

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Procoralan 5 mg

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

Excipient: 63.91 mg lactose monohydrate

Procoralan 7.5 mg


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.

Procoralan 5 mg: 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.

Procoralan 7.5 mg: 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

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.

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.

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).

Special population

Elderly

Since ivabradine has been studied in a limited number of patients aged 75 years or more, a lower starting dose should be considered for these patients (2.5 mg twice daily 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

- Heart failure patients with NYHA functional classification III-IV
- Pacemaker dependent
- 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).

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 appropriately controlled before considering ivabradine treatment. The use of ivabradine is contra-indicated in heart failure patients with NYHA functional classification III-IV and should be used with caution in heart failure patients with NYHA functional classification I-II (see section 4.3).

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.

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. pimozide, 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 not restricted and therefore were routinely combined with ivabradine with no evidence of safety concerns:

angiotensin converting enzyme inhibitors, angiotensin II antagonists, diuretics, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet 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. Ivabradine has no influence on the ability to drive and use machines. However, 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.

4.8 Undesirable effects

Procoralan has been studied in clinical trials involving nearly 5,000 participants.

Approximately 2,900 patients have been treated with ivabradine in phase II-III studies.

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
Vascular disorders	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 Procoralan 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 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 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).

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 (≥ 65 years) or very elderly patients (≥ 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 (E 171)

Macrogol 6000

Glycerol (E 422)

Magnesium stearate (E 470 B)

Yellow iron oxide (E 172)

Red iron oxide (E 172)

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)

Procoralan 5 mg EU/1/05/316/003 (pack of 56 tablets)
Procoralan 7.5 mg EU/1/05/316/010 (pack of 56 tablets)

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

09/2011

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