Attachment 1: Product information for AusPAR Coralan Ivabradine Servier Laboratories (Australia) Pty Ltd PM-2010-03269-3 Final 31 October 2012. This Product Information was approved at the time this AusPAR was published.

CORALAN®

Product Information

NAME OF THE MEDICINE

CORALAN®

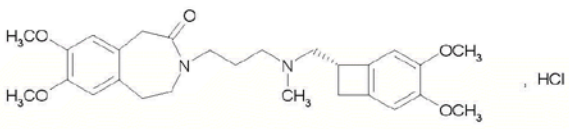
Ivabradine (as the hydrochloride) 5 mg, 7.5 mg film coated tablets

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

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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.

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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 50 mg once daily versus placebo with atenolol 50 mg 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.

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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.

<u>Coronary Artery Disease (CAD) with Left Ventricular Dysfunction (LVD):</u>
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 (HF).The study showed no difference in the primary composite endpoint (relative risk 1.00, p=0.945).

<u>Chronic Heart Failure:</u>
A large outcome study, SHIFT, was performed in 6505 adult patients with moderate to severe symptoms of chronic heart failure (CHF), with a reduced left ventricular ejection fraction (LVEF ≤ 35%).

The SHIFT study was a multi-centre, international, randomised double-blind placebo controlled trial. The trial population included patients with systolic chronic heart failure with

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NYHA class II to IV and in stable condition for ≥ 4 weeks. Patients had documented hospital admission for worsening heart failure within 12 months prior to selection, and were in sinus rhythm at selection with resting heart rate ≥ 70 bpm. Main exclusion criteria included recent (< 2 months) myocardial infarction, ventricular or atrioventricular pacing operative for 40% or more of the day, sustained atrial fibrillation or flutter, and symptomatic hypotension. The average age of the trial population was 60·4 (SD 11·4) years. Elderly patients i.e. those aged > 65 years comprised 38% (N=2474) of the overall population.
Ivabradine should be used with caution in patients with NYHA Class IV due to limited number of patients studied (1.7%,N=111, of the overall population) (see PRECAUTIONS).

In the trial, patients received optimised background therapy in accordance with guidelines for treatment of heart failure. Background treatment included beta-blockers (89%), ACE inhibitors and/or angiotensin II antagonists (91%), diuretics (83%), and anti-aldosterone agents (60%). Approximately 10% of patients were not able to take beta-blockers due to contraindications. Those able to tolerate beta-blockers were required to be on a maximally tolerated daily beta-blocker dose at randomisation as part of the study protocol. Due to intolerances 56% of patients were administered at least half the target daily dose. 26% of patients on beta-blockers were at target doses at randomisation. The relative effects of ivabradine are therefore applicable to those treated with ivabradine in combination with optimal standard chronic heart failure treatment.

In the ivabradine group, 67% of patients were treated with 7.5 mg twice a day. The median follow-up duration was 22.9 months. After 4 weeks of treatment and from a mean baseline heart rate value of 80 bpm, patients randomised to ivabradine had a mean heart rate reduction of 15 bpm. A heart rate reduction versus placebo was maintained throughout the study.

The primary endpoint was a composite of cardiovascular mortality and hospitalisation for worsening heart failure.

The superiority of ivabradine as compared to placebo was tested on the time to first occurrence of the primary composite endpoint. A Cox proportional hazards model adjusted on beta-blocker intake at randomisation was used to estimate the treatment effect, 95% confidence interval (CI) and associated p value.

In the randomised set (RS), the study demonstrated a statistically significant relative risk reduction of 18% p<0.0001 in the rate of the primary composite endpoint for which the study was powered. The absolute risk reduction was 4.2% (refer to Table 2). The results on the primary endpoint were mainly driven by the heart failure endpoints, hospitalisation for worsening heart failure (absolute risk reduced by 4.7%) and deaths from heart failure (absolute risk reduced by 1.1%). The Kaplan-Meier curves of the time to first event of the primary composite endpoint are presented in Figure 1. The curves can be seen to diverge at 3 months from treatment initiation indicating an early treatment effect in favour of ivabradine (lower curve).Treatment with ivabradine for one year would prevent one cardiovascular death or hospital admission for worsening heart failure for every 26 patients treated.
There was a significant improvement in NYHA class at last recorded value, 887 (28%) of patients on ivabradine improved versus 776 (24%) of patients on placebo (p=0.001).

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Figure 1- Kaplan-Meier analysis of time to first event of primary composite endpoint (CV death and Hospitalisation for worsening heart failure) in the Randomised Set (RS)

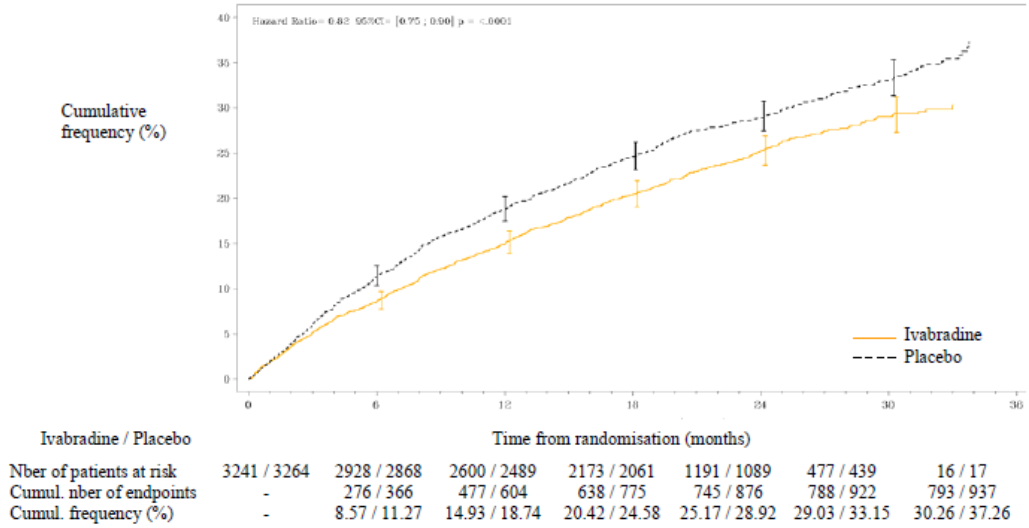

Table 2. Treatment effect on the primary composite endpoint, its components and secondary endpoints in the Randomised Set (RS)

	Ivabradine (N=3241) n (%)	Placebo (N=3264) n (%)	Hazard ratio E [95% CI];	RRR (%)	p-value
Primary composite endpoint	793 (24.47)	937 (28.71)	0.82 [0.75; 0.90];	18	<0.0001
Components of the composite:					
- CV death	449 (13.85)	491 (15.04)	0.91 [0.80; 1.03];	9	0.128
- Hospitalisation for worsening HF	514 (15.86)	672 (20.59)	0.74 [0.66; 0.83];	26	<0.0001
Other secondary endpoints:					
- All cause death	503 (15.52)	552 (16.91)	0.90 [0.80; 1.02];	10	0.092
- Death from HF	113 (3.49)	151 (4.63)	0.74 [0.58; 0.94];	26	0.014
- Hospitalisation for any cause	1231 (37.98)	1356 (41.54)	0.89 [0.82; 0.96];	11	0.003
- Hospitalisation for CV reason	977 (30.15)	1122 (34.38)	0.85 [0.78; 0.92];	15	0.0002

Sub-group analysis of the primary composite endpoint in the RS population showed an effect in favour of ivabradine in all pre-specified sub-groups: age, gender, beta-blocker treatment or not, ischaemic or non-ischaemic heart failure aetiology, NYHA class, and background history of diabetes or hypertension, and baseline heart rate (refer to Figure 2).

Efficacy results in the sub-group of patients aged ≥ 65 years were consistent with those in the overall population, although the benefits tended to be less marked compared with patients aged < 65 years (refer to Figure 2). The relative risk reduction of the primary composite endpoint was 24% in those aged < 65 years compared to 11% in those aged ≥

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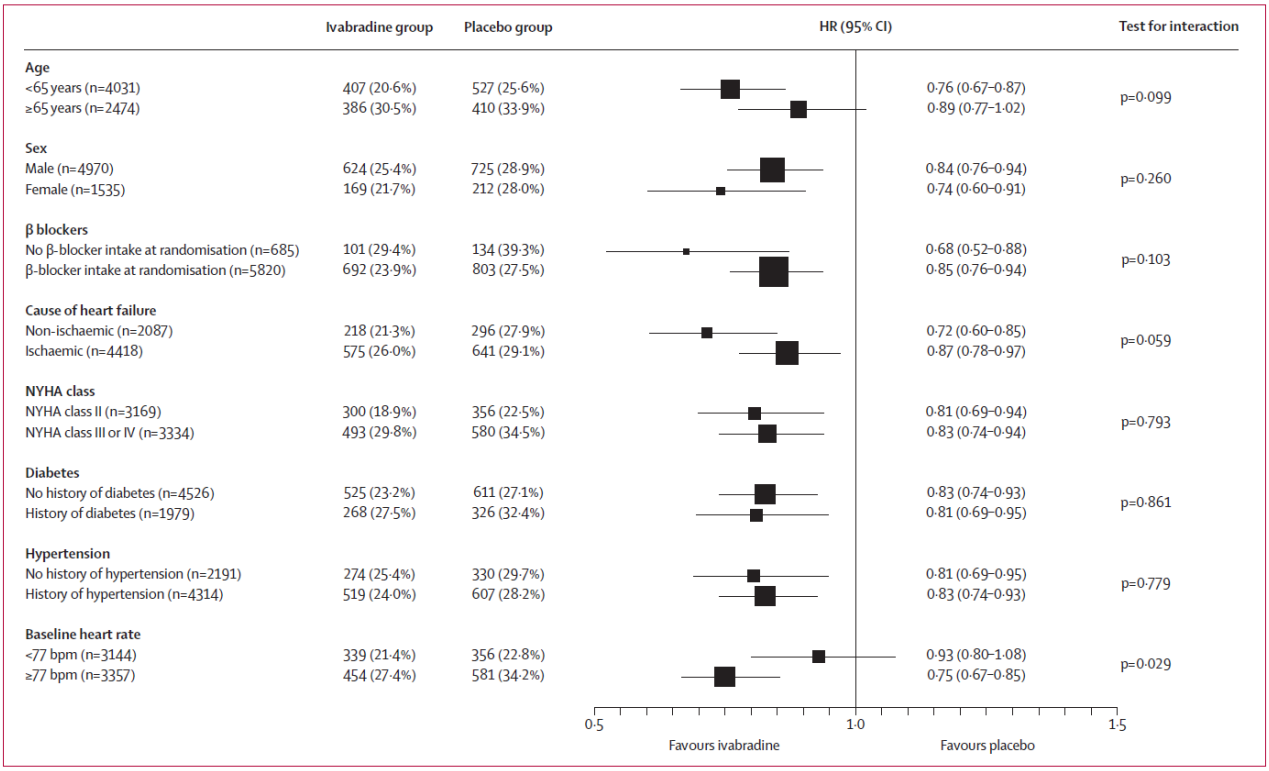
65 years. Interaction tests showed that the differences were not statistically significant, and there was no heterogeneity between these groups. Furthermore, the benefits in patients aged ≥ 75 years old were similar to those of the overall population.

The study demonstrated an effect in the primary composite endpoint in favour of ivabradine in both sub-groups of patients according to baseline heart rate < 77 bpm and ≥ 77 bpm. This effect was statistically significantly greater in patients with baseline heart rate ≥ 77 bpm (n=3357, hazard ratio = 0.75, 95% CI [0.67, 0.85]) compared to those with baseline heart rate < 77 bpm (n=3144, hazard ratio = 0.93, 95% CI [0.80, 1.08]) (refer to Figure 2).
This finding was not unexpected from the known pharmacology of ivabradine and particularly given that the effect of the drug in blocking sinoatrial node I_f channels is greatest when these channels are most likely to be open i.e. when heart rate is highest. The SHIFT trial results demonstrate that baseline heart rate is a treatment effect modifier.

Figure 2: Effect of treatment on primary composite endpoint in the pre-specified sub-groups of the SHIFT trial.



n.b Data are number (%) of patients with first events. HR=hazard ratio. NYHA=New York Heart Association. bpm=beats per minute.

Treatment effect in patients with baseline heart rate ≥ 77 bpm:
The median baseline heart rate was a pre-specified sub-group analysis (77 bpm).The baseline characteristics in this patient population did not differ substantially from the Randomised Set (RS), nor were there any relevant differences between the treatment groups.

Approximately 13.5% of patients were not able to take beta-blockers due to contraindications. Of those able to tolerate beta-blockers, 54% were able to be

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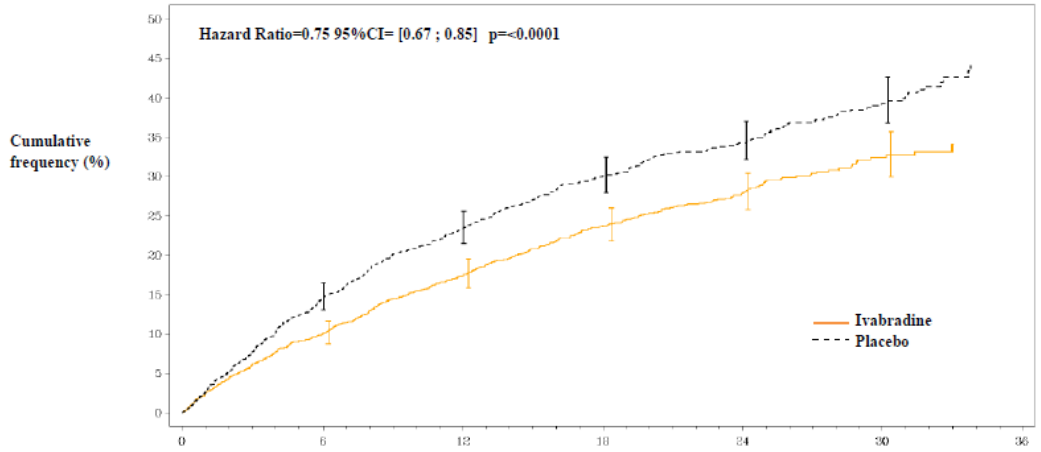
administered at least half the target daily dose at randomisation, and 25% of patients on beta-blockers were at target doses at randomisation.
In ivabradine-treated patients with a baseline heart rate ≥ 77 bpm, the primary composite endpoint was reduced by 25% (p<0.0001); cardiovascular death by 19% (p=0.0137) (absolute risk reduced by 3.0%); and hospitalisation for worsening heart failure by 31% (p=<0.0001) (absolute risk reduced by 6.6%) (refer to Table 3), compared to patients on placebo. In those patients, treatment with ivabradine led to a significant improvement of all outcomes, including CV and all-cause mortality.
The Kaplan-Meier curves of the time to first event of the primary composite endpoint are presented in Figure 3. The curves can be seen to diverge as early as 1 month from treatment initiation. This early treatment effect in favour of ivabradine (lower curve) is consistent with the effect seen in the RS (refer to Figure 1).

Figure 3- Kaplan-Meier analysis of time to first event of primary composite endpoint (CV death and Hospitalisation for worsening heart failure) in patients with heart rate (HR) ≥ 77 bpm



Ivabradine/Placebo							
Nber of patients at risk	1657/1700	1472/1436	1291/1210	1054/970	566/518	211/208	7/8
Cumul nber of endpoints	0/0	165/244	284/392	379/492	426/542	451/571	454/581
Cumul frequency (%)	0/0	10.03/14.44	17.39/23.41	23.74/30.04	27.89/34.25	32.39/39.29	34.13/44.32

Table 3. Treatment effect on the primary composite endpoint, its components and secondary endpoints in patients with heart rate (HR) ≥ 77 bpm

	Ivabradine (N=1657) n (%)	Placebo (N=1700) n (%)	Hazard ratio E [95% CI];	RRR (%)	p-value
Primary composite endpoint	454(27.40)	581 (34.18)	0.75 [0.67; 0.85];	25	<0.0001
Components of the composite endpoint: - CV death - Hospitalisation for worsening HF	 255 (15.39) 298 (17.98)	 312 (18.35) 418 (24.59)	 0.81 [0.69; 0.96]; 0.69 [0.59; 0.80];	 19 31	 0.0137 <0.0001
Other secondary endpoints: - All cause death - Death from HF - Hospitalisation for any cause - Hospitalisation for CV reason	 285 (17.20) 67 (4.04) 667 (40.25) 534 (32.23)	 350 (20.59) 107 (6.29) 778 (45.76) 647 (38.06)	 0.81 [0.69; 0.94]; 0.61 [0.45;0.83]; 0.82 [0.74;0.91]; 0.79 [0.71; 0.89];	 19 39 18 21	 0.0074 0.0017 0.0002 <0.0001

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In ivabradine-treated patients with a baseline heart rate < 77 bpm, the primary composite endpoint was reduced by 7% [hazard ratio = 0.93, 95% CI [0.80;1.08]] and did not reach statistical significance compared to patients on placebo. The components of the primary composite endpoint; cardiovascular death [hazard ratio = 1.07, 95% CI [0.87;1.31]] and hospitalisation for worsening heart failure [hazard ratio = 0.83, 95% CI[0.69;1.00]] did not differ statistically from placebo.

Systolic heart failure in Australian clinical practice:
The population in Australian clinical practice that is most relevant to the SHIFT study population comprises patients with unpreserved systolic function, with elevated heart rate in sinus rhythm.

The National Benchmarking and Evidence-Based National Clinical Guidelines for Heart Failure Management Programs (BENCH) study was an Australian multi-centre prospective cohort study of systolic heart failure designed to examine the characteristics and components of heart failure management programs and their effect on patient outcomes. The baseline characteristics of the usual-care arm of this study is compared to overall SHIfT population in Table 4. Both studies recruited patients with systolic heart failure with at least one prior hospitalisation for worsening heart failure. Table 4 shows that overall the two populations are similar therefore the SHIfT study is applicable to Australian patients with systolic heart failure.

Table 4: Baseline characteristics of the BENCH and SHIfT study populations

	BENCH Usual-care arm (n=255)*	Overall SHIfT population (n=6505)	SHIfT patients with baseline HR ≥ 77bpm (n=3357)
Age, mean (years)	69.8	60.0	59.4
Male	69%	76%	77%
Ejection fraction %, mean	27%	29%	29%
NYHA I	31%	0%	0%
NYHA II	37%	49%	45%
NYHA III	25%	50%	53%
NYHA IV	7%	2%	2%
Beta-blocker at target dose	35%	26%	25%
Previous myocardial infarct	46%	56%	54%
Diabetes	29%	30%	32%

*Reference: Driscoll, A et al. Nurse-Led Titration of β-Adrenoreceptor Blocking Agents in Chronic Heart Failure Patients in the Community. Journal of Cardiac Failure, Vol. 17 No. 3 (2011).

INDICATIONS

Treatment of coronary artery disease
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.

Treatment of chronic heart failure

Treatment of symptomatic chronic heart failure of NYHA Classes II or III and with documented left ventricular ejection fraction (LVEF) ≤ 35% in adult patients in sinus rhythm and with heart rate at or above 77 bpm, in combination with optimal standard chronic heart failure treatment.

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
- Unstable or acute heart failure
- Resting heart rate below 60 bpm 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 50 bpm 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 50 bpm 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).
The risk of developing atrial fibrillation may be higher in chronic heart failure patients treated with ivabradine. Atrial fibrillation has been more common in patients on concomitant amiodarone or potent class I anti-arrhythmics treatment. Chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be monitored closely.

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).

Blood pressure treatment modification

Blood pressure should be monitored in ivabradine-treated chronic heart failure patients, following blood pressure treatment modification.
In the SHIFT trial, of the patients receiving concomitant blood pressure treatments, those treated with ivabradine experienced episodes of transient increased blood pressure (ivabradine 7.1%, placebo 6.1%) (See ADVERSE EFFECTS). These episodes occurred most frequently shortly after blood pressure treatment was modified. This did not affect the treatment effect of ivabradine.

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.

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Renal Insufficiency

There are no data available in patients with creatinine clearance below 15 mL/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 30 mL/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

Caution is needed in asymptomatic left ventricular dysfunction due to the limited number of patients studied. Heart failure must be stable before considering ivabradine treatment. Ivabradine should also be used with caution in patients with NYHA Class IV- severe functional status due to limited number of patients studied (n=111 (1.7%) (ivabradine n=50(1.5%) placebo n=61(1.9%)).

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).

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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 contraindicated 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).

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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 5 bpm.

Other moderate CYP3A4 inhibitors:
Concomitant use with ivabradine can be used with caution if resting heart rate is at or above 60 bpm, 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

<u>Concomitant use with Heart rate reducing anti anginal therapies:</u>
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 routinely combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, aldosterone antagonists, 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. In post-marketing experience, cases of impaired driving ability due to visual symptoms have been reported. 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.
Ivabradine has no influence on the ability to operate machinery.

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ADVERSE EFFECTS

Ivabradine has been studied in two broadly distinct populations i.e. anginal/ischaemic (nearly 10,000 patients) and CHF (about 3,200 patients), in clinical trials involving a total of nearly 13,000 patients.

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.

Anginal/ischaemic population:
The frequency of emergent adverse effects reported by > 1% of patients treated in double-blind studies in the two populations are listed hereafter:

Table 5- Frequency of emergent adverse effects (reported by >1% of patients in the ivabradine group, N=1651) in double-blind studies in the anginal /ischaemic population.

	Double blind clinical studies with ivabradine			
Event	Ivabradine 5 & 7.5 mg 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

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*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) with ivabradine:
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
General Disorders and Administration Site Condition: asthenia[§] (possibly related to bradycardia), fatigue[§] (possibly related to bradycardia)
Investigations: elevated creatinine in blood
Metabolism and nutrition disorders: hyperuricaemia
Musculoskeletal and connective tissue disorders: muscle cramps
Nervous system disorders: syncope[§] (possibly linked to bradycardia)
Respiratory, thoracic and mediastinal disorders: dyspnoea
Vascular disorders: hypotension[§] (possibly related to bradycardia)
Skin and subcutaneous tissue disorders: angioedema[§] rash [§]

Rare adverse effects (reported by ≥ 0.01%, < 0.1% of patients) with ivabradine:
General Disorders and Administration Site Condition: malaise[§] (possibly related to bradycardia)
Skin and subcutaneous tissue disorders: erythema[§], pruritis[§], urticaria[§]

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*

[§] Adverse effect detected from spontaneous reports. Frequency is calculated from adverse event in clinical trials.

[§] Adverse effect detected from spontaneous reports. Frequency is calculated from adverse event in clinical trials.

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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%.

Chronic heart failure population:

Table 6 – Frequency of emergent adverse events regardless of causality (reported by >1.0% of patients in the ivabradine group, N=3232) in SHIFT study.

System organ class Event	**Ivabradine 2.5, 5 & 7.5 mg (N=3232)**	**Placebo (N=3260)**
	Frequency %	Frequency %
Cardiac disorders		
Cardiac failure	21.7	26
Atrial fibrillation	8.3	6.7
Sinus tachycardia	1.2	3.1
Supraventricular extrasystoles	1.3	1.5
Atrial flutter	1.1	1.1
Ventricular extrasystoles	4.5	4.2
Ventricular tachycardia	1.9	2.2
AV block 1st degree	1.1	1.1
Bradycardia symptomatic	4.6	0.9
Bradycardia asymptomatic	5.6	1.4
Angina pectoris	4.1	4.4
Angina unstable	3.7	3.9
Acute myocardial infarction	1.9	1.7
Myocardial infarction	1.8	1.6
Infections and infestations		
Pneumonia	3.7	4.1
Bronchitis acute	2.1	2.6
Bronchitis	1.3	1.2
Nasopharyngitis	2.0	2.2
Upper respiratory tract infection	1.1	1.7
Respiratory tract infection	1.4	1.0
Influenza	2.1	2.2
Metabolism and nutrition disorders	4.2	4.3
Diabetes mellitus inadequately controlled	1.1	1.1
Diabetes mellitus	1.0	1.0
Hypercholesterolemia	1.0	0.8
Hypokalaemia	1.5	1.6
Hyperuricaemia		
Vascular disorders		
Blood pressure inadequately controlled	7.1	6.1

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Hypotension	1.9	2.7
Investigations Transaminases increased Blood creatinine increased	 1.4 1.7	 1.3 1.4
Nervous system disorders Ischaemic stroke Dizziness Headache	 1.1 1.7 1.4	 1.4 1.4 1.8
Gastrointestinal disorders Diarrhoea Gastritis	 1.0 1.2	 1.1 1.2
General disorders and administration site conditions Sudden death Sudden cardiac death	 3.4 2.3	 3.7 2.1
Respiratory, thoracic and mediastinal disorders Cough Chronic obstructive pulmonary disease	 1.3 2.0	 1.4 2.4
Renal an urinary disorders Renal failure	 2.0	 2.6
Eye disorders Phosphenes	 2.8	 0.5
Injury, poisoning and procedural complications Fall	 1.3	 1.4
Blood and lymphatic system disorders Anaemia	3.0	3.1

The incidence of adverse drug reactions related to ivabradine (reported by > 1.0% of patients in the ivabradine group, N=3232) in the SHIFT study were:
Cardiac disorders: bradycardia symptomatic, bradycardia asymptomatic
Eye disorders: phosphenes

Additional adverse effects reported with ivabradine:
Common (reported by > 1% to ≤ 10% of patients):
Vascular disorders: blood pressure inadequately controlled (see PRECAUTIONS)

Very rare (reported by < 0.0001% of patients):
Cardiac disorders: atrial fibrillation, AV 2nd degree block, AV 3rd degree block, sick sinus syndrome

DOSAGE AND ADMINISTRATION

Coronary artery disease (CAD):

The recommended starting dose for patients with stable angina, alone or in combination with atenolol 50 mg, is ivabradine 5 mg twice daily (BD) when heart rate is at or above 60 bpm.

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After three to four weeks of treatment, and during ongoing treatment the dose should be reviewed and depending on the therapeutic response, adjusted according to Table 7 if necessary.

Chronic heart failure (CHF):

The recommended starting dose for patients with heart failure is ivabradine 5 mg twice daily (BD) when heart rate is at or above 77 bpm.

After two weeks of treatment, and during ongoing treatment the dose should be reviewed and depending on the heart rate, adjusted according to Table 7 if necessary.

Treatment must be discontinued if heart rate below 50 bpm or symptoms of bradycardia persist (See PRECAUTIONS).

Table 7. Dose titration according to heart rate

Resting Heart Rate	Ivabradine Dose
Persistently at or above 60 bpm →	Increase dose to the next upper dose (maximum dose 7.5 mg BD)
Persistently between 50 bpm and 60 bpm →	Maintain dose
Persistently below 50 bpm or symptoms related to bradycardia** →	Decrease dose to the next lowest dose (minimum dose 2.5 mg BD)

**Such as dizziness, fatigue or hypotension

Administration:

Ivabradine should be taken 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.

Special populations:

Elderly

In patients aged 75 years or more, a lower starting dose (2.5 mg twice daily) should be considered before up-titration if necessary.

Renal insufficiency

No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 mL/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 impairment. (See PRECAUTIONS). Ivabradine is contraindicated in patients with severe hepatic insufficiency (See CONTRAINDICATIONS).

Attachment 1: Product information for AusPAR Coralan Ivabradine Servier Laboratories (Australia) Pty Ltd PM-2010-03269-3 Final 31 October 2012. This Product Information was approved at the time this AusPAR was published.

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

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POISONS SCHEDULE OF MEDICINE

S4: Prescription-only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

31 October, 2006

DATE OF MOST RECENT AMENDMENT

27 August, 2012