**COMPOSITION**

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

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

**PHARMACEUTICAL FORM**

**Film-coated tablet**

**Coralan 5 mg:**
Salmon-coloured, oblong, film-coated tablet scored on both sides, engraved with "5" on one (ace) and on the other face. The tablet can be divided into equal halves.

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

**CLINICAL PARTICULARS**

**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 Pharmacodynamic properties section)

**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 Special warnings and precautions for use section).

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 Special warnings and precautions for use section)

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 Pharmacokinetics properties section).

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 Contraindications, and Pharmacokinetics properties sections).

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 Pharmacokinetics properties section).

CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- 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 Interaction with other medicinal products and other forms of interaction, and Pharmacokinetic properties sections)
- Pregnancy, lactation (see Pregnancy and lactation section)

SPECIAL WARNINGS AND SPECIAL 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 Contraindications section).

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 Posotogy and method of administration section).

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 interaction with other medicinal products and other forms of interaction section). 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 Pharmacodynamic properties section).

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 Pharmacodynamic properties section). 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 Contraindications section).

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 hour 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 Interaction with other medicinal products and other forms of interaction section). If the combination appears necessary, close cardiac monitoring is
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 Undesirable effects section)

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.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Pharmacodynamic interactions

Concomitant use not recommended

QT prolonging medicinal products
- Cardiovascular QT prolonging medical 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 noncardiovascular 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 Special warnings and special precautions for use section)

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 pharmacokinetic 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 Special warnings and special precautions for use section).

Contraindication 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 Contraindications section). 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 Special warnings and special precautions for use section).

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 Worl should be restricted during the treatment with ivabradine.

Other concomitant use

Specific drug-drug interaction 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 antidiabetic, aspirin and other anti-platelet medicinal products.

Paediatric population

Interaction studies have only been performed in adults.

**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 "Preclinical safety data"). The potential risk for humans is unknown. Therefore, ivabradine is contra-indicated during pregnancy (see Contraindications section).

**Breastfeeding**

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

**Fertility**

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

**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 Undesirable effects section). 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.

**UNDESIRABLE EFFECTS**

Ivabradine has been studied in clinical trials involving nearly 14,000 participants. The most common adverse reaction 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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Preferred Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Uncommon</td>
<td>Eosinophilia.</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Uncommon</td>
<td>Hyperuricaemia.</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Common</td>
<td>Headache, generally during the first month of treatment.</td>
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<tr>
<td></td>
<td></td>
<td>Dizziness, possibly related to bradycardia.</td>
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<tr>
<td></td>
<td>Uncommon*</td>
<td>Syncope, possibly related to bradycardia</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Preferred Term</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
<td>-----------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Eye disorders</strong></td>
<td>Very common</td>
<td>Luminous phenomena (phosphenes).</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Blurred vision.</td>
</tr>
<tr>
<td><strong>Ear and labyrinth disorders</strong></td>
<td>Uncommon</td>
<td>Vertigo.</td>
</tr>
<tr>
<td><strong>Cardiac disorders</strong></td>
<td>Common</td>
<td>Bradycardia.</td>
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<tr>
<td></td>
<td></td>
<td>AV 1&lt;sup&gt;st&lt;/sup&gt; degree block (ECG prolonged PQ interval).</td>
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<td></td>
<td></td>
<td>Ventricular extrasystoles.</td>
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<tr>
<td></td>
<td>Uncommon</td>
<td>Palpitations, supraventricular extrasystoles</td>
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<tr>
<td></td>
<td>Very rare</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AV 2&lt;sup&gt;nd&lt;/sup&gt; degree block, AV 3&lt;sup&gt;rd&lt;/sup&gt; degree block</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sick sinus syndrome</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td>Common</td>
<td>Uncontrolled blood pressure</td>
</tr>
<tr>
<td></td>
<td>Uncommon*</td>
<td>Hypotension, possibly related to bradycardia.</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td>Uncommon</td>
<td>Dyspnoea.</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td>Uncommon</td>
<td>Nausea.</td>
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<td></td>
<td></td>
<td>Constipation.</td>
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<tr>
<td></td>
<td></td>
<td>Diarrhoea.</td>
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<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td>Uncommon*</td>
<td>Angioedema</td>
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<tr>
<td></td>
<td></td>
<td>Rash</td>
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<td></td>
<td>Rare*</td>
<td>Erythema</td>
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<td></td>
<td></td>
<td>Pruritus</td>
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<td></td>
<td></td>
<td>Urticaria</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td>Uncommon</td>
<td>Muscle cramps.</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Frequency</td>
<td>Preferred Term</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
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<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Uncommon*</td>
<td>Asthenia, possibly related to bradycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fatigue, possibly related to bradycardia</td>
</tr>
<tr>
<td></td>
<td>Rare*</td>
<td>Malaise, possibly related to bradycardia</td>
</tr>
<tr>
<td>Investigations</td>
<td>Uncommon</td>
<td>Elevated creatinine in blood.</td>
</tr>
</tbody>
</table>

‘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.

**OVERDOSE**

Overdose may lead to severe and prolonged bradycardia (see Undesirable effects section). Severe bradycardia should be treated symptomatically in a specialised environment. In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment including intravenous betastimulating medicinal products such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.

**PHARMACOLOGICAL PROPERTIES**

**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 /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 /h which closely resembles cardiac /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 /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 Undesirable effects section).

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 Undesirable effects section).

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 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 (34 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 ≤ 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) | **Placebo** (n=3264) | **Hazard ratio** [95% CI] | **P- value** |
| N (%) | N (%) | | |
The reduction in 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 ≥ 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).

**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 Posology and method of administration section).

**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 (S18982) 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 Interaction with other medicinal products and other forms of interaction section).

**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 Cmax) have been observed between elderly (> 65 years) or very elderly patients (>75 years) and the overall population (see Posology and method of administration section).
- 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 S18982 (see Posology and method of administration section).
- 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 Posology and method of administration, and Contraindications sections).

**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 Contraindications, Special warnings and special precautions for use, and Interaction with other medicinal products and other forms of interaction sections).

**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 ectrodactyly in the rabbit. In dogs given ivabradine (doses of 2, 7 or 24mg/kg/day) for one year, reversible changes in retinal function were observed but were no 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 environmental.

**STORAGE CONDITIONS**
Store below 30°C. Shelf-life : 3 years.

**PACK SIZES**
Coralan 5 mg
- Box of 2 blisters of 14 tablets
- Box of 4 blisters of 14 tablets

Coralan 7.5 mg
- Box of 2 blisters of 14 tablets.
- Box of 4 blisters of 14 tablets

**HARUS DENGAN RESEP DOKTER**
Manufactured by:
Les Laboratoires Servier Industrie
45520 Gidy - France

Marketed by:
PT. Servier Indonesia
Jakarta - Indonesia

Registered by:
PT. Prafa
Bogor Indonesia