LVEF ≥ 35%	3	0.9	0.6	5	1.3	0.9
LVEF < 35%	4	1.2	1.0	8	2.6	1.8
NYHA Class II	6	1.2	0.9	9	1.7	1.2
NYHA Class III	2	1.2	0.9	4	2.3	1.6

EAE: emergent adverse event; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association

Risk-Benefit Analysis

Efficacy

In the pivotal study, CL3-057, it was shown that over the 4-month treatment period, patients treated with ivabradine showed greater increase in mean total exercise duration (TED) compared with placebo-treated patients in the FAS-E dataset (change in mean ± SD: 24.3 ± 65.3 s and 7.7 ± 63.8 in the ivabradine and placebo groups, respectively with a placebo-subtracted difference = 16.3 s, 95% CI [7.9, 24.7], $p < 0.001$). These results were supported by sub-group analyses in the BEAUTIFUL study, in particular the sub-group of patients with stable angina (or angina at baseline) and patients with stable angina taking beta-blockers. However, given that the primary objective of the BEAUTIFUL study was not met, these sub-group analyses are strictly only hypothesis-generating. While inclined to accept that ivabradine may have positive benefits in some patients with chronic stable angina on concomitant beta blocker therapy, the Delegate expressed a number of concerns. Contrary to the assertion of the sponsor that most issues of contention raised in the clinical evaluation reports have been resolved, there are still areas of concern. Thus in the view of the Delegate, there remained numerous unresolved issues. These are listed below with the sponsor's response in italics.

The sample size in the study had 95% power to detect at least a 30 second difference between treatment groups; however, the observed placebo-subtracted difference was of the order of half of this; how was the study powered to detect a smaller difference?

In the statistical assumptions for the study the <u>expected</u> Standard Deviation (SD) of the TED change was 110 s. In reality the actual SD observed in the study was 65.3 s in the ivabradine group and 63.8 s in the placebo group. As a result of this lower than expected variance 95% power to detect the smaller effect observed was preserved- (95% to detect a 16 s difference).

The huge diversity of results amongst countries; if such significant variability is inherent in employing ETT for the primary outcome measure then this would surely raise doubts about the very validity of ETT results used in such a way.

Significant variability is inherent in employing ETT as the primary outcome measure as required by the TGA-adopted EMA guideline. This inherent variability is reflected in the current analysis and is an expected finding. Indeed the guidelines acknowledge this- "…measurements of exercise capacity using standardised exercise testing should be, in spite of an intrinsic amount of variability, the major criteria of efficacy".

Study CL3-057 involved 219 centres in 20 countries. The variability observed in this study is not unusual in studies involving a large number of international centres. In fact, similar variability was observed in the ranolazine study CVT 3033. Of the 118 individual centres, 19 centres had 10 or more patients. One site was a possible outlier with highly statistically significant treatment effects whilst all other 18 centres had non-significant treatment effect. The EMA approved the indication for the use of ranolazine on top of beta-blockers on the basis of this clinical trial that was similar to study CL3-057, and that was performed in accordance with the TGA-adopted EU guideline.

Despite a number of requests, the sponsor has not provided the analysis of the proportion of patients who made no improvement or got worse on ivabradine, compared with placebo. Also the supplementary clinical evaluation report indicated that, overall, 70% of ivabradine-treated patients showed an improvement in TED and 49% of ivabradine-treated patients showed an improvement in TED of > 30 s. However, the corresponding proportions of placebo-treated patients were not provided. The sponsor was requested to provide all of this information, that is, the full analysis of the proportions of ivabradine and of placebo patients who made no improvement or got worse, who made any improvement and who showed an improvement of more than 30 s.

A full analysis of the proportions of ivabradine and of placebo patients who made no improvement or got worse, who made any improvement and who showed an improvement of more than 30 s, was provided.

Of the 875 patients in the FAS-E, 69.1% of ivabradine-treated patients had an improvement (> 0 s) in TED compared with 54.0% of placebo-treated patients. The proportion of patients in whom the improvement was >30 s was 48.5% in the ivabradine group and 33.8% in the placebo group. 0.9% and 0. 5% of patients in the ivabradine and placebo groups respectively, had no change in TED. The proportion of patients who experienced a worsening in TED was considerably smaller in the ivabradine group, 29.9% compared to the placebo group, 45.2%.

Overall, over the 4-month treatment period, patients treated with ivabradine showed greater increase in mean total exercise duration (TED) compared with placebo-treated patients in the Full Analysis Set (FAS-E) (change in mean ± SD: 24.3 ± 65.3 s and 7.7 ± 63.8 in the ivabradine and placebo groups, respectively with a placebo-subtracted difference = 16.3 s, 95% CI ([7.9, 24.7], p < 0.001). The clinical relevance of this effect size is highlighted by the METS analysis accepted by the clinical evaluator.

The specific exclusion of patients on atenolol 100 mg once daily or equivalent with the result that any claim that ivabradine would be effective on such doses of beta-blockers was not actually put to the test in the trial.

A justification for the indication in combination with <u>all</u> beta blockers when in fact the only beta-blocker tested in combination with ivabradine in the pivotal clinical trial was atenolol and only at one specific dose, namely 50 mg once daily.

The EMA recently granted approval for treatment of ivabradine in combination with all beta-blockers, on the basis of the same data included in this current submission. The proposed indication is consistent with the EU indication.

For patients having received other beta-blocker treatment the following doses were considered equivalent to atenolol 50 mg od: atenolol 25 mg bd; bisoprolol 5-10 mg od; metoprolol 50 mg bd; propranolol 80-160 mg od; carvedilol 12.5 mg bd. The validity of the dose equivalences employed in the study was borne out by the stability of clinical markers of beta-blockade during the run-in period.

In accordance with the Delegate's advice that the indication 'must reflect that the dose of beta-blocker studied was atenolol 50 mg once daily or equivalent', the sponsor was agreeable to amending the proposed indication. It suggested that the wording '…OR in combination with beta blockers (that is, atenolol 50mg once daily or equivalent)' with a table of beta-blocker doses equivalent to atenolol 50 mg twice daily in the Clinical Trials section of the PI would properly reflect the evidence, bearing in mind the fact that the degree of beta-blockade remained stable switching from other beta-blockers to atenolol 50mg using the same table of equivalences. The proposition reflects the belief that the study demonstrates efficacy in the setting of a level of beta blockade, and that this more clinically relevant than the precise agent employed in the trial.

The sponsor also noted that there are recent precedents of ACPM-recommended and subsequent TGA-approved combination use of a drug with an entire drug class, despite that class being represented by only one drug in pivotal clinical trials. The requested indication to allow treatment of ivabradine on top of beta-blockers on the basis of the ASSOCIATE pivotal trial where ivabradine was tested in combination with atenolol 50 mg twice daily is consistent with these previous decisions.

Whilst the sponsor firmly believed that its proposed indication is justified on the basis of the above information, the sponsor would be prepared to consider the following indication:

'Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm who are unable to tolerate or have a contraindication to the use of beta blockers, OR in combination with atenolol 50mg once daily (or equivalent) in patients whose heart rate is ≥ 60 bpm and angina is inadequately controlled.'

No comparison of efficacy in the sub-group on maximal beta-blockade with those who received sub-maximal beta-blocker doses.

A table comparing the change from baseline in TED in the subgroup of patients whose beta-blocker dose was judged to be maximal with those whose beta-blocker dose was sub-maximal, was provided. It should be stressed that patients whose beta-blocker dose was sub-maximal (in mg) were not necessarily on a sub-optimal beta-blocker dose (on clinical grounds). Doses may have been limited by adverse effects or other tolerability issues.

There were 731 patients who received a sub-maximal beta-blocker dose in the pivotal study, that is, 83.5% of the study population. In this group of patients, the placebo-subtracted difference in the gain in mean TED was 15.7 s 95% CI [6.62 ; 24.86], p<0.001. This was comparable to the result observed in patients with maximal beta-blockade (16.3 s, 95% CI [-5.0;37.7], p=0.066), and to the result in the full study population (16.3 s, 95% CI [7.9;24.7], p<0.001).

The trends in the usage of short acting nitrates were actually in favour of placebo.

SAN use is a patient-driven response to a subjective symptom. Patients will not always have SAN available at the time of an attack, whilst others that do may prefer to rest rather than

administer an SAN due to the potential for adverse reactions, notably headache. Patients also do not universally perceive SAN to be effective; for example in a recently published representative study in Australian primary care, only 51% of stable angina patients reported relief with SAN despite 93% reporting classic substernal chest discomfort.[15] *Additionally patients may sometimes self-administer SAN for pain of non-cardiac origin. Patient-related factors hence contribute to considerable variability in this parameter. The considerable limitations of SAN usage as an efficacy endpoint are acknowledged in the TGA-adopted EU guideline; 'The concomitant use of short acting nitrates has been classically accepted as a supportive clinical measurement. This parameter is highly variable and today is considered of limited clinical value and should only be considered as a secondary end point'. In response to the Delegate's question the sponsor examined the relationship between the change in SAN usage and the change in angina symptoms reported during the 4-month double-blind period of the 057 study. A weak association (Pearson correlation coefficient = 0.357) was seen and angina frequency was a poor predictor of SAN use (on regression analysis). The sponsor believed that this weak relationship between SAN use and clinical symptom status means that minimal weight should be afforded to the SAN data in assessing efficacy in the study. It suggested that the primary focus should remain on the objective ETT criteria, as required by the guideline.*

A more reliable secondary endpoint is angina episodes. Whilst not significant this endpoint trends in favour of the ivabradine treatment arm.

In the sub-group analysis of efficacy in the 247 patients with refractory angina, how does one adjust for the fact that, at baseline, patients in the placebo group appeared to be worse off clinically.

In the sub-group analysis of efficacy in the 247 patients with refractory angina, at baseline, the placebo group appeared worse off clinically as there were more patients with CCS-III angina, with a history of heart failure and comprised patients whose mean time since angina diagnosis was longer. There was also a greater proportion of females in the ivabradine group.

In light of these baseline characteristics, the superiority of ivabradine versus placebo in terms of change in TED and time to 1 mm ST segment depression (TST) in patients with refractory angina, was re-analysed with adjustments for country, sex, history of HF, duration of CAD, and CCS Class.

The results show that the improvement in TED (end-baseline) was 32.23 seconds in the active group, or 17.53 seconds when adjusted for the placebo response. The intergroup difference remains significant. TST was 331 seconds in ivabradine-treated patients and 357 seconds in placebo-treated patients. The placebo-corrected difference in improvement in TST was significant at 32.14 seconds.

Statistically significant and clinically relevant changes in exercise tolerance were still seen in response to ivabradine in patients with refractory angina, even when one adjusts for country, sex, history of HF, duration of CAD and CCS Class. These results still support the efficacy of the product in reducing angina symptoms and cardiac ischaemia.

In the BEAUTIFUL study, how comparable are those patients with limiting angina at baseline to the patients with chronic stable angina in the pivotal study, CL3-057?

[15] Beltrame J, Weekes AJ, Morgan C, Tavella R, Spertus JA. The prevalence of weekly angina amongst chronic stable angina patients in primary care practices – The Coronary Artery Disease in General Practice (CADENCE) study. Arch Intern Med 2009; 169: 1491-1499.

A comparison of criteria at randomisation of patients in study 057 and patients in the limiting angina subgroup of the BEAUTIFUL study was provided. The two patient populations are relatively similar concerning demographics although the population from the 057 study is slightly younger. Regarding medical history, a much higher proportion of patients in the BEAUTIFUL angina group had a history of myocardial infarction. Major differences are also found in the cardiac parameters heading and more specifically concerning left ventricular ejection fraction that is much lower in the BEAUTIFUL angina group as dictated by protocol. The NYHA Classes and CCS Classes proved difficult to compare, as they were not systematically rated in both studies.

Concomitant medications at randomisation were also similar except those related to heart failure, ACE inhibitors and diuretics were used extensively in the BEAUTIFUL angina group. The choice of beta-blocker was also different between both populations as protocol dictated atenolol 50 mg in study 057 and the BEAUTIFUL population had a high proportion of patients on beta-blockers with indications for heart failure (carvedilol, bisoprolol).

It must be noted that the comparison of these two populations was a post-hoc analysis and therefore the number of parameters that were recorded in both the BEAUTIFUL study and in study 057 which could be used for comparison was limited.

Safety

Analysis of the safety data did not reveal new safety concerns. In general more adverse events were reported in the ivabradine group than in the placebo group. The majority or reported adverse events related to the known effects on heart rate and visual disturbances. Sub-group analyses of data from the BEAUTIFUL study were reassuring (patients who had their physical activity limited by anginal pain at baseline, patients taking and not taking beta-blockers), particularly with adjudicated endpoints with an outcome of death, investigator assigned AEs with an outcome of death, AEs related to cardiac arrhythmias, bradycardia and angina pectoris as an AE.

The Delegate proposed to approve the submission provided that there is satisfactory resolution of efficacy issues outlined above for the following indication:

Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm who are unable to tolerate or have a contraindication to the use of beta-blockers, OR in combination with atenolol in patients whose heart rate is > 60 bpm and whose angina is inadequately controlled with atenolol 50 mg once daily.

The sponsor should address the all the efficacy issues identified under the Risk/Benefit discussion.

The Delegate posed the following questions to The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC):

- Does the ACPM agree that the finding of a placebo-subtracted difference of 16.3 s in the gain in mean TED is also clinically significant?
- Is the ACPM concerned by the disparity in results in the primary efficacy endpoint from different countries in the pivotal trial, CL3-057?
- Does the ACPM agree with the Delegate that the indication must reflect the actual pivotal clinical trial evidence and that therefore the use of the phrase "*in patients inadequately controlled with an optimal beta-blocker dose*" is inappropriate? Does the ACPM also agree with the Delegate that the data only supports the combination of

ivabradine with atenolol 50 mg once daily and cannot be generalised to support combination with all beta-blockers at any dose?

- Is the ACPM satisfied that the sub-group of patients in the BEAUTIFUL study who had limiting angina at baseline is sufficiently similar to the patients with chronic stable angina in the pivotal study to allow valid comparisons of efficacy and safety data between the two groups?

Advisory Committee Consideration

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, disagreed with the Delegate's proposal and recommended rejection of the submission.

In making this recommendation, the ACPM considered the submitted efficacy and safety evidence and advised that while the improvement in total exercise duration has been shown to be statistically significant; there was an absence of meaningful clinical benefit as evidenced by the small overall improvement. In addition, the pivotal study failed to demonstrate a significant difference in improvement in angina symptomatology between the two groups under investigation. The ACPM also expressed concern regarding the validity of the change to the statistical plan for the primary endpoint.

Following the ACPM's recommendation, the Delegate was minded to accept the advice of the ACPM and reject the submission. Prior to the Delegate proceeding to make any decision in the matter, the sponsor was invited to comment on the Delegate's proposal to reject the submission. The sponsor's response is summarised below in italics.

The sponsor has demonstrated that the primary result of the study meets the statutory test for efficacy required by The Act and has used the MET tool in accordance with the relevant TGA-adopted EU Guideline to further demonstrate that the primary efficacy outcome does translate to a clinically meaningful benefit. The clinical relevance of these findings was acknowledged by the clinical evaluator and the Delegate. The sponsor was therefore surprised that the ACPM was of the opinion that the primary result of the study was of doubtful clinical benefit and requested clarification on what tool/guideline or standard the ACPM used to reject the MET evidence presented.

Assurance was provided that the statistical analyses performed on the primary endpoint were predefined in the statistical analysis plan completed before unblinding. The ACPM concluded that there was a lack of significant difference in the mean number of angina attacks per week over the 4 months of the study. The sponsor responded that the pivotal study CL3-057 was not powered to detect the change of this secondary endpoint and that the ACPM's view was inconsistent with the requirements of the relevant TGA-adopted EU Guideline.

The study population in CL3-057 has been compared to 2031 Australian patients with stable angina and found to be representative. The selection of patients for inclusion in the study was consistent with the requirements outlined in the relevant TGA-adopted EMEA Guidelines and exclusions from the study are a direct result of applying these Guidelines.

The sponsor demonstrated that published evidence and Australian clinical practice are counter to the ACPM's view that a 50 mg/day atenolol dose in stable angina patients is a sub-optimal dose. A number of studies, including an Australian observational study CADENCE with 452 patients receiving atenolol have demonstrated that the average dose of atenolol used in Australian patients with stable angina is ~ 50mg/day. It is more relevant for study CL3-057 to have been conducted with the most common used dose than an idealistic optimal dose.

In a subsequent letter discussing aspects of the PI, the Delegate accepted that the placebo-subtracted increase in total exercise duration (TED), 16.3 seconds, was indeed shown to be highly statistically significant at a level of $p<0.001$ and that the increase in TED was achieved in Stage 3 of the Bruce protocol, that is, at a point of high demand, although not for all patients (at this stage of the Bruce protocol the functional capacity was shown to be equivalent to 9 METs, corresponding to activities of high intensity).

As already noted in the Delegate's overview, analysis of the safety data did not reveal any new safety concerns. In light of this, and the fact that the pivotal study did, in the view of the Delegate, demonstrate a benefit of some clinical relevance the Delegate approved the application, provided that there was satisfactory resolution of the request for PI changes.

Thus the Delegate was satisfied that the demonstrated efficacy benefits, as well as being statistically significant, may also be regarded as being of clinical relevance or benefit to some patients.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Coralan containing ivabradine indicated for:

Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm, who are unable to tolerate or have a contraindication to the use of beta blockers, OR in combination with atenolol 50 mg once daily when heart rate is at or above 60 bpm and angina is inadequately controlled.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

CORALAN®

Product Information

NAME OF THE MEDICINE

CORALAN®

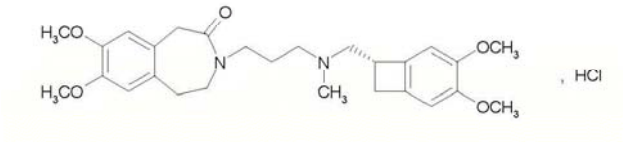
Ivabradine (as the hydrochloride) 5 mg, 7.5 mg film coated tablets

DESCRIPTION

Description of substance and solubility: The chemical structure of ivabradine contains two rings: one benzazepinone and one benzocyclobutane linked with an azapentane chain. The structural form of ivabradine includes one asymmetric carbon and ivabradine corresponds to the S enantiomer. The hydrochloride salt is a white hygroscopic powder, soluble in water (50 mg/mL) and in 0.9% saline solution (14 mg/mL). The pH is 5.1 – 5.4 in aqueous solutions at concentration of 10 mg/mL.

Excipients: Core- lactose, magnesium stearate, starch maize, maltodextrin, silica (colloidal anhydrous). Film-coating- hypromellose, titanium dioxide (E 171), macrogol 6000, glycerol, magnesium stearate, yellow iron oxide (E 172), red iron oxide (E 172).

Chemical Name: 3-(3-{[(7S)-3,4-Dimethoxybicyclo[4,2,0]octa-1,3,5-trien-7-yl) methyl] methylamino}propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2*H*-3-benzazepin-2-one, hydrochloride.
CAS Number (base): 155974-00-8
Molecular formula: $C_{27}H_{36}N_2O_5$, HCl
Molecular weight (hydrochloride): 505.06
Chemical Structure:



PHARMACOLOGY

Pharmacotherapeutic group: Cardiovascular System - Heart Rate Reducing Agents. ATC code: C01EB17

Pharmacodynamics

Ivabradine is a heart rate lowering agent, acting by selective inhibition of the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate.

The cardiac effects are relatively specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, myocardial contractility or ventricular repolarisation in humans at the therapeutic dose. In experimental models the adaptability

of myocardial contractility, cardiac output, mean coronary blood flow velocity and vascular resistance observed during exercise are preserved.
In animal models used to mimic exercise-induced ischaemia that causes angina pectoris in humans, ivabradine significantly reduces myocardial ischaemia and myocardial contractility dysfunction induced by stunning.

Ivabradine can also interact with the retinal current I_h which closely resembles cardiac I_f. It participates in the temporal resolution of the visual system, by curtailing the retinal response to bright light stimuli. Under triggering circumstances (e.g. rapid changes in luminosity), partial inhibition of I_h by ivabradine underlies the luminous phenomena that may be occasionally experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field.

The main pharmacodynamic property of ivabradine in humans is a specific dose-dependant reduction in heart rate. At usual recommended doses, heart rate reduction is approximately 10 beats per minute (bpm) at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption. Analysis of heart rate reduction indicates a trend towards a plateau effect at doses over 20 mg twice daily.

Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarisation:
- In clinical electrophysiology studies, ivabradine had no effect on atrioventricular or intraventricular conduction times or corrected QT intervals;
- In specific studies including over 100 patients with left ventricular dysfunction, ivabradine was shown to preserve myocardial contractility.

Pharmacokinetics

Under physiological conditions, ivabradine is rapidly released from tablets and is highly soluble (>10 mg/mL, pH 2 –7.5). Ivabradine is the S-enantiomer with no bioconversion demonstrated *in vivo*. The N-desmethylated derivative of ivabradine has been identified as the main active metabolite in humans.

Absorption and bioavailability

Ivabradine is rapidly and almost completely absorbed after oral administration with a peak plasma level reached in approximately 1 hour under fasting condition. The absolute bioavailability of ivabradine tablets is around 40%, due to a first-pass effect in the gut and liver.

Food delayed absorption by approximately 1 hour, and increased plasma exposure by 20 to 30%. To minimise intra-individual variability in exposure, ivabradine should be taken during meals (See DOSAGE AND ADMINISTRATION).

Distribution

Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady state is close to 100L in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily is about 20ng/mL. The average plasma concentration is 10ng/mL at steady state.

Biotransformation

Ivabradine is extensively metabolised by the liver and the gut by oxidation through cytochrome P4503A4 (CYP3A4) only. The major active metabolite is the N-desmethylated derivative, and its exposure (measured by AUC) is about 40% of that of the parent compound with similar pharmacokinetic and pharmacodynamic properties. The metabolism of this active metabolite also involves CYP3A4. Ivabradine has low affinity for

CYP3A4, shows no clinically relevant CYP3A4 induction or inhibition and is therefore unlikely to modify CYP3A4 substrate metabolism or plasma concentrations. Conversely, potent inhibitors and inducers may substantially affect ivabradine plasma concentrations (See CONTRAINDICATIONS and PRECAUTIONS-Drug Interactions).

Elimination

The main elimination half-life of ivabradine is 2 hours (70 to 75% of the AUC) in plasma, and an effective half-life is 11 hours. The total clearance is about 400mL/min and the renal clearance is about 70mL/min. Metabolites are equally excreted in the faeces and urine. About 4% of an oral dose is excreted unchanged in urine.

The kinetics of ivabradine are linear over an oral dose range of 0.5 to 24 mg.

Special populations:
The impact of renal impairment (creatinine clearance from 15 to 60mL/min) on ivabradine pharmacokinetics is minimal, in relation with the low contribution of renal clearance (about 20%) to total elimination for both ivabradine and its main active metabolite S 18982 (See PRECAUTIONS).

In patients with mild hepatic impairment (Child Pugh score up to 7) AUC of unbound ivabradine and the main active metabolite were about 20% higher than in subjects with normal hepatic function. Data are limited in patients with moderate hepatic impairment (See PRECAUTIONS). No data are available in patients with severe hepatic impairment (See CONTRAINDICATIONS).

Pharmacokinetic/Pharmacodynamic (PK/PD) Relationship

PK/PD relationship analysis has shown that heart rate decreases almost linearly with increasing ivabradine and the N-desmethylated derivative plasma concentrations for doses of up to 15 to 20 mg twice daily. At higher doses, the decrease in heart rate is no longer proportional to ivabradine plasma concentrations and tends to reach a plateau. High exposures to ivabradine that may occur when ivabradine is given in combination with potent CYP3A4 inhibitors may result in an excessive decrease in heart rate although this risk is reduced with moderate CYP3A4 inhibitors (See CONTRAINDICATIONS, and PRECAUTIONS).

CLINICAL TRIALS

The anti-anginal and anti-ischaemic efficacy of ivabradine was demonstrated in five double blind randomised trials (three versus placebo, and one each versus atenolol and amlodipine). These trials included a total of 4,111 patients with coronary artery disease (CAD) and chronic stable angina pectoris, of whom 2,617 received ivabradine.

Stable angina- Monotherapy

Ivabradine 5 mg twice daily was shown to be effective on exercise test parameters within 3 to 4 weeks of treatment (Table 1). Efficacy was confirmed with 7.5 mg twice daily. In particular, the additional benefit over 5 mg twice daily was established in a reference-controlled study versus atenolol: total exercise duration at trough was increased by about 1 minute after one month of treatment with 5 mg twice daily and further improved by almost 25 seconds after an additional 3-month period with forced titration to 7.5 mg twice daily. In this study, the anti-anginal and anti-ischaemic benefits of ivabradine were also confirmed in patients aged 65 years or more. The efficacy of 5 and 7.5 mg twice daily was consistent across studies on exercise test parameters (total exercise duration, time to limiting angina, time to angina onset and time to 1mm ST segment depression) and was

associated with a decrease of about 70% in the rate of angina attacks. The twice-daily dosing regimen of ivabradine showed uniform efficacy over 24 hours.

Table 1– Total Exercise Duration (TED) (seconds) (s) during bicycle or treadmill Exercise Tolerance Test (ETT) at the trough of drug activity

TREADMILL ETT				
1 month treatment period[1]				
	Ivabradine 5 mg twice daily (n=595)		Atenolol 50 mg once daily (n=286)	
TED (s)	Baseline	End minus Baseline	Baseline	End minus Baseline
Mean (SD)	594 (142)	64.2 (104)	578 (144)	60 (114)
95% CI [4]		-7.44 to 20.8		
p value [5]		p<0.001 (non-inferior)		
4 month treatment period[2]				
	Ivabradine 7.5 mg twice daily (n=300)		Atenolol 100 mg once daily (n=286)	
TED (s)	Baseline	End minus Baseline	Baseline	End minus Baseline
Mean (SD)	595 (142)	86.8 (129)	578 (144)	78.8 (133)
95% CI [4]		-8.28 to 28.8		
p value [5]		P<0.001 (non-inferior)		
BICYCLE ETT				
3 month treatment period[3]				
	Ivabradine 7.5 mg twice daily (n=381)		Amlodipine 10 mg once daily (n=398)	
TED (s)	Baseline	End minus Baseline	Baseline	End minus Baseline
Mean (SD)	414 (133)	27.6 (92)	400 (132)	31.2 (92)
95% CI [4]		-14.64 to 11.06		
p value [5]		P<0.001 (non-inferior)		

[1]: *Non-inferiority tests of ivabradine (5 mg) as compared to atenolol 50 mg. Non-inferiority limit: -35s. One-sided type 1 error rate: 0.025*
[2]: *Non-inferiority tests of ivabradine (7.5 mg) as compared to atenolol 100 mg. Non-inferiority limit: -35s. One-sided type 1 error rate: 0.025*
[3]: *Non-inferiority tests of ivabradine (7.5 mg, 10 mg) versus amlodipine 10 mg. Non-inferiority limit: -30s. One-sided type 1 error rate: 0.025*
[4]: *95% CI of the estimate (two-sided) of ivabradine-comparators effects, compared to non-inferiority limit (parametric approach)*
[5]: *Student's test based on the overall general linear model (least-squares norm) with baseline as a covariate and country as a random factor*

Stable angina- Combination therapy

In a 725-patients randomised placebo-controlled study, ivabradine did not show additional efficacy on top of amlodipine at the trough of drug activity (12 hours after oral intake) while additional efficacy was shown at peak (3 to 4 hours after oral intake).

Ivabradine efficacy was fully maintained throughout the 3- or 4-month treatment periods in the efficacy trials. There is no evidence of pharmacological tolerance (loss of efficacy) developing during treatment or of rebound phenomena after abrupt treatment discontinuation.

A sustained reduction of heart rate was demonstrated in patients treated with ivabradine for at least one year. No influence on glucose or lipid metabolism was observed. The anti-anginal and anti-ischaemic efficacy of ivabradine was preserved in diabetic patients (n=457) with a similar safety profile as compared to the overall population.

The anti-anginal and anti-ischaemic effects of ivabradine were associated with dose-dependent reductions in heart rate and with a significant decrease in rate pressure

product (heart rate x systolic blood pressure) at rest and during exercise. No clinically-relevant effect on blood pressure was observed.

The efficacy of ivabradine versus placebo on top of a background therapy with atenolol 50 mg once daily in patients with stable angina was demonstrated in a randomised, double-blind, placebo-controlled, parallel-group, international multicentre study. The ASSOCIATE study involved 219 centres in 20 countries with a diversity of results across different countries. The analysis in the intention to treat (ITT) population is presented below.

Patients included in the study were aged between 18 and 75 years, with a history of stable chronic effort angina pectoris for at least 3 months prior to pre-selection, with no angina at rest and no angina of class IV, with clinical stability, and with documented CAD. Overall, 58% of patients received atenolol 50 mg once daily within the 3 months before inclusion in the study, and 42% received another beta-blocker (i.e. metoprolol, bisoprolol, carvedilol, propanolol) at an equivalent dose. Patients on a different beta-blocker to atenolol 50 mg were switched to atenolol 50 mg once daily at the start of the run-in period, so that during the run-in period all patients received atenolol 50mg once daily

Three Exercise Tolerance Tests (ETTs) were performed during the 6-8 week run-in period (the first two at selection visits SEL1 and SEL2 and the third prior to the inclusion visit M0). In accordance with the requirements for patient inclusion outlined in the relevant TGA guideline, patients eligible for inclusion into the study were required to have a positive ETT result at the SEL1 visit and two positive stable ETTs at SEL2 and M0 visits. Patients selected for SEL2 were required to have had a positive result at the SEL1 visit.
Stability was defined as time to 1 mm ST segment depression (TST) within ± 20 %, or ± 1 min at the two visits.

Of the 2681 patients screened, a total of 889 patients met the inclusion criteria, and were thus included and randomised to the study. A total of 1792 patients failed to meet either pre-selection, selection or inclusion criteria. The majority of those not included in the study (1508/1792; 84.2%) did not produce a positive ETT result at SEL1 or did not meet the stability criteria.

After a run-in period lasting 6 to 8 weeks on atenolol (50 mg once daily) and placebo (twice daily), 889 patients complying with inclusion criteria were randomised to receive either ivabradine 5 mg twice daily then 7.5 mg twice daily given orally for 2 months each (n = 449) or placebo (n = 440), in combination with atenolol (50 mg once daily). The treatments compared were ivabradine with atenolol 50mg once daily versus placebo with atenolol 50mg once daily.

The primary efficacy endpoint was the improvement between baseline and end of 4 months of treatment (M4) in 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.

Statistically, the between group difference in TED over the 4-month period was significant in favour of a greater increase in the ivabradine group (16.3 s (95% CI [7.9; 24.7]). An improvement was also observed over the 2-month period (8.2 s (95% CI [0.6 ; 15.7]).
The improvement in TED of 16.3 s ($p < 0.001$) was achieved, most commonly, during the third stage of the standard Bruce protocol, where the functional capacity of an individual is approximately 9 Metabolic Equivalents (METs) corresponding to activities considered to be of high intensity i.e. cycling at ~25km/h, jogging at ~9km/h, cross-country skiing at ~ 8km/h.

Of the 875 patients in the full analysis set, 69.1% of ivabradine-treated patients had an improvement in TED compared with 54.0% of placebo-treated patients. The proportion of patients in whom the improvement was >30 s was 48.5% in the ivabradine group and 33.8% in the placebo group. 0.9% and 0.5% of patients in the ivabradine and placebo groups respectively, had no change in TED. The proportion of patients who experienced a worsening in TED was considerably smaller in the ivabradine group, 29.9% compared to the placebo group 45.2%.

There were a number of secondary endpoints, parameters measured included: Time to 1mm ST segment depression (TST, s), time to angina onset (TAO, s), time to limiting angina (TLA, s), heart rate (HR) at rest and at peak of exercise (bpm), rate pressure product (RPP) at rest and at peak of exercise (bpm x mmHg), and reason for stopping exercise. Adding ivabradine to atenolol 50 mg once daily increased TAO of 25.5 s, TST of 28.5 s and TLA of 16.3 s, relative to placebo. These results were statistically significant and consistent with the primary endpoint.
No between group differences were observed in the number of angina attacks or short acting nitrates (SAN) over the 4 months of the study.

Mean change resting HR was -10.8 ± 10.8 bpm in ivabradine group *versus* -2.2 ± 10.1 bpm in placebo group (diff of -8.8 bpm; 95% CI: [-10.0 ; -7.6]). At the peak of exercise this was -11.3 ± 13.2 bpm *versus* -0.9 ± 12.3 bpm, respectively (difference of -10.8 bpm; 95%CI: [-12.4 ; -9.1]). The overall evolution in heart rate at rest in supine position observed in the ivabradine group was 67.0 ± 6.9 bpm at baseline to 58.4 ± 8.7 bpm at month 4. In the ivabradine group, 20.2% (89/441) of patients experienced a reduction in HR of more than 20bpm. This was only experienced in patients with a high resting HR at baseline i.e. patients with HR > 70 bpm at baseline.

Coronary Artery Disease (CAD) with Left Ventricular Dysfunction (LVD):
A large outcome study, BEAUTIFUL, studied the use of ivabradine compared with placebo in patients with CAD and Left Ventricular Dysfunction (LVD) receiving treatment appropriate to their cardiovascular condition. A total of 10 917 patients with Left Ventricular Ejection Fractions (LVEF) between >20% and <40% were randomised with 87% receiving beta-blockers- most commonly carvedilol, metoprolol succinate/tartrate, and bisoprolol. Angina was the main limiting factor for 14% of randomised patients. The main efficacy criterion was the composite of cardiovascular death, hospitalisation for acute MI or hospitalisation for new onset or worsening heart failure. The study showed no difference in the primary composite endpoint (relative risk 1.00, p=0.945).

INDICATIONS

Treatment of chronic stable angina due to atherosclerotic coronary artery disease in patients with normal sinus rhythm, who are unable to tolerate or have a contraindication to the use of beta-blockers, OR in combination with atenolol 50mg once daily when heart rate is at or above 60 bpm and angina is inadequately controlled.

CONTRAINDICATIONS

- Known hypersensitivity to ivabradine or any of the excipients
- Conditions in which the sinus node is no longer the cardiac pacemaker: e.g. artificial pacemaker, sick sinus syndrome
- 3rd degree Atrioventricular (AV) block
- Heart failure patients with NYHA functional classification III-IV due to a lack of data (See PRECAUTIONS)
- Resting heart rate below 60bpm prior to treatment

- Severe hypotension (< 90/50 mmHg) (See PRECAUTIONS)
- Unstable angina
- Cardiogenic shock
- Acute myocardial infarction
- Sino-atrial block
- Patients with Hypertrophic Cardiomyopathy (HOCM) unless co-existing Coronary Artery Disease (CAD) is proven (See PRECAUTIONS)
- Combination with potent cytochrome P450 3A4 (CYP 3A4) inhibitors (See PRECAUTIONS – Drug interactions)
- Severe hepatic insufficiency (See PRECAUTIONS)
- Pregnancy and Lactation (See PRECAUTIONS)

PRECAUTIONS

Pulse Rate Monitoring

Where heart rate monitoring is recommended, estimation of pulse rate by radial, brachial, or carotid pulse palpation will usually be sufficient.

Low Heart Rate

If, during treatment, resting heart rate decreases persistently below 50bpm or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward (See DOSAGE AND ADMINISTRATION). If heart rate remains below 50bpm or symptoms of bradycardia persist, treatment with ivabradine should be discontinued.

Congenital QT Syndrome or Treatment with QT-Prolonging Medicines

The use of ivabradine in patients with QT prolongation, congenital QT syndrome or treated with QT prolonging medicinal products should be avoided (See PRECAUTIONS – Drug interactions). If the combination appears necessary, close cardiac monitoring is needed.

Cardiac Arrhythmias

Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and likely loses its efficacy when a tachyarrhythmia occurs (eg. ventricular or supraventricular tachycardia). Ivabradine is not recommended in patients with atrial fibrillation or with other cardiac arrhythmias that interfere with sinus node function. It is recommended to regularly clinically monitor ivabradine-treated patients for the occurrence of atrial fibrillation (sustained or paroxysmal), which should also include ECG monitoring if clinically indicated (e.g. in case of exacerbated angina, palpitations, irregular pulse).

There is no evidence of risk of (excessive) bradycardia on return to sinus rhythm when pharmacological cardioversion is initiated in patients treated with ivabradine. However, in the absence of extensive data, non-urgent DC-cardioversion should be considered 24 hours after the last dose of ivabradine.

Aortic Stenosis

Experience with the use of ivabradine in patients with aortic stenosis is limited and should be used with caution in this patient population. A low initiation dose, slow dose titration and patient monitoring are recommended.

Use in patients with 2nd degree AV block

Ivabradine should be used with caution in patients with 2nd degree AV block.

Patients with Hypotension

Limited data are available in patients with mild to moderate hypotension, and ivabradine should therefore be used with caution in these patients. Ivabradine is contraindicated in patients with severe hypotension (blood pressure < 90/50 mmHg).

Stroke

The use of ivabradine is not recommended immediately after a stroke since no data is available in these situations.

Wolf Parkinson White syndrome

Ivabradine has not been studied in patients with Wolf Parkinson White syndrome.

Hepatic Insufficiency

Studies in patients with mild hepatic insufficiency (AST/ALT 1.5 to 2 times ULN or Child Pugh score up to 7) support the use of ivabradine in this patient population. Caution should be exercised when using ivabradine in patients with moderate hepatic insufficiency. The use of ivabradine in patients with severe hepatic insufficiency is contraindicated as it has not been studied in this population and a large increase in systemic exposure is expected.

Renal Insufficiency

There are no data available in patients with creatinine clearance below 15mL/min therefore ivabradine should be used with caution in patients with end stage renal disease. There is limited safety data in patients with a creatinine clearance of 15 to 30mL/min. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals in patients with renal insufficiency, particularly following a dose increase.

Heart Failure

In patients with left ventricular dysfunction, Ivabradine did not have any deleterious influence on left ventricular ejection fraction (LVEF) between 30% and 45%. Caution is needed in asymptomatic left ventricular dysfunction, as well as in heart failure patients with NYHA function classification II due to the limited number of patients studied. Ivabradine is contraindicated in patients with concurrent severe heart failure (NYHA functional classification III-IV), as it has not been studied in this population. Heart failure must be appropriately managed before considering ivabradine treatment.

Hypertrophic Cardiomyopathy

Ivabradine should be used with caution in patients with HOCM and coexisting CAD due to limited data in this patient population.

Cardiac and Non-cardiac surgery

Ivabradine should not be commenced peri-operatively due to limited safety data available in this population.

Visual Effects

Changes in retinal function were observed in dogs at ivabradine exposures similar to or higher (i.e. about 1 to 46 times) than those in patients treated with 7.5 mg ivabradine twice daily, based on AUC. These changes were reversible after cessation of treatment, and were not associated with any damage to ocular structures. These data are consistent with the pharmacological effect of ivabradine related to its interaction with hyperpolarisation-activated I_h currents in the retina, which share extensive homology with the cardiac pacemaker I_f current.

Ivabradine may influence retinal function in humans (See PHARMACOLOGY). To date, there is no evidence of a toxic effect of ivabradine on the retina, however the effects on retinal function in humans beyond one year treatment with ivabradine are currently not known. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.

Lactose Intolerance

Ivabradine tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption should not take this medicine.

Use in the Elderly

No pharmacokinetic differences (AUC and Cmax) have been observed between elderly (≥65 years) or very elderly patients (≥75 years) and the overall population. However, since ivabradine has been studied in a limited number of patients aged ≥75 years, a lower starting dose should be considered before up-titration if necessary, in this population (See DOSAGE AND ADMINISTRATION).

Carcinogenicity

Long term studies in mice at oral doses up to 450 mg/kg.day (reduced to 180 mg/kg/day after 80 weeks of treatment) and in rats at 120 mg/kg/day (reduced to 60 mg/kg/day after one year of treatment) showed no increase in tumour incidences. These doses resulted in ivabradine exposures 10 to 100 times human exposure at 7.5 mg twice daily based on AUC.

Mutagenicity

The weight of evidence from a battery of in vivo and in vitro studies supports a conclusion that ivabradine is unlikely to pose a genotoxic risk in patients.
Ivabradine did not induce gene mutation in bacteria (Ames test), chromosome aberration in mice or rats in vivo, or DNA damage in rat hepatocytes in vivo.
Weakly positive or equivocal results were observed at high concentrations (of more than 10,000 times the maximum observed concentrations seen in patients at therapeutic doses) in several *in vitro* tests, which examined the potential for gene mutation in mouse lymphoma cells, chromosome aberration in human lymphocytes and DNA damage in rat hepatocytes.

Effects on Fertility

Reproductive toxicity studies showed no effect of ivabradine on fertility in male and female rats at oral doses up to 175 mg/kg/day, which result in plasma ivabradine levels approximately 50 to 110 times the average clinical levels at 7.5 mg twice daily, based on AUC).

Use in Pregnancy

Pregnancy Category D: There are no adequate data concerning the use of ivabradine in pregnant women. Animal reproduction studies have shown embryotoxic and teratogenic effects (cardiac defects in rats and ectrodactylia) at exposures (based on AUC) close to the clinical exposure at 7.5 mg twice daily Ivabradine is contraindicated during pregnancy as the potential risk for humans is unknown. (See CONTRAINDICATIONS).

Use in Lactation

Animal studies indicate that ivabradine is excreted in milk. Treatment of dams during gestation and lactation resulted in postnatal mortalities and enlarged heart in the offspring from exposures (based on AUC) 3.1 times the expected clinical exposure at 7.5 mg twice

daily Therefore, ivabradine is contra-indicated in breast feeding women (See CONTRAINDICATIONS).

Paediatric Use

Ivabradine is not recommended in children and adolescents, as efficacy and safety have not been studied in these populations.

Interactions With Other Medicines

Concomitant use with Cytochrome P450 3A4 (CYP3A4) inhibitors or inducers:

Ivabradine is metabolised by CYP3A4 only and is a very weak inhibitor of this cytochrome. Ivabradine is therefore unlikely to influence the metabolism and plasma concentrations of other CYP3A4 substrates. Drug-drug interaction studies have established that CYP3A4 inhibitors increase ivabradine plasma concentrations, while inducers decrease them. Increased plasma concentrations of ivabradine may be associated with a risk of excessive bradycardia. (See PHARMACOLOGY).

Potent CYP3A4 inhibitors (e.g. ketoconazole, macrolide antibiotics, cyclosporin, gestodene and anti-retroviral drugs):

Concomitant use with ivabradine is contraindicated (See CONTRAINDICATIONS). Specific clinical interaction studies have shown that the concomitant use of ivabradine (10 mg twice daily) and ketoconazole (200 mg once daily) produced 7 to 8-fold increases in ivabradine mean plasma exposure.

Moderate CYP3A4 inhibitors (e.g. diltiazem, verapamil) with heart rate reducing properties:

Concomitant use of ivabradine with diltiazem or verapamil is not recommended due to the potential for additive heart rate lowering effects.

Specific interaction studies in healthy volunteers and patients have shown that the combination of ivabradine with diltiazem or verapamil resulted in an increase in ivabradine exposure (2 to 3-fold increase in AUC) with an additional heart rate reduction of 5bpm.

Other moderate CYP3A4 inhibitors:

Concomitant use with ivabradine can be used with caution if resting heart rate is at or above 60bpm, and heart rate is carefully monitored (See DOSAGE AND ADMINISTRATION).

Ivabradine exposure was increased by 2-fold following the co-administration with grapefruit juice. Therefore the intake of grapefruit juice should be restricted during treatment with ivabradine.

CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, St John's Wort (Hypericum perforatum):

Prolonged concomitant use of these agents with ivabradine may decrease ivabradine exposure and therefore require an adjustment of the ivabradine dose depending on the therapeutic response (See DOSAGE AND ADMINISTRATION). In this case, heart rate monitoring is recommended when discontinuing CYP3A4 inducers.

The combination of ivabradine 10 mg twice daily with St John's Wort was shown to reduce ivabradine AUC by half. The intake of St John's Wort should be restricted during the treatment with ivabradine

Concomitant use with Heart rate reducing anti anginal therapies:

Beta-Blockers:

In patients with CAD, receiving ivabradine (10 mg twice daily) on top of atenolol (50 mg once daily), heart rate reducing effects of the two medicines were additive. There was no pharmacokinetic interaction.

On the basis of long-term safety data from the BEAUTIFUL study and efficacy data from a 12-week randomised placebo-controlled study (see CLINICAL TRIALS), ivabradine can be used in combination with atenolol 50 mg once daily if resting heart rate is at or above 60 bpm, and heart rate is monitored (See DOSAGE AND ADMINISTRATION and ADVERSE EFFECTS).

Non-dihydropyridine calcium channel blockers:

In 11 healthy volunteers who were receiving ivabradine (10 mg twice daily) in addition to verapamil (120 mg twice daily), co-administration led to a slightly further heart rate lowering effect of ivabradine.

In 6 healthy volunteers on ivabradine (10 mg twice daily) and diltiazem (120 mg twice daily), and in 11 patients with CAD on ivabradine (2.5 mg twice daily for 2 days then 5 mg twice daily for 2.5 days) and diltiazem (120 mg twice daily), co-administration produced an increased exposure to ivabradine and a slightly further heart rate lowering effect of ivabradine.

The combinations of ivabradine and diltiazem, or ivabradine and verapamil were well tolerated. However in view of the potential for additive heart rate lowering effects, the concomitant use of ivabradine with heart rate reducing calcium channel blockers such as diltiazem or verapamil is not recommended.

Other anti anginal therapies:

No safety issue has been raised on the combination of ivabradine with nitrates and the dihydropyridine calcium channel blocker amlodipine. Specific drug interaction studies with other dihydropyridine calcium channel blockers (i.e. nifedipine, felodipine and lercanidipine) have not been conducted, however in vitro data have indicated a very weak CYP3A4 inhibition with these medicines. Additional efficacy of ivabradine in combination with dihydropyridine calcium channel blockers has not been established (see PHARMACODYNAMICS).

Concomitant use with QT-prolonging medicines:

The concomitant use of cardiovascular (eg: quinidine, disopyramide, sotalol, amiodarone) or non-cardiovascular (eg: tricyclic antidepressants, antipsychotics, erythromycin IV, pentamidine, pimozide, mefloquine) QT prolonging medicines with ivabradine should be avoided since QT prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is needed (See PRECAUTIONS).

Concomitant use with other medicines:

Specific drug-drug interaction studies have shown no clinically significant pharmacokinetic or pharmacodynamic interactions between ivabradine and any of the following: digoxin, HMG CoA reductase inhibitors (simvastatin), sildenafil, proton pump inhibitors (omeprazole, lansoprazole), dihydropyridine calcium channel blockers (amlodipine), aspirin and warfarin.

In pivotal phase III clinical trials the following drugs were not restricted and therefore were routinely combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, diuretics, short and long acting

nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet agents.

Effects on Laboratory Tests

Ivabradine has no clinically relevant effects on blood chemistry or haematology.

Effects on Driving

A specific study to assess the possible influence of ivabradine on driving performance has been performed in healthy volunteers where there was no evidence of alteration to driving performance. Ivabradine had no influence on the ability to drive and use machines. However, ivabradine may cause transient luminous phenomena consisting mainly of phosphenes. The possible occurrence of such luminous phenomena should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur, especially when driving at night.

ADVERSE EFFECTS

Ivabradine has been studied in clinical trials involving nearly 5,000 participants. More than 2,900 patients have been treated with ivabradine in phase II-III studies, with more than 1,200 included in one-year safety studies. The most commonly reported adverse events with ivabradine are visual symptoms, of which, luminous phenomena were reported in approximately 14.5% of patients at the recommended doses, and sinus bradycardia.

Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity and occur within the first 2 months of treatment. In clinical trials they were well tolerated, usually reported as mild to moderate (97%) in intensity. Phosphenes resolved spontaneously during treatment in 77.5% of patients, or were reversible when treatment ceased. Fewer than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

The frequency of emergent adverse effects reported by >1% of patients treated in double-blind studies are listed in Table 2.

Table 2 Frequency of emergent adverse effects (reported by >1% of patients in the ivabradine group, N=1651) in double-blind studies.

	Double blind clinical studies with ivabradine			
Event	Ivabradine 5+7.5mg group (N=1651) Frequency (%)	Amlodipine 10 mg o.d. (N=404) Frequency (%)	Atenolol (N=408) Frequency (%)	Placebo (N=313) Frequency (%)
Eye disorders				
Very common:				
Phosphene like events	14.5	3.5	3.2	1.9
Common:				
Blurred vision	1.5	0.5	3.2	1.0
Cardiac disorders				
Common:				
Bradycardia (sinus & NOS)	3.3*	1.7	5.8	1.0

Ventricular extrasystoles	3.0	2.7	1.2	1.3
Atrioventricular first degree block (ECG prolonged PQ interval)	1.4	0.5	2.0	1.0
Nervous system disorders				
Common:				
Headache NOS	2.2	2.0	2.7	1.9
Dizziness (exc.vertigo)	1.5	0.2	1.7	0.3

*0.5% of total patients in the ivabradine group experienced severe bradycardia below or equal to 40bpm. When this analysis was restricted to patients with a baseline heart rate greater or equal to 60bpm, 0.3% of patients experienced severe bradycardia.

The following events reported by >1% of patients during clinical trials were of similar incidence to comparators and/or possibly related to the underlying disease: unstable angina (2%), angina pectoris aggravated (2%) and myocardial ischaemia (1.2%).

Uncommon adverse effects (reported by ≤1%, >0.1% of patients) in the ivabradine group included:
Blood and lymphatic system disorders: eosinophila
Cardiac disorders: palpitations, supraventricular extrasystoles. The following events reported by ≤1%, >0.1% of ivabradine patients during clinical trials were of similar incidence to comparators and/or possibly related to the underlying disease: sinus arrhythmia, atrial fibrillation, myocardial infarction and ventricular tachycardia.
Ear and labyrinth disorders: vertigo
Gastrointestinal disorders: nausea, constipation, diarrhoea
Investigations: elevated creatinine in blood
Metabolism and nutrition disorders: hyperuricaemia
Musculoskeletal and connective tissue disorders: muscle cramps
Respiratory, thoracic and mediastinal disorders: dyspnoea

Ivabradine in combination with atenolol 50 mg once daily
In a randomised, double-blind, placebo-controlled, parallel-group study ASSOCIATE, the profile of the adverse effects reported was similar to the above. The incidence of treatment-related emergent adverse events with ivabradine in combination with atenolol 50 mg (ivabradine) was 9.1% versus 2.7% with atenolol 50 mg alone (placebo). This difference was mainly due to bradycardia (ivabradine 4.2% versus placebo 0.5%), mostly asymptomatic (ivabradine 3.1% versus placebo 0.5%) (see PRECAUTIONS).

Principal Emergent Adverse Events (EAEs) in study BEAUTIFUL
In the large outcome study, BEAUTIFUL (see CLINICAL TRIALS), the overall incidence of EAEs was similar in the ivabradine and placebo groups (55.7% versus 55.5%).The most frequent EAEs included (ivabradine versus placebo) atrial fibrillation (5.2% *versus* 4.9%), symptomatic bradycardia (3.8% *versus* 1.0%), asymptomatic bradycardia (3.1% *versus* 0.6%), phosphenes (3.8% *versus* 0.9%), blood pressure inadequately controlled (3.6% *versus* 3.5%), ventricular extrasystoles (2.0% *versus* 1.9%).

Serious Adverse Events (SAEs) and discontinuation
In the Overall Safety Set (N=2907), the most frequently reported SAEs with ivabradine were cardiac disorders, where the only SAE reported with a ≥1% incidence was unstable angina (1.5%).

Ivabradine in combination with atenolol 50 mg once daily

No serious adverse event nor events leading to treatment discontinuation were reported with a ≥1% incidence. Unstable angina was reported as serious in 0.4% (with ivabradine in combination with atenolol 50 mg od) vs 0.2% (with atenolol 50 mg od) and led to treatment discontinuation in 0.2% vs 0.2% .

Post-Marketing experience

The following adverse reactions (frequency unknown) have been reported in post-marketing use with ivabradine; rash, erythema, pruritis, hypotension, malaise, syncope (possibly linked to bradycardia).

DOSAGE AND ADMINISTRATION

The usual recommended starting dose of ivabradine is 5 mg orally twice daily, i.e. once in the morning and once in the evening during meals (See Pharmacokinetics). If a dose is missed, the next scheduled dose should be taken at the usual time without doubling it.

After 3 to 4 weeks of treatment, the dose may be increased to 7.5 mg twice daily depending on the therapeutic response.

If during treatment heart rate decreases persistently below 50bpm at rest, or the patient experiences symptoms related to bradycardia, the dosage must be titrated downward. If necessary, the dose may be reduced to 2.5 mg twice daily (one half 5 mg tablet twice daily). Treatment must be discontinued if heart rate below 50bpm or symptoms of bradycardia persist (See PRECAUTIONS).

Elderly

Since ivabradine has been studied in a limited number of patients aged 75 years or more, a lower starting dose should be considered for these patients (2.5 mg twice daily) before up-titration if necessary.

Renal insufficiency

No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15mL/min (See PRECAUTIONS).

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment. (See PRECAUTIONS). Caution should be exercised when using ivabradine in patients with moderate hepatic insufficiency (See PRECAUTIONS). Ivabradine is contraindicated in patients with severe hepatic insufficiency (See CONTRAINDICATIONS).

Concomitant use with atenolol 50 mg

Ivabradine treatment can be initiated at the usual recommended dose of 5 mg twice daily in patients whose heart rate is at or above 60 bpm. The dose may be increased to 7.5 mg twice daily depending on the therapeutic response and heart rate. If during treatment heart rate decreases below 50bpm at rest, or the patient experiences symptoms related to bradycardia, the dose may be reduced to 2.5 mg twice daily. If heart rate remains below 50bpm on 2.5 mg twice daily, or symptoms of bradycardia persist, treatment with ivabradine should be discontinued.

Concomitant use with Cytochrome P450 3A4 (CYP3A4) inhibitors or inducers:

Potent CYP3A4 inhibitors such as ketoconazole, macrolide antibiotics, cyclosporin, gestodene and anti-retroviral drugs: ivabradine is contraindicated (See CONTRAINDICATIONS).

Moderate CYP 3A4 inhibitors: The concomitant use of ivabradine with verapamil or diltiazem is not recommended.

Other moderate CYP3A4 inhibitors (See PRECAUTIONS): ivabradine treatment should be initiated at the starting dose of 2.5 mg twice daily if resting heart rate is at or above 60bpm, with monitoring of heart rate.

CYP3A4 inducers: ivabradine treatment can be initiated at the usual recommended dose of 5 mg twice daily. In the event of prolonged concomitant use, the dose of ivabradine may need to be titrated upward.

OVERDOSAGE

Overdose may lead to symptomatic bradycardia.

Severe bradycardia should be treated symptomatically in a specialised environment. In the event of bradycardia with poor haemodynamic tolerance, supportive treatment including intravenous beta-stimulating agents such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.
Due to ivabradine's rapid absorption, activated charcoal is unlikely to be of benefit in overdose. Neither haemodialysis nor peritoneal dialysis is likely to significantly affect the pharmacokinetics of ivabradine so their use is not recommended in overdose.

Advice on overdose management can be obtained from the national Poisons Information Centre by telephoning 131126.

PRESENTATION AND STORAGE CONDITIONS

Supplied calendar packs of aluminium/PVC blister strips packed in cardboard boxes containing 14 or 56 film-coated tablets.

Coralan 5 mg: salmon-pink coloured, rod-shaped, film-coated tablet scored on both edges, engraved with "5" on one face and on the other.

Coralan 7.5 mg: salmon-pink coloured, triangular, film-coated tablet engraved with "7.5" on one face and on the other.

Store below 30°C.

NAME AND ADDRESS OF SPONSOR

SERVIER LABORATORIES (AUST.) PTY LTD
8 Cato Street
Hawthorn, Victoria 3122
Australia
ABN 54 004 838 500

POISONS SCHEDULE OF MEDICINE

S4: Prescription-only Medicine

DATE OF APPROVAL

3 September, 2010

Therapeutic Goods Administration

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