

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Procoralan 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 5 mg ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).

Excipient: 63.91 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Salmon-coloured, oblong, film-coated tablet scored on both sides, engraved with “5” on one face and  on the other face.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of coronary artery disease

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

- in adults 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.

Treatment of chronic heart failure

Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. (see section 5.1)

4.2 Posology and method of administration

Posology

For the different doses, film-coated tablets containing 5 mg and 7.5 mg ivabradine are available.

Treatment of coronary artery disease

The usual recommended starting dose of ivabradine is 5 mg twice daily. After three to four 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 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the possible dose of 2.5 mg twice daily (one half 5 mg tablet twice daily). Treatment must be discontinued if heart rate below 50 bpm or symptoms of bradycardia persist (see section 4.4).

Treatment of chronic heart failure

The treatment has to be initiated only in patient with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic heart failure.

The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

If during treatment, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. If heart rate increases persistently above 60 beats per minute at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5 mg twice daily or 5 mg twice daily.

Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist (see section 4.4).

Special population

Elderly

In patients aged 75 years or more, a lower starting dose should be considered for these patients (2.5 mg twice daily i.e. one half 5 mg tablet twice daily) before up-titration if necessary.

Renal impairment

No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min (see section 5.2).

No data are available in patients with creatinine clearance below 15 ml/min. Ivabradine should therefore be used with precaution in this population.

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment. Caution should be exercised when using ivabradine in patients with moderate hepatic impairment. Ivabradine is contra-indicated for use in patients with severe hepatic insufficiency, since it has not been studied in this population and a large increase in systemic exposure is anticipated (see sections 4.3 and 5.2).

Paediatric population

The safety and efficacy of ivabradine in children aged below 18 years have not yet been established. No data are available.

Method of administration

Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1)
- Resting heart rate below 60 beats per minute prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (< 90/50 mmHg)
- Severe hepatic insufficiency
- Sick sinus syndrome
- Sino-atrial block
- Unstable or acute heart failure
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)

- Unstable angina
- AV-block of 3rd degree
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin *per os*, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone (see sections 4.5 and 5.2)
- Pregnancy, lactation (see section 4.6)

4.4 Special warnings and precautions for use

Special warnings

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 therefore not recommended in patients with atrial fibrillation or 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 using concomitantly amiodarone or potent class I anti-arrhythmics.

Chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be monitored closely.

Use in patients with AV-block of 2nd degree

Ivabradine is not recommended in patients with AV-block of 2nd degree.

Use in patients with a low heart rate

Ivabradine must not be initiated in patients with a pre-treatment resting heart rate below 60 beats per minute (see section 4.3).

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 or treatment discontinued if heart rate below 50 bpm or symptoms of bradycardia persist (see section 4.2).

Combination with calcium channel blockers

Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is not recommended (see section 4.5). No safety issue has been raised on the combination of ivabradine with nitrates and dihydropyridine calcium channel blockers such as amlodipine. Additional efficacy of ivabradine in combination with dihydropyridine calcium channel blockers has not been established (see section 5.1).

Chronic heart failure

Heart failure must be stable before considering ivabradine treatment. Ivabradine should be used with caution in heart failure patients with NYHA functional classification IV due to limited amount of data in this population.

Stroke

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

Visual function

Ivabradine influences on retinal function (see section 5.1). To date, there is no evidence of a toxic effect of ivabradine on the retina, but the effects of long-term ivabradine treatment beyond one year

on retinal function 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.

Precautions for use

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 contra-indicated in patients with severe hypotension (blood pressure < 90/50 mmHg) (see section 4.3).

Atrial fibrillation - Cardiac arrhythmias

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.

Use in patients with congenital QT syndrome or treated with QT prolonging medicinal products

The use of ivabradine in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided (see section 4.5). If the combination appears necessary, close cardiac monitoring is needed.

Hypertensive patients requiring blood pressure treatment modifications.

In the SHIFT trial more patients experienced episodes of increased blood pressure while treated with ivabradine (7.1%) compared to patients treated with placebo (6.1%). These episodes occurred most frequently shortly after blood pressure treatment was modified, were transient, and did not affect the treatment effect of ivabradine. When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval (see section 4.8).

Excipients

Since tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Concomitant use not recommended

QT prolonging medicinal products

- Cardiovascular QT prolonging medicinal products (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone).
- Non cardiovascular QT prolonging medicinal products (e.g. pimozone, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin).

The concomitant use of cardiovascular and non cardiovascular QT prolonging medicinal products with ivabradine should be avoided since QT prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is needed (see section 4.4).

Pharmacokinetic interactions

Cytochrome P450 3A4 (CYP3A4)

Ivabradine is metabolised by CYP3A4 only and it is a very weak inhibitor of this cytochrome. Ivabradine was shown not to influence the metabolism and plasma concentrations of other CYP3A4 substrates (mild, moderate and strong inhibitors). CYP3A4 inhibitors and inducers are liable to interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant extent. 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 the risk of excessive bradycardia (see section 4.4).

Contra-indication of concomitant use

The concomitant use of potent CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin *per os*, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone is contra-indicated (see section 4.3). The potent CYP3A4 inhibitors ketoconazole (200 mg once daily) and josamycin (1 g twice daily) increased ivabradine mean plasma exposure by 7 to 8 fold.

Concomitant use not recommended

Moderate CYP3A4 inhibitors: specific interaction studies in healthy volunteers and patients have shown that the combination of ivabradine with the heart rate reducing agents diltiazem or verapamil resulted in an increase in ivabradine exposure (2 to 3 fold increase in AUC) and an additional heart rate reduction of 5 bpm. The concomitant use of ivabradine with these medicinal products is not recommended (see section 4.4).

Concomitant use with precautions

- Moderate CYP3A4 inhibitors: the concomitant use of ivabradine with other moderate CYP3A4 inhibitors (e.g. fluconazole) may be considered at the starting dose of 2.5 mg twice daily and if resting heart rate is above 60 bpm, with monitoring of heart rate.
- Grapefruit juice: ivabradine exposure was increased by 2-fold following the co-administration with grapefruit juice. Therefore the intake of grapefruit juice should be restricted during the treatment with ivabradine.
- CYP3A4 inducers: CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, *Hypericum perforatum* [St John's Wort]) may decrease ivabradine exposure and activity. The concomitant use of CYP3A4 inducing medicinal products may require an adjustment of the dose of ivabradine. 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.

Other concomitant use

Specific drug-drug interaction studies have shown no clinically significant effect of the following medicinal products on pharmacokinetics and pharmacodynamics of ivabradine: proton pump inhibitors (omeprazole, lansoprazole), sildenafil, HMG CoA reductase inhibitors (simvastatin), dihydropyridine calcium channel blockers (amlodipine, lacidipine), digoxin and warfarin. In addition there was no clinically significant effect of ivabradine on the pharmacokinetics of simvastatin, amlodipine, lacidipine, on the pharmacokinetics and pharmacodynamics of digoxin, warfarin and on the pharmacodynamics of aspirin.

In pivotal phase III clinical trials the following medicinal products were routinely combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, anti-aldosterone agents, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet medicinal products.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of ivabradine in pregnant women.

Studies in animals have shown reproductive toxicity. These studies have shown embryotoxic and teratogenic effects (see section 5.3). The potential risk for humans is unknown. Therefore, ivabradine is contra-indicated during pregnancy (see section 4.3).

Breastfeeding

Animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contra-indicated during breast-feeding (see section 4.3).

Fertility

Studies in rats have shown no effect on fertility in males and females (see section 5.3).

4.7 Effects on ability to drive and use machines

A specific study to assess the possible influence of ivabradine on driving performance has been performed in healthy volunteers where no alteration of the driving performance was evidenced. However, 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 (see section 4.8). 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 use machines.

4.8 Undesirable effects

Ivabradine has been studied in clinical trials involving nearly 14,000 participants.

The most common adverse reactions with ivabradine, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product.

The following adverse reactions have been reported during clinical trials and are ranked using the following frequency: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Preferred Term
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Metabolism and nutrition disorders	Uncommon	Hyperuricaemia
Nervous system disorders	Common	Headache, generally during the first month of treatment
		Dizziness, possibly related to bradycardia
	Uncommon*	Syncope, possibly related to bradycardia
Eye disorders	Very common	Luminous phenomena (phosphenes)
	Common	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Common	Bradycardia
		AV 1 st degree block (ECG prolonged PQ interval)
		Ventricular extrasystoles
	Uncommon	Palpitations, supraventricular extrasystoles
	Very rare	Atrial fibrillation
AV 2 nd degree block, AV 3 rd degree block		
Vascular disorders	Common	Uncontrolled blood pressure
	Uncommon*	Hypotension, possibly related to bradycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Uncommon	Nausea

		Constipation
		Diarrhoea
Skin and subcutaneous tissue disorders	Uncommon*	Angioedema
		Rash
	Rare*	Erythema
		Pruritus
Urticaria		
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps
General disorders and administration site conditions	Uncommon*	Asthenia, possibly related to bradycardia
		Fatigue, possibly related to bradycardia
	Rare*	Malaise, possibly related to bradycardia
Investigations	Uncommon	Elevated creatinine in blood

* Frequency calculated from clinical trials for adverse events detected from spontaneous report

Luminous phenomena (phosphenes) were reported by 14.5% of patients, described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity. The onset of phosphenes is generally within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment, of which a majority (77.5%) resolved during treatment. Fewer than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

Bradycardia was reported by 3.3% of patients particularly within the first 2 to 3 months of treatment initiation. 0.5% of patients experienced a severe bradycardia below or equal to 40 bpm.

4.9 Overdose

Overdose may lead to severe and prolonged bradycardia (see section 4.8).

Severe bradycardia should be treated symptomatically in a specialised environment. In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment including intravenous beta-stimulating medicinal products such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, other cardiac preparations, ATC code: C01EB17.

Mechanism of action

Ivabradine is a pure heart rate lowering agent, acting by selective and specific 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 specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.

Ivabradine can interact also 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 (see section 4.8).

Pharmacodynamic effects

The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. Analysis of heart rate reduction with doses up to 20 mg twice daily indicates a trend towards a plateau effect which is consistent with a reduced risk of severe bradycardia below 40 bpm (see section 4.8).

At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption. 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 patients with left ventricular dysfunction (left ventricular ejection fraction (LVEF) between 30 and 45%), ivabradine did not have any deleterious influence on LVEF.

Clinical efficacy and safety

The antianginal and anti-ischaemic efficacy of ivabradine was studied 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 chronic stable angina pectoris, of whom 2,617 received ivabradine.

Ivabradine 5 mg twice daily was shown to be effective on exercise test parameters within 3 to 4 weeks of treatment. 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 antianginal and anti-ischaemic benefits of ivabradine were 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 1 mm 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 gave uniform efficacy over 24 hours.

In a 889-patients randomised placebo-controlled study, ivabradine given on top of atenolol 50 mg o.d. showed additional efficacy on all ETT parameters at the trough of drug activity (12 hours after oral intake).

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 an additional efficacy was shown at peak (3-4 hours after oral intake).

Ivabradine efficacy was fully maintained throughout the 3- or 4-month treatment periods in the efficacy trials. There was no evidence of pharmacological tolerance (loss of efficacy) developing during treatment nor of rebound phenomena after abrupt treatment discontinuation. The antianginal 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. The effects on blood pressure and peripheral vascular resistance were minor and not clinically significant.

A sustained reduction of heart rate was demonstrated in patients treated with ivabradine for at least one year (n = 713). No influence on glucose or lipid metabolism was observed.

The antianginal and anti-ischaemic efficacy of ivabradine was preserved in diabetic patients (n = 457) with a similar safety profile as compared to the overall population.

A large outcome study, BEAUTIFUL, was performed in 10917 patients with coronary artery disease and left ventricular dysfunction (LVEF<40%) on top of optimal background therapy with 86.9% of patients receiving beta-blockers. The main efficacy criterion was the composite of cardiovascular death, hospitalization for acute MI or hospitalization for new onset or worsening heart failure. The study showed no difference in the rate of the primary composite outcome in the ivabradine group by comparison to the placebo group (relative risk ivabradine:placebo 1.00, p=0.945).

In a post-hoc subgroup of patients with symptomatic angina at randomisation (n=1507), no safety signal was identified regarding cardiovascular death, hospitalization for acute MI or heart failure (ivabradine 12.0% versus placebo 15.5%, p=0.05).

The SHIFT study was a large multicentre, international, randomised double-blind placebo controlled outcome trial conducted in 6505 adult patients with stable chronic CHF (for ≥ 4 weeks), NYHA class II to IV, with a reduced left ventricular ejection fraction (LVEF $\leq 35\%$) and a resting heart rate ≥ 70 bpm.

Patients received standard care including beta-blockers (89 %), ACE inhibitors and/or angiotensin II antagonists (91 %), diuretics (83 %), and anti-aldosterone agents (60 %). 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. Treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm from a baseline value of 80 bpm. The difference in heart rate between ivabradine and placebo arms was 10.8 bpm at 28 days, 9.1 bpm at 12 months and 8.3 bpm at 24 months.

The study demonstrated a clinically and statistically significant relative risk reduction of 18% in the rate of the primary composite endpoint of cardiovascular mortality and hospitalisation for worsening heart failure (hazard ratio: 0.82, 95%CI [0.75;0.90] – p<0.0001) apparent within 3 months of initiation of treatment. The absolute risk reduction was 4.2%. The results on the primary endpoint are 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 %).

Treatment effect on the primary composite endpoint, its components and secondary endpoints

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

The reduction in the primary endpoint was observed consistently irrespective of gender, NYHA class, ischaemic or non-ischaemic heart failure aetiology and of background history of diabetes or hypertension.

In the subgroup of patients with HR ≥ 75 bpm (n=4150), a greater reduction was observed in the primary composite endpoint of 24 % (hazard ratio: 0.76, 95%CI [0.68;0.85] – p<0.0001) and for other secondary endpoints, including all cause death (hazard ratio: 0.83, 95%CI [0.72;0.96] – p=0.0109)

and CV death (hazard ratio: 0.83, 95% CI [0.71;0.97] – p=0.0166). In this subgroup of patients, the safety profile of ivabradine is in line with the one of the overall population.

A significant effect was observed on the primary composite endpoint in the overall group of patients receiving beta blocker therapy (hazard ratio: 0.82, 95% CI [0.76;0.94]). In the subgroup of patients with HR \geq 75 bpm and on the recommended target dose of beta-blocker, no statistically significant benefit was observed on the primary composite endpoint (hazard ratio: 0.97, 95% CI [0.74;1.28]) and other secondary endpoints, including hospitalisation for worsening heart failure (hazard ratio: 0.79, 95% CI [0.56;1.10]) or death from heart failure (hazard ratio: 0.69, 95% CI [0.31;1.56]).

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).

5.2 Pharmacokinetic properties

Under physiological conditions, ivabradine is rapidly released from tablets and is highly water-soluble (>10 mg/ml). 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 about 1 hour under fasting condition. The absolute bioavailability of the film-coated tablets is around 40%, due to first-pass effect in the gut and liver.

Food delayed absorption by approximately 1 hour, and increased plasma exposure by 20 to 30 %. The intake of the tablet during meals is recommended in order to decrease intra-individual variability in exposure (see section 4.2).

Distribution

Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady-state is close to 100 l in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily is 22 ng/ml (CV=29%). The average plasma concentration is 10 ng/ml (CV=38%) at steady-state.

Biotransformation

Ivabradine is extensively metabolised by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. The major active metabolite is the N-desmethylated derivative (S 18982) with an exposure about 40% of that of the parent compound. 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. Inversely, potent inhibitors and inducers may substantially affect ivabradine plasma concentrations (see section 4.5).

Elimination

Ivabradine is eliminated with a main half-life of 2 hours (70-75% of the AUC) in plasma and an effective half-life of 11 hours. The total clearance is about 400 ml/min and the renal clearance is about 70 ml/min. Excretion of metabolites occurs to a similar extent via faeces and urine. About 4% of an oral dose is excreted unchanged in urine.

Linearity/non linearity

The kinetics of ivabradine is linear over an oral dose range of 0.5 – 24 mg.

Special populations

- Elderly: no pharmacokinetic differences (AUC and C_{max}) have been observed between elderly (\geq 65 years) or very elderly patients (\geq 75 years) and the overall population (see section 4.2).

- Renal insufficiency: the impact of renal impairment (creatinine clearance from 15 to 60 ml/min) on ivabradine pharmacokinetic is minimal, in relation with the low contribution of renal clearance (about 20 %) to total elimination for both ivabradine and its main metabolite S 18982 (see section 4.2).
- Hepatic impairment: in patients with mild hepatic impairment (Child Pugh score up to 7) unbound AUC of ivabradine and the main active metabolite were about 20% higher than in subjects with normal hepatic function. Data are insufficient to draw conclusions in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment (see sections 4.2 and 4.3).

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

PK/PD relationship analysis has shown that heart rate decreases almost linearly with increasing ivabradine and S 18982 plasma concentrations for doses of up to 15-20 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 strong CYP3A4 inhibitors may result in an excessive decrease in heart rate although this risk is reduced with moderate CYP3A4 inhibitors (see sections 4.3, 4.4 and 4.5).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Reproductive toxicity studies showed no effect of ivabradine on fertility in male and female rats. When pregnant animals were treated during organogenesis at exposures close to therapeutic doses, there was a higher incidence of foetuses with cardiac defects in the rat and a small number of foetuses with ectrodactylia in the rabbit.

In dogs given ivabradine (doses of 2, 7 or 24 mg/kg/day) for one year, reversible changes in retinal function were observed but 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.

Other long-term repeat dose and carcinogenicity studies revealed no clinically relevant changes.

Environmental Risk Assessment (ERA)

The environmental risk assessment of ivabradine has been conducted in accordance to European guidelines on ERA.

Outcomes of these evaluations support the lack of environmental risk of ivabradine and ivabradine does not pose a threat to the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Lactose monohydrate
Magnesium stearate (E 470 B)
Maize starch
Maltodextrin
Silica, colloidal anhydrous (E 551)

Film-coating

Hypromellose (E 464)
Titanium dioxide (E171)
Macrogol 6000
Glycerol (E 422)
Magnesium stearate (E 470 B)

Yellow iron oxide (E172)

Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/PVC blister packed in cardboard boxes.

Pack sizes

Calendar packs containing 14, 28, 56, 84, 98, 100 or 112 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier

50, rue Carnot

92284 Suresnes cedex

France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/316/001-007

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/10/2005

Date of latest renewal: 31/08/2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

1. NAME OF THE MEDICINAL PRODUCT

Procoralan 7.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains 7.5 mg ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).

Excipient: 61.215 mg lactose monohydrate
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Salmon-coloured, triangular, film-coated tablet engraved with “7.5” on one face and  on the other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of coronary artery disease

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

- in adults 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.

Treatment of chronic heart failure

Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated. (see section 5.1)

4.2 Posology and method of administration

Posology

For the different doses, film-coated tablets containing 5 mg and 7.5 mg ivabradine are available.

Treatment of coronary artery disease

The usual recommended starting dose of ivabradine is 5 mg twice daily. After three to four 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 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the possible dose of 2.5 mg twice daily (one half 5 mg tablet twice daily). Treatment must be discontinued if heart rate below 50 bpm or symptoms of bradycardia persist (see section 4.4).

Treatment of chronic heart failure

The treatment has to be initiated only in patient with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic heart failure.

The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily) if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

If during treatment, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. If heart rate increases persistently above 60 beats per minute at rest, the dose can be up titrated to the next upper dose in patients receiving 2.5 mg twice daily or 5 mg twice daily.

Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist (see section 4.4).

Special population

Elderly

In patients aged 75 years or more, a lower starting dose should be considered for these patients (2.5 mg twice daily i.e. one half 5 mg tablet twice daily) before up-titration if necessary.

Renal impairment

No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min (see section 5.2).

No data are available in patients with creatinine clearance below 15 ml/min. Ivabradine should therefore be used with precaution in this population.

Hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment. Caution should be exercised when using ivabradine in patients with moderate hepatic impairment. Ivabradine is contra-indicated for use in patients with severe hepatic insufficiency, since it has not been studied in this population and a large increase in systemic exposure is anticipated (see sections 4.3 and 5.2).

Paediatric population

The safety and efficacy of ivabradine in children aged below 18 years have not yet been established. No data are available.

Method of administration

Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals (see section 5.2).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients (see section 6.1)
- Resting heart rate below 60 beats per minute prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (< 90/50 mmHg)
- Severe hepatic insufficiency
- Sick sinus syndrome
- Sino-atrial block
- Unstable or acute heart failure
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
- Unstable angina

- AV-block of 3rd degree
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin *per os*, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone (see sections 4.5 and 5.2)
- Pregnancy, lactation (see section 4.6)

4.4 Special warnings and precautions for use

Special warnings

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 therefore not recommended in patients with atrial fibrillation or 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 using concomitantly amiodarone or potent class I anti-arrhythmics.

Chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be monitored closely.

Use in patients with AV-block of 2nd degree

Ivabradine is not recommended in patients with AV-block of 2nd degree.

Use in patients with a low heart rate

Ivabradine must not be initiated in patients with a pre-treatment resting heart rate below 60 beats per minute (see section 4.3).

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 or treatment discontinued if heart rate below 50 bpm or symptoms of bradycardia persist (see section 4.2).

Combination with calcium channel blockers

Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is not recommended (see section 4.5). No safety issue has been raised on the combination of ivabradine with nitrates and dihydropyridine calcium channel blockers such as amlodipine. Additional efficacy of ivabradine in combination with dihydropyridine calcium channel blockers has not been established (see section 5.1).

Chronic heart failure

Heart failure must be stable before considering ivabradine treatment. Ivabradine should be used with caution in heart failure patients with NYHA functional classification IV due to limited amount of data in this population.

Stroke

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

Visual function

Ivabradine influences on retinal function (see section 5.1). To date, there is no evidence of a toxic effect of ivabradine on the retina, but the effects of long-term ivabradine treatment beyond one year on retinal function 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.

Precautions for use

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 contra-indicated in patients with severe hypotension (blood pressure < 90/50 mmHg) (see section 4.3).

Atrial fibrillation - Cardiac arrhythmias

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.

Use in patients with congenital QT syndrome or treated with QT prolonging medicinal products

The use of ivabradine in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided (see section 4.5). If the combination appears necessary, close cardiac monitoring is needed.

Hypertensive patients requiring blood pressure treatment modifications.

In the SHIFT trial more patients experienced episodes of increased blood pressure while treated with ivabradine (7.1%) compared to patients treated with placebo (6.1%). These episodes occurred most frequently shortly after blood pressure treatment was modified, were transient, and did not affect the treatment effect of ivabradine. When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval (see section 4.8).

Excipients

Since tablets contain lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Concomitant use not recommended

QT prolonging medicinal products

- Cardiovascular QT prolonging medicinal products (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone).
- Non cardiovascular QT prolonging medicinal products (e.g. pimozone, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin).

The concomitant use of cardiovascular and non cardiovascular QT prolonging medicinal products with ivabradine should be avoided since QT prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is needed (see section 4.4).

Pharmacokinetic interactions

Cytochrome P450 3A4 (CYP3A4)

Ivabradine is metabolised by CYP3A4 only and it is a very weak inhibitor of this cytochrome. Ivabradine was shown not to influence the metabolism and plasma concentrations of other CYP3A4 substrates (mild, moderate and strong inhibitors). CYP3A4 inhibitors and inducers are liable to interact with ivabradine and influence its metabolism and pharmacokinetics to a clinically significant extent. 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 the risk of excessive bradycardia (see section 4.4).

Contra-indication of concomitant use

The concomitant use of potent CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin *per os*, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone is contra-indicated (see section 4.3). The potent CYP3A4 inhibitors ketoconazole (200 mg once daily) and josamycin (1 g twice daily) increased ivabradine mean plasma exposure by 7 to 8 fold.

Concomitant use not recommended

Moderate CYP3A4 inhibitors: specific interaction studies in healthy volunteers and patients have shown that the combination of ivabradine with the heart rate reducing agents diltiazem or verapamil resulted in an increase in ivabradine exposure (2 to 3 fold increase in AUC) and an additional heart rate reduction of 5 bpm. The concomitant use of ivabradine with these medicinal products is not recommended (see section 4.4).

Concomitant use with precautions

- Moderate CYP3A4 inhibitors: the concomitant use of ivabradine with other moderate CYP3A4 inhibitors (e.g. fluconazole) may be considered at the starting dose of 2.5 mg twice daily and if resting heart rate is above 60 bpm, with monitoring of heart rate.
- Grapefruit juice: ivabradine exposure was increased by 2-fold following the co-administration with grapefruit juice. Therefore the intake of grapefruit juice should be restricted during the treatment with ivabradine.
- CYP3A4 inducers: CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, *Hypericum perforatum* [St John's Wort]) may decrease ivabradine exposure and activity. The concomitant use of CYP3A4 inducing medicinal products may require an adjustment of the dose of ivabradine. 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.

Other concomitant use

Specific drug-drug interaction studies have shown no clinically significant effect of the following medicinal products on pharmacokinetics and pharmacodynamics of ivabradine: proton pump inhibitors (omeprazole, lansoprazole), sildenafil, HMG CoA reductase inhibitors (simvastatin), dihydropyridine calcium channel blockers (amlodipine, lacidipine), digoxin and warfarin. In addition there was no clinically significant effect of ivabradine on the pharmacokinetics of simvastatin, amlodipine, lacidipine, on the pharmacokinetics and pharmacodynamics of digoxin, warfarin and on the pharmacodynamics of aspirin.

In pivotal phase III clinical trials the following medicinal products were routinely combined with ivabradine with no evidence of safety concerns: angiotensin converting enzyme inhibitors, angiotensin II antagonists, beta-blockers, diuretics, anti-aldosterone agents, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet medicinal products.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of ivabradine in pregnant women.

Studies in animals have shown reproductive toxicity. These studies have shown embryotoxic and teratogenic effects (see section 5.3). The potential risk for humans is unknown. Therefore, ivabradine is contra-indicated during pregnancy (see section 4.3).

Breastfeeding

Animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contra-indicated during breast-feeding (see section 4.3).

Fertility

Studies in rats have shown no effect on fertility in males and females (see section 5.3).

4.7 Effects on ability to drive and use machines

A specific study to assess the possible influence of ivabradine on driving performance has been performed in healthy volunteers where no alteration of the driving performance was evidenced. However, 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 (see section 4.8). 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 use machines.

4.8 Undesirable effects

Ivabradine has been studied in clinical trials involving nearly 14,000 participants.

The most common adverse reactions with ivabradine, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product.

The following adverse reactions have been reported during clinical trials and are ranked using the following frequency: very common ($\geq 1/10$); common ($\geq 1/100$ to, $< 1/10$); uncommon ($\geq 1/1,000$ to, $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

System Organ Class	Frequency	Preferred Term
Blood and lymphatic system disorders	Uncommon	Eosinophilia
Metabolism and nutrition disorders	Uncommon	Hyperuricaemia
Nervous system disorders	Common	Headache, generally during the first month of treatment
		Dizziness, possibly related to bradycardia
	Uncommon*	Syncope, possibly related to bradycardia
Eye disorders	Very common	Luminous phenomena (phosphenes)
	Common	Blurred vision
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Common	Bradycardia
		AV 1 st degree block (ECG prolonged PQ interval)
		Ventricular extrasystoles
	Uncommon	Palpitations, supraventricular extrasystoles
	Very Rare	Atrial fibrillation
AV 2 nd degree block, AV 3 rd degree block Sick sinus syndrome		
Vascular disorders	Common	Uncontrolled blood pressure
	Uncommon*	Hypotension, possibly related to bradycardia
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
Gastrointestinal disorders	Uncommon	Nausea
		Constipation

		Diarrhoea
Skin and subcutaneous tissue disorders	Uncommon*	Angioedema
		Rash
	Rare*	Erythema
		Pruritus
Urticaria		
Musculoskeletal and connective tissue disorders	Uncommon	Muscle cramps
General disorders and administration site conditions	Uncommon*	Asthenia, possibly related to bradycardia
		Fatigue, possibly related to bradycardia
	Rare*	Malaise, possibly related to bradycardia
Investigations	Uncommon	Elevated creatinine in blood

* Frequency calculated from clinical trials for adverse events detected from spontaneous report

Luminous phenomena (phosphenes) were reported by 14.5% of patients, described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity. The onset of phosphenes is generally within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment, of which a majority (77.5%) resolved during treatment. Fewer than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

Bradycardia was reported by 3.3% of patients particularly within the first 2 to 3 months of treatment initiation. 0.5% of patients experienced a severe bradycardia below or equal to 40 bpm.

4.9 Overdose

Overdose may lead to severe and prolonged bradycardia (see section 4.8).

Severe bradycardia should be treated symptomatically in a specialised environment. In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment including intravenous beta-stimulating medicinal products such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cardiac therapy, other cardiac preparations, ATC code: C01EB17.

Mechanism of action

Ivabradine is a pure heart rate lowering agent, acting by selective and specific 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 specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.

Ivabradine can interact also 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 (see section 4.8).

Pharmacodynamic effects

The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. Analysis of heart rate reduction with doses up to 20 mg twice daily indicates a trend towards a plateau effect which is consistent with a reduced risk of severe bradycardia below 40 bpm (see section 4.8).

At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption. 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 patients with left ventricular dysfunction (left ventricular ejection fraction (LVEF) between 30 and 45%), ivabradine did not have any deleterious influence on LVEF.

Clinical efficacy and safety

The antianginal and anti-ischaemic efficacy of ivabradine was studied 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 chronic stable angina pectoris, of whom 2,617 received ivabradine.

Ivabradine 5 mg twice daily was shown to be effective on exercise test parameters within 3 to 4 weeks of treatment. 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 antianginal and anti-ischaemic benefits of ivabradine were 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 1 mm 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 gave uniform efficacy over 24 hours.

In a 889-patients randomised placebo-controlled study, ivabradine given on top of atenolol 50 mg o.d. showed additional efficacy on all ETT parameters at the trough of drug activity (12 hours after oral intake).

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 an additional efficacy was shown at peak (3-4 hours after oral intake).

Ivabradine efficacy was fully maintained throughout the 3- or 4-month treatment periods in the efficacy trials. There was no evidence of pharmacological tolerance (loss of efficacy) developing during treatment nor of rebound phenomena after abrupt treatment discontinuation. The antianginal 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. The effects on blood pressure and peripheral vascular resistance were minor and not clinically significant.

A sustained reduction of heart rate was demonstrated in patients treated with ivabradine for at least one year (n = 713). No influence on glucose or lipid metabolism was observed.

The antianginal and anti-ischaemic efficacy of ivabradine was preserved in diabetic patients (n = 457) with a similar safety profile as compared to the overall population.

A large outcome study, BEAUTIFUL, was performed in 10917 patients with coronary artery disease and left ventricular dysfunction (LVEF<40%) on top of optimal background therapy with 86.9% of patients receiving beta-blockers. The main efficacy criterion was the composite of cardiovascular death, hospitalization for acute MI or hospitalization for new onset or worsening heart failure. The study showed no difference in the rate of the primary composite outcome in the ivabradine group by comparison to the placebo group (relative risk ivabradine:placebo 1.00, p=0.945).

In a post-hoc subgroup of patients with symptomatic angina at randomisation (n=1507), no safety signal was identified regarding cardiovascular death, hospitalization for acute MI or heart failure (ivabradine 12.0% versus placebo 15.5%, p=0.05).

The SHIFT study was a large multicentre, international, randomised double-blind placebo controlled outcome trial. conducted in 6505 adult patients with stable chronic CHF (for ≥ 4 weeks), NYHA class II to IV, with a reduced left ventricular ejection fraction (LVEF $\leq 35\%$) and a resting heart rate ≥ 70 bpm.

Patients received standard care including beta-blockers (89 %), ACE inhibitors and/or angiotensin II antagonists (91 %), diuretics (83 %), and anti-aldosterone agents (60 %). 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. Treatment with ivabradine was associated with an average reduction in heart rate of 15 bpm from a baseline value of 80 bpm. The difference in heart rate between ivabradine and placebo arms was 10.8 bpm at 28 days, 9.1 bpm at 12 months and 8.3 bpm at 24 months.

The study demonstrated a clinically and statistically significant relative risk reduction of 18% in the rate of the primary composite endpoint of cardiovascular mortality and hospitalisation for worsening heart failure (hazard ratio: 0.82, 95%CI [0.75;0.90] – p<0.0001) apparent within 3 months of initiation of treatment. The absolute risk reduction was 4.2%. The results on the primary endpoint are 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 %).

Treatment effect on the primary composite endpoint, its components and secondary endpoints

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

The reduction in the primary endpoint was observed consistently irrespective of gender, NYHA class, ischaemic or non-ischaemic heart failure aetiology and of background history of diabetes or hypertension.

In the subgroup of patients with HR ≥ 75 bpm (n=4150), a greater reduction was observed in the primary composite endpoint of 24 % (hazard ratio: 0.76, 95%CI [0.68;0.85] – p<0.0001) and for other secondary endpoints, including all cause death (hazard ratio: 0.83, 95%CI [0.72;0.96] – p=0.0109)

and CV death (hazard ratio: 0.83, 95%CI [0.71;0.97] – p=0.0166). In this subgroup of patients, the safety profile of ivabradine is in line with the one of the overall population.

A significant effect was observed on the primary composite endpoint in the overall group of patients receiving beta blocker therapy (hazard ratio: 0.82, 95%CI [0.76;0.94]). In the subgroup of patients with HR \geq 75 bpm and on the recommended target dose of beta-blocker, no statistically significant benefit was observed on the primary composite endpoint (hazard ratio: 0.97, 95%CI [0.74;1.28]) and other secondary endpoints, including hospitalisation for worsening heart failure (hazard ratio: 0.79, 95% CI [0.56;1.10]) or death from heart failure (hazard ratio: 0.69, 95% CI [0.31;1.56]).

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).

5.2 Pharmacokinetic properties

Under physiological conditions, ivabradine is rapidly released from tablets and is highly water-soluble (>10 mg/ml). 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 about 1 hour under fasting condition. The absolute bioavailability of the film-coated tablets is around 40%, due to first-pass effect in the gut and liver.

Food delayed absorption by approximately 1 hour, and increased plasma exposure by 20 to 30 %. The intake of the tablet during meals is recommended in order to decrease intra-individual variability in exposure (see section 4.2).

Distribution

Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady-state is close to 100 l in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily is 22 ng/ml (CV=29%). The average plasma concentration is 10 ng/ml (CV=38%) at steady-state.

Biotransformation

Ivabradine is extensively metabolised by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. The major active metabolite is the N-desmethylated derivative (S 18982) with an exposure about 40% of that of the parent compound. 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. Inversely, potent inhibitors and inducers may substantially affect ivabradine plasma concentrations (see section 4.5).

Elimination

Ivabradine is eliminated with a main half-life of 2 hours (70-75% of the AUC) in plasma and an effective half-life of 11 hours. The total clearance is about 400 ml/min and the renal clearance is about 70 ml/min. Excretion of metabolites occurs to a similar extent via faeces and urine. About 4% of an oral dose is excreted unchanged in urine.

Linearity/non linearity

The kinetics of ivabradine is linear over an oral dose range of 0.5 – 24 mg.

Special populations

- Elderly: no pharmacokinetic differences (AUC and C_{max}) have been observed between elderly (\geq 65 years) or very elderly patients (\geq 75 years) and the overall population (see section 4.2).
- Renal insufficiency: the impact of renal impairment (creatinine clearance from 15 to 60 ml/min) on ivabradine pharmacokinetic is minimal, in relation with the low contribution of renal clearance

(about 20 %) to total elimination for both ivabradine and its main metabolite S 18982 (see section 4.2).

- Hepatic impairment: in patients with mild hepatic impairment (Child Pugh score up to 7) unbound AUC of ivabradine and the main active metabolite were about 20% higher than in subjects with normal hepatic function. Data are insufficient to draw conclusions in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment (see sections 4.2 and 4.3).

Pharmacokinetic/pharmacodynamic (PK/PD) relationship

PK/PD relationship analysis has shown that heart rate decreases almost linearly with increasing ivabradine and S 18982 plasma concentrations for doses of up to 15-20 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 strong CYP3A4 inhibitors may result in an excessive decrease in heart rate although this risk is reduced with moderate CYP3A4 inhibitors (see sections 4.3, 4.4 and 4.5).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Reproductive toxicity studies showed no effect of ivabradine on fertility in male and female rats. When pregnant animals were treated during organogenesis at exposures close to therapeutic doses, there was a higher incidence of foetuses with cardiac defects in the rat and a small number of foetuses with ectrodactylia in the rabbit.

In dogs given ivabradine (doses of 2, 7 or 24 mg/kg/day) for one year, reversible changes in retinal function were observed but 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.

Other long-term repeat dose and carcinogenicity studies revealed no clinically relevant changes.

Environmental Risk Assessment (ERA)

The environmental risk assessment of ivabradine has been conducted in accordance to European guidelines on ERA.

Outcomes of these evaluations support the lack of environmental risk of ivabradine and ivabradine does not pose a threat to the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core

Lactose monohydrate
Magnesium stearate (E 470 B)
Maize starch
Maltodextrin
Silica, colloidal anhydrous (E 551)

Film-coating

Hypromellose (E 464)
Titanium dioxide (E171)
Macrogol 6000
Glycerol (E 422)
Magnesium stearate (E 470 B)
Yellow iron oxide (E172)
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/PVC blister packed in cardboard boxes.

Pack sizes

Calendar packs containing 14, 28, 56, 84, 98, 100 or 112 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/316/008-014

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 25/10/2005

Date of latest renewal: 31/08/2010

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDERS
RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A MANUFACTURING AUTHORISATION HOLDERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Les Laboratoires Servier Industrie, 905, route de Saran - 45520 Gidy, France
Servier (Ireland) Industries Ltd, Gorey Road – Arklow – Co. Wicklow, Ireland
Przedsiębiorstwo Farmaceutyczne ANPHARM S.A., ul. Annopol 6B – 03-236 Warszawa, Poland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

Medicinal product subject to medical prescription.

• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Not applicable.

• OTHER CONDITIONS

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Procoralan 5 mg film-coated tablets
ivabradine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One film-coated tablet contains 5 mg ivabradine (equivalent to 5.39 mg ivabradine as hydrochloride)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.
See package leaflet for the other excipients.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
[28 film-coated tablets]
[56 film-coated tablets]
[84 film-coated tablets]
[98 film-coated tablets]
[100 film-coated tablets]
[112 film-coated tablets]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/316/001
[EU/1/05/316/002]
[EU/1/05/316/003]
[EU/1/05/316/004]
[EU/1/05/316/005]
[EU/1/05/316/006]
[EU/1/05/316/007]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PROCORALAN 5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Procoralan 5 mg film-coated tablets
ivabradine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

Abbreviations for days of the week

MON
TUE
WED
THU
FRI
SAT
SUN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Procoralan 7.5 mg film-coated tablets
ivabradine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One film-coated tablet contains 7.5 mg ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride)

3. LIST OF EXCIPIENTS

Contains lactose monohydrate.
See package leaflet for the other excipients.

4. PHARMACEUTICAL FORM AND CONTENTS

14 film-coated tablets
[28 film-coated tablets]
[56 film-coated tablets]
[84 film-coated tablets]
[98 film-coated tablets]
[100 film-coated tablets]
[112 film-coated tablets]

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/05/316/008
[EU/1/05/316/009]
[EU/1/05/316/010]
[EU/1/05/316/011]
[EU/1/05/316/012]
[EU/1/05/316/013]
[EU/1/05/316/014]

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PROCORALAN 7.5 mg

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Procoralan 7.5 mg film-coated tablets
ivabradine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Les Laboratoires Servier

3. EXPIRY DATE

EXP

4. BATCH NUMBER

LOT

5. OTHER

Abbreviations for days of the week

MON
TUE
WED
THU
FRI
SAT
SUN

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Procoralan 5 mg film-coated tablets Procoralan 7.5 mg film-coated tablets ivabradine

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Procoralan is and what it is used for
2. Before you take Procoralan
3. How to take Procoralan
4. Possible side effects
5. How to store Procoralan
6. Further information

1. WHAT PROCORALAN IS AND WHAT IT IS USED FOR

Procoralan (ivabradine) is a heart medicine used to treat:

- Stable angina pectoris which causes chest pain. It is used in adult patients who do not tolerate or cannot take heart medicines called beta-blockers. It is also used in combination with beta-blockers in adult patients whose condition is not fully controlled with a beta-blocker and whose heart rate is too high (over 60 beats per minute).
- Chronic heart failure in adult patients whose heart rate is too high (over or equal to 75 beats per minute). It is used in combination with standard therapy, including beta-blocker therapy or when beta-blockers are contraindicated or not tolerated.

About stable angina pectoris (usually referred to as “angina”):

Stable angina is a heart disease which happens when the heart does not receive enough oxygen. It usually appears between 40 and 50 years of age. The most common symptom of angina is chest pain or discomfort. Angina is more likely to happen when the heart beats faster in situations such as exercise, emotion, exposure to the cold or after eating. This increase in heart rate can cause the chest pain in people who suffer from angina.

About chronic heart failure :

Chronic heart failure is a heart disease which happens when your heart cannot pump enough blood to the rest of your body. The most common symptoms of heart failure are breathlessness, fatigue, tiredness and ankle swelling.

How does Procoralan work?

Procoralan mainly works by reducing the heart rate by a few beats per minute. This lowers the heart's need for oxygen especially in the situations when an angina attack is more likely to happen. In this way Procoralan helps to control and reduce the number of angina attacks.

Furthermore as elevated heart rate adversely affects the heart functioning and vital prognosis in patients with chronic heart failure, the specific heart rate lowering action of ivabradine helps to improve the heart functioning and vital prognosis in these patients.

2. BEFORE YOU TAKE PROCORALAN

Do not take Procoralan

- if you are allergic (hypersensitive) to ivabradine or any of the other ingredients of Procoralan (see “further information” for a list of all ingredients);
- if your resting heart rate before treatment is too slow (below 60 beats per minute);
- if you are suffering from cardiogenic shock (a heart condition treated in hospital);
- if you suffer from a heart rhythm disorder;
- if you are having a heart attack;
- if you suffer from very low blood pressure;
- if you suffer from unstable angina (a severe form in which chest pain occurs very frequently and with or without exertion);
- if you have heart failure which has recently become worse;
- if your heart beat is exclusively imposed by your pacemaker;
- if you suffer from severe liver problems;
- if you are already taking medicines for the treatment of fungal infections (such as ketoconazole, itraconazole), macrolide antibiotics (such as josamycin, clarithromycin, telithromycin or erythromycin given orally), medicines to treat HIV infections (such as nelfinavir, ritonavir) or nefazodone (medicine to treat depression) (see “Taking other medicines”);
- if you are pregnant;
- if you are breast-feeding.

Take special care with Procoralan

- if you suffer from heart rhythm disorders (such as irregular heartbeat, palpitation, increase in chest pain) or sustained atrial fibrillation (a type of irregular heartbeat),
- if you have symptoms such as tiredness, dizziness or shortness of breath (this could mean that your heart is slowing down too much),
- if you have had a recent stroke (cerebral attack),
- if you suffer from mild to moderate low blood pressure,
- if you suffer from uncontrolled blood pressure, especially after a change in your antihypertensive treatment,
- if you suffer from severe heart failure,
- if you suffer from chronic eye retinal disease,
- if you suffer from moderate liver problems,
- if you suffer from severe renal problems.

If any of the above applies to you, talk straight away to your doctor before or while taking Procoralan.

Children

Procoralan is not intended for use in children and adolescents younger than 18 years.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Make sure to tell your doctor if you are taking any of the following medicines, as a dose adjustment of Procoralan or monitoring should be required:

- diltiazem, verapamil (used for high blood pressure or angina pectoris)
- fluconazole (an antifungal medicine)
- rifampicin (an antibiotic)
- barbiturates (for difficult sleeping or epilepsy)
- phenytoin (for epilepsy)
- *Hypericum perforatum* or St John’s Wort (herbal treatment for depression)
- QT prolonging medicines to treat either heart rhythm disorders or other conditions :
 - quinidine, disopyramide, ibutilide, sotalol, amiodarone (to treat heart rhythm disorders)
 - bepridil (to treat angina pectoris)

- certain types of medicines to treat anxiety, schizophrenia or other psychoses (such as pimozide, ziprasidone, sertindole)
- anti-malarial medicines (such as mefloquine or halofantrine)
- intravenous erythromycin (an antibiotic)
- pentamidine (an antiparasitic medicine)
- cisapride (against the gastro-oesophageal reflux)

Taking Procoralan with food and drink

Limit your consumption of grapefruit juice during treatment with Procoralan.

Pregnancy and breast-feeding

Do not take Procoralan if you are pregnant or planning a pregnancy (see “Do not take Procoralan”).

If you are pregnant and have taken Procoralan, talk to your doctor.

Do not take Procoralan if you are breast-feeding (see “Do not take Procoralan”).

Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

Procoralan may cause temporary luminous visual phenomena (a temporary brightness in the field of vision, see “Possible side effects”). If this happens to you, be careful when driving or using machines at times when there could be sudden changes in light intensity, especially when driving at night.

Important information about some of the ingredients of Procoralan

Procoralan contains lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO TAKE PROCORALAN

Always take Procoralan exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. The usual recommended starting dose is one tablet of Procoralan 5 mg twice daily increasing if necessary to one tablet of Procoralan 7.5 mg twice daily. Your doctor will decide the right dose for you. The usual dose is one tablet in the morning and one tablet in the evening. In some cases (e.g. if you are elderly), your doctor may prescribe half the dose i.e., one half 5 mg tablet of Procoralan 5 mg (corresponding to 2.5 mg ivabradine) in the morning and one half 5 mg tablet in the evening.

Procoralan should be taken during meals.

If you take more Procoralan than you should:

A large dose of Procoralan could make you feel breathless or tired because your heart slows down too much. If this happens, contact your doctor immediately.

If you forget to take Procoralan:

If you forget to take a dose of Procoralan, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.

The calendar printed on the blister containing the tablets should help you remember when you last took a tablet of Procoralan.

If you stop taking Procoralan:

As the treatment for angina is usually life-long, you should discuss with your doctor before stopping this medicinal product.

If you think that the effect of Procoralan is too strong or too weak, talk to your doctor or pharmacist.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Procoralan can cause side effects, although not everybody gets them. The frequency of possible side effects listed below is defined using the following convention:
very common (affects more than 1 user in 10)
common (affects 1 to 10 users in 100)
uncommon (affects 1 to 10 users in 1,000)
rare (affects 1 to 10 users in 10,000)
very rare (affects less than 1 user in 10,000)
not known (frequency cannot be estimated from the available data)

Very common:

Luminous visual phenomena (brief moments of increased brightness, most often caused by sudden changes in light intensity).

Common:

Modification in the heart functioning (the symptoms are a slowing down of the heart rate), abnormal perception of heartbeat, uncontrolled blood pressure, headache, dizziness and blurred vision.

Uncommon:

Palpitations and cardiac extra beats, feeling sick (nausea), constipation, diarrhoea, spinning sensation (vertigo), difficulty breathing (dyspnoea), muscle cramps, changes in laboratory parameters : high blood levels of uric acid, an excess of eosinophils (a type of white blood cell) and elevated creatinine in blood (a breakdown product of muscle), skin rash, angioedema (such as swollen face, tongue or throat, difficulty in breathing or swallowing), low blood pressure, fainting, feeling of tiredness, feeling of weakness.

Rare:

Urticaria, itching, skin reddening, feeling unwell.

Very rare:

Irregular heart beats.

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE PROCORALAN

Keep out of the reach and sight of children.

Do not use Procoralan after the expiry date which is stated on the carton and blister after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Procoralan contains

- The active substance is ivabradine (as hydrochloride).
Procoralan 5 mg: one film-coated tablet contains 5 mg ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).

Procoralan 7.5 mg: one film-coated tablet contains 7.5 mg ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).

- The other ingredients in the tablet core are: lactose monohydrate, magnesium stearate (E 470 B), maize starch, maltodextrin, colloidal anhydrous silica (E 551), and in the tablet coating: hypromellose (E 464), titanium dioxide (E 171), macrogol 6000, glycerol (E 422), magnesium stearate (E 470 B), yellow iron oxide (E 172), red iron oxide (E 172).

What Procoralan looks like and contents of the pack

Procoralan 5 mg tablets are salmon-coloured, oblong film-coated tablets scored on both sides, engraved with “5” on one face and  on the other.

Procoralan 7.5 mg tablets are salmon-coloured, triangular, film-coated tablets engraved with “7.5” on one face and  on the other.

The tablets are available in calendar packs (Aluminium/PVC blisters) of 14, 28, 56, 84, 98, 100 or 112 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer:

Marketing Authorisation Holder:

Les Laboratoires Servier
50, rue Carnot
92284 Suresnes cedex - France

Manufacturer:

Les Laboratoires Servier Industrie
905 route de Saran
45520 Gidy – France

Servier (Ireland) Industries Ltd
Gorey Road
Arklow - Co. Wicklow – Ireland

Przedsiębiorstwo Farmaceutyczne ANPHARM S.A.
ul. Annopol 6B – 03-236 Warszawa – Poland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

België/Belgique/Belgien

S.A. Servier Benelux N.V.
Tél/Tel: +32 (0)2 529 43 11

Luxembourg/Luxemburg

S.A. Servier Benelux N.V.
Tél/Tel: +32 (0)2 529 43 11

България

Сервие Медикал ЕООД
Тел.: +359 2 921 57 00

Magyarország

Servier Hungaria Kft.
Tel.: + 36 1 238 77 99

Česká republika

Servier s.r.o.
Tel: +420 222 118 111

Malta

GALEPHARMA Ltd
Tel: +(356) 21 247 082

Danmark

Servier Danmark A/S
Tlf: +45 36 44 22 60

Deutschland

Servier Deutschland GmbH
Tel: +49 (0)89 57095 01

Eesti

CentralPharma Communications OÜ
Tel: +372 640 00 07

Ελλάδα

ΣΕΡΒΙΕ ΕΛΛΑΣ ΦΑΡΜΑΚΕΥΤΙΚΗ ΕΠΕ
Τηλ: +30 210 939 1000

España

Laboratorios Servier S.L.
Tel: +34 91 748 96 30

France

Les Laboratoires Servier
Tél: +33 (0)1 55 72 60 00

Ireland

Servier Laboratories (Ireland) Ltd.
Tel: +353 (0)1 6638110

Ísland

Servier Laboratories
c/o Icepharma hf
Sími: +354 540 8000

Italia

Servier Italia S.p.A.
Tel: +39 (06) 669081

Κύπρος

Χ.Α.Παπαέλληνας & Σία Λτδ
Τηλ: +357 22741741

Latvija

SIA Servier
Latvia
Tel: + 371 67502039

Lietuva

UAB "SERVIER PHARMA"
Tel: +370 (5) 2 63 86 28

Nederland

Servier Nederland Farma B.V.
Tel: +31 (0)71 5246700

Norge

Servier Danmark A/S
Tlf: +45 36 44 22 60

Österreich

Servier Austria GmbH
Tel: +43 (1) 524 39 99

Polska

Servier Polska SP. Z O.O.
Tel.: + 48 (0) 22 594 90 00

Portugal

Servier Portugal, Lda
Tel: +351 21 312 20 00

România

Servier Pharma SRL
Tel: +4 021 528 52 80

Slovenija

Servier Pharma d.o.o.
Tel: +386 (0)1563 48 11

Slovenská republika

Servier Slovensko spol. s r.o.
Tel: +421 0(2) 5920 41 11

Suomi/Finland

Servier Finland Oy
Puh/Tel: +358 (0)9 279 80 80

Sverige

Servier Sverige AB
Tel: +46 (8)5 225 08 00

United Kingdom

Servier Laboratories Ltd
Tel: +44 (0)1 753 666409

This leaflet was last approved in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>