Coralan 5mg

Ivabradine **film-coated tablets**

Coralan 7 .5mg

Ivabradine **film-coated tablets**

COMPOSITION

Coralan 5 mg
One film-coated tablet contains 5 mg ivabradine (equivalent to 5.390 mg ivabradine as hydrochloride).
Excipient with known effect: 63.91 mg lactose monohydrate

Coralan 7.5 mg
One film-coated tablet contains 7.5 mg ivabradine (equivalent to 8.085 mg ivabradine as hydrochloride).
Excipient with known effect: 61.215 mg lactose monohydrate

PHARMACEUTICAL FORM

Film-coated tablet
Coralan 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 doses.

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

Symptomatic treatment of chronic stable angina pectoris
Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 bpm. Ivabradine is indicated :

- in adults unable to tolerate or with a contraindication to the use of beta-blockers
- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

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.

Symptomatic treatment of chronic stable angina pectoris
It is recommended that the decision to initiate or titrate treatment takes place with the availability of serial heart rate measurements, ECG or ambulatory 24-hour monitoring.
The starting dose of ivabradine should not exceed 5 mg twice daily in patients aged below 75 years. After three to four weeks of treatment, if the patient is still symptomatic, if the initial dose is well tolerated and if resting heart rate remains above 60 bpm, the dose may be increased to the next higher dose in patients receiving 2.5 mg twice daily or 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.
If there is no improvement in symptoms of angina within 3 months after start of treatment, treatment of ivabradine should be discontinued.
In addition, discontinuation of treatment should be considered if there is only limited symptomatic response and when there is no clinically relevant reduction in resting heart rate within three months.
If, during treatment, heart rate decreases 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 lowest dose of 2.5 mg twice daily (one half 5 mg tablet twice daily). After dose reduction, heart rate should be monitored (see Special warnings and precautions for use section). Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dose reduction.

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 (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 contraindicated 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).

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CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Resting heart rate below 70 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)
- Combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties (see Interaction with other medicinal products and other forms of interaction)
- Pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures (see Pregnancy and lactation section)

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Special warnings

Lack of benefit on clinical outcomes in patients with symptomatic chronic stable angina pectoris
Ivabradine is indicated only for symptomatic treatment of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death) (see Pharmacodynamic Properties).

Measurement of heart rate
Given that the heart rate may fluctuate considerably over time, serial heart rate measurements, ECG or ambulatory 24-hour monitoring should be considered when determining resting heart rate before initiation of ivabradine treatment and in patients on treatment with ivabradine when titration is considered. This also applies to patients with a low heart rate, in particular when heart rate decreases below 50 bpm, or after dose reduction (see Posology and Method of Administration).

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.
In patients treated with ivabradine the risk of developing atrial fibrillation is increased (see section Undesirable Effects). Atrial fibrillation has been more common in patients using concomitantly amiodarone or potent class I anti-arrhythmics.
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).
Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their physician if these occur.
If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.
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 70 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 Posology 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 contraindicated (see Contraindication, and 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 retinal function. There is no evidence of a toxic effect of long-term ivabradine treatment on the retina (see Pharmacodynamic properties). 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 contraindicated 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 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 Interaction with other medicinal products and other forms of interaction section). If the combination appears necessary, close cardiac monitoring is needed.
Heart rate reduction, as caused by ivabradine, may exacerbate QT prolongation, which may give rise to severe arrhythmias, in particular *Tosarde de pointes*

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 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 Special warnings and special precautions for use section)

Concomitant use with precautions

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Potassium-depleting diuretics (thiazide diuretics and loop diuretics): hypokalaemia can increase the risk of arrhythmia. As ivabradine may cause bradycardia, the resulting combination of hypokalaemia and bradycardia is a predisposing factor to the onset of severe arrhythmias, especially in patients with long QT syndrome, whether congenital or substance-induced.

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 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 contraindicated (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.

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 contraindicated (see Contraindicated section).

Concomitant use not recommended
Grapefruit juice: ivabradine exposure was increased by 2-fold following the co-administration with grapefruit juice. Therefore the intake of grapefruit juice should be avoided.

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 70 bpm, with monitoring of heart rate.
- 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.

FERTILITY, PREGNANCY AND LACTATION

Women of childbearing potential
Women of child-bearing potential should use appropriate contraceptive measures during treatment (see Contraindications)

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 "Precinical safety data"). The potential risk for humans is unknown. Therefore, ivabradine is contraindicated during pregnancy (see Contraindications section)

Breastfeeding
Animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contraindicated during breast-feeding (see Contraindications section)
Women that need treatment with ivabradine should stop breast-feeding, and choose for another way of feeding their child.

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

Summary of the safety profile
Ivabradine has been studied in clinical trials involving nearly 45,000 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.

Tabulated list of adverse reactions
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 (can not 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.
	Uncommon*	Diplopia
		Visual impairment
Ear and labyrinth disorders	Uncommon	Vertigo.
Cardiac disorders	Common	Bradycardia.
		AV 1st degree block (ECG

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		prolonged PQ interval).
		Ventricular extrasystoles.
		Atrial fibrillation
	Uncommon	Palpitations, supraventricular extrasystoles.
	Very rare	AV 2nd degree block, AV 3rd 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.
		Abdominal pain*
Skin and subcutaneous tissue disorders	Uncommon*	Angioedema
		Rash
	Rare*	Erythema
		Pruritus
		Urticaria
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasms
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.
		ECG prolonged QT interval

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

Description of selected adverse reactions
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. Phosphenes may also be describe as a halo, image decomposition (strobospic or kaleidoscopic effects), coloured bright lights, or multiple image (retinal persistency). 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.

In the SIGNIFY study atrial fibrillation was observed in 5.3% of patients taking ivabradine compared to 3.8% in the placebo group. In a pooled analysis of all the Phase II/III double blind controlled clinical trials with a duration of at least 3 months including more than 40,000 patients, the incidence of atrial fibrillation was 4.86% in ivabradine treated patients compared to 4.08% in controls, corresponding to a hazard ratio of 1.26, 95% CI [1.15-1.39].

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via e-meso subsite at https://e-meso.pom.go.id, or reporting to Pusat Farmakovigilasn / MESO Nasional, Badan Pengawas Obat dan Makanan: Phone: (+62 21) 4244691 Ext 1079 and Email: pv-center@pom.go.id.

OVERDOSE

Symptoms
Overdose may lead to severe and prolonged bradycardia (see Undesirable effects section).

Management
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 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 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

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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 (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).

A large outcome study, SIGNIFY, was performed in 19102 patients with coronary artery disease and without clinical heart failure (LVEF > 40%), on top of optimal background therapy. A therapeutic scheme higher than the approved posology was used (starting dose 7.5 mg b.i.d. (5 mg b.i.d, if age ≥ 75 years) and titration up to 10 mg b.i.d). The main efficacy criterion was the composite of cardiovascular death or non-fatal MI. The study showed no difference in the rate of the primary composite endpoint (PCE) in the ivabradine group by comparison to the placebo group (relative risk ivabradine/placebo 1.08, p=0.197). Bradycardia was reported by 17.9 % of patients in the ivabradine group (2.1% in the placebo group). Verapamil, diltiazem or strong CYP 3A4 inhibitors were received by 7.1% of patients during the study.
A small statistically significant increase in the PCE was observed in a pre-specified subgroup of patients with angina patients in CCS class II or higher at baseline (n=12049) (annual rates 3.4% versus 2.9%, relative risk ivabradine/placebo 1.18, p=0.018), but not in the subgroup of the overall angina population in CCS class ≥ I (n=14286) (relative risk ivabradine/placebo 1.11, p=0.110).
The higher than approved dose used in the study did not fully explain these findings.

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) 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: 0.85, 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

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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;1.53]).

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).
In a 97-patient randomised placebo-controlled study, the data collected during specific ophthalmologic investigations, aiming at documenting the function of the cone and rod systems and the ascending visual pathway (i.e electroretinogram, static and kinetic visual fields, colour vision, visual acuity), in patients treated with ivabradine for chronic stable angina pectoris over 3 years, did not show any retinal toxicity.

Paediatric population.
The European Medicines Agency has waived the obligation to submit the results of studies with Coralan in all subsets of the paediatric population for the treatment of angina pectoris.
The European Medicines Agency has deferred the obligation to submit the results of studies with Coralan in one or more subsets of the paediatric population in the treatment of chronic heart failure (see section Posology and method of administration for information on paediatric use).

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 (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 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 impairment: 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 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, repetated 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.

Enviromental Risk Assessment (ERA)
The environmental risk assessment of ivabradine has been conducted in accordance to European gudelines on ERA.
Outcomes of these evaluations support the lack of environmental risk of ivabradine and ivabradine does not pose a threat to the environmental.

List of Excipients
Lactose monohydrate, magnesium stearate, maize starch, maltodextrin, silica, colloidal anhydrous, hypromellose, titanium dioxide, macrogol 6000, glycerol, magnesium stearate, yellow iron oxide , red iron oxide

STORAGE CONDITIONS

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

PACK SIZES

Coralan 5 mg Reg. No. : DKI1168601317A1
- Box of 4 blisters of 14 tablets

Coralan 7.5 mg Reg. No. : DKI1168601317B1
- 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. Darya-Varia Laboratoria Tbk
Bogor - Indonesia

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Informasi untuk pasien
CORALAN 5 MG, Tablet Salut Selaput
CORALAN 7.5 MG, Tablet Salut Selaput
Ivabradine

Bacalah seluruh leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisi informasi yang penting bagi Anda.
- Simpan lembar informasi obat ini. Anda mungkin perlu membacanya lagi.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter atau apoteker Anda.
- Obat ini telah diresepkan untuk Anda. Jangan berikan kepada orang lain. Hal ini dapat membahayakan mereka, meskipun tanda-tanda penyakit mereka sama dengan Anda.
- Jika Anda mendapatkan efek samping, bicarakan dengan dokter atau apoteker Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam selebaran ini. Lihat bagian 4.

Apa yang ada di selebaran ini:

1. APA ITU CORALAN, DAN APAKAH KEGUNAANNYA

CORALAN (Ivabradine) adalah obat jantung yang digunakan untuk mengobati:
- Angina pektoris stabil simtomatik (yang menyebabkan nyeri dada) pada pasien dewasa yang detak jantungnya lebih dari atau sama dengan 70 denyut per menit. Ini digunakan pada pasien dewasa yang tidak mentolerir atau tidak dapat minum obat jantung yang disebut beta-blocker. Ini juga digunakan dalam kombinasi dengan beta-blocker pada pasien dewasa yang kondisinya tidak sepenuhnya terkontrol dengan beta-blocker.
- Gagal jantung kronis pada pasien dewasa yang detak jantungnya lebih dari atau sama dengan 75 denyut per menit. Ini digunakan dalam kombinasi dengan terapi standar, termasuk terapi beta-blocker atau ketika beta-blocker dikontraindikasikan atau tidak ditoleransi.

Tentang angina pektoris stabil (biasanya disebut sebagai "angina"):
Angina stabil adalah penyakit jantung yang terjadi ketika jantung tidak menerima cukup oksigen. Biasanya muncul antara usia 40 dan 50 tahun. Gejala angina yang paling umum adalah nyeri dada atau ketidaknyamanan. Angina lebih mungkin terjadi ketika jantung berdetak lebih cepat dalam situasi seperti olahraga, emosi, paparan dingin atau setelah makan. Peningkatan detak jantung ini dapat menyebabkan nyeri dada pada orang yang menderita angina.

Tentang gagal jantung kronis :
Gagal jantung kronis adalah penyakit jantung yang terjadi ketika jantung Anda tidak dapat memompa cukup darah ke seluruh tubuh Anda. Gejala gagal jantung yang paling umum adalah sesak napas, kelelahan, keletihan, dan pembengkakan pergelangan kaki.

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Bagaimana cara kerja CORALAN?
CORALAN terutama bekerja dengan mengurangi detak jantung beberapa denyut per menit. Ini menurunkan kebutuhan jantung akan oksigen terutama dalam situasi ketika serangan angina lebih mungkin terjadi. Dengan cara ini CORALAN membantu mengontrol dan mengurangi jumlah serangan angina.
Selain itu, karena peningkatan detak jantung berdampak buruk pada fungsi jantung dan prognosis vital pada pasien dengan gagal jantung kronis, tindakan penurunan detak jantung spesifik ivabradine membantu meningkatkan fungsi jantung dan prognosis vital pada pasien ini.

2. APA YANG PERLU ANDA KETAHUI SEBELUM MEMINUM CORALAN

Jangan minum CORALAN
- jika Anda alergi terhadap ivabradine atau bahan lain dari obat ini (tercantum di bagian 6);
- jika detak jantung istirahat Anda sebelum perawatan terlalu lambat (di bawah 70 denyut per menit);
- jika Anda menderita syok kardiogenik (kondisi jantung yang dirawat di rumah sakit);
- jika Anda menderita gangguan irama jantung;
- jika Anda mengalami serangan jantung;
- jika Anda menderita tekanan darah yang sangat rendah;
- jika Anda menderita angina tidak stabil (bentuk parah di mana nyeri dada sangat sering terjadi dan dengan atau tanpa pengerahan tenaga);
- jika Anda menderita gagal jantung yang baru-baru ini menjadi lebih buruk;
- jika detak jantung Anda secara eksklusif dipaksakan oleh alat pacu jantung Anda;
- jika Anda menderita masalah hati yang parah;
- jika Anda sudah minum obat untuk pengobatan infeksi jamur (seperti ketoconazole, itraconazole), antibiotik makrolida (seperti josamycin, klaritromisin, telithromycin atau eritromisin yang diberikan secara oral), obat-obatan untuk mengobati infeksi HIV (seperti nelfinavir, ritonavir) atau nefazodone (obat untuk mengobati depresi) atau diltiazem, verapamil (digunakan untuk tekanan darah tinggi atau angina pektoris);
- jika Anda seorang wanita yang dapat memiliki anak dan tidak menggunakan kontrasepsi yang andal;
- jika Anda hamil atau mencoba untuk hamil;
- jika Anda sedang menyusui.

Peringatan dan tindakan pencegahan
Bicaralah dengan dokter atau apoteker Anda sebelum mengonsumsi CORALAN
- jika Anda menderita gangguan irama jantung (seperti detak jantung tidak teratur, jantung berdebar-debar, peningkatan nyeri dada) atau fibrilasi atrium berkelanjutan (sejenis detak jantung tidak teratur), atau kelainan elektrokardiogram (EKG) yang disebut 'sindrom QT panjang',
- jika Anda memiliki gejala seperti kelelahan, pusing atau sesak napas (ini bisa berarti jantung Anda terlalu melambat),
- jika Anda menderita gejala fibrilasi atrium (denyut nadi saat istirahat yang sangat tinggi (lebih dari 110 denyut per menit) atau tidak teratur, tanpa alasan yang jelas, sehingga sulit untuk diukur),
- jika Anda mengalami stroke baru-baru ini (serangan otak),
- jika Anda menderita tekanan darah rendah ringan hingga sedang,
- jika Anda menderita tekanan darah yang tidak terkontrol, terutama setelah perubahan dalam pengobatan antihipertensi Anda,
- jika Anda menderita gagal jantung parah atau gagal jantung dengan kelainan EKG yang disebut 'blok cabang bundel',
- jika Anda menderita penyakit retina mata kronis,
- jika Anda menderita masalah hati sedang,
- Jika Anda menderita masalah ginjal yang parah.

Jika salah satu dari hal di atas berlaku untuk Anda, bicarakan langsung dengan dokter Anda sebelum atau saat mengonsumsi CORALAN.

Anak
CORALAN tidak dimaksudkan untuk digunakan pada anak-anak dan remaja di bawah 18 tahun.

Obat-obatan lain dan CORALAN
Beri tahu dokter atau apoteker Anda jika Anda sedang meminum, baru saja mengonsumsi atau mungkin mengonsumsi obat lain.

Pastikan untuk memberi tahu dokter Anda jika Anda mengonsumsi salah satu obat berikut, karena penyesuaian dosis CORALAN atau pemantauan harus diperlukan:
- fluconazole (obat antijamur)
- rifampisin (antibiotik)
- barbiturat (untuk sulit tidur atau epilepsi)
- fenitoin (untuk epilepsi)
- *Hypericum perforatum* atau St John's Wort (pengobatan herbal untuk depresi)
- Obat perpanjangan QT untuk mengobati gangguan irama jantung atau kondisi lainnya :
  - Quinidine, Disopyramide, Ibutilide, Sotalol, Amiodarone (untuk mengobati gangguan irama jantung)
  - bepridil (untuk mengobati angina pektoris)
  - Jenis obat tertentu untuk mengobati kecemasan, skizofrenia atau psikosis lainnya (seperti pimozide, ziprasidone, sertindole)
  - Obat anti-malaria (seperti mefloquine atau halofantrine)
  - Eritromisin intravena (antibiotik)
  - pentamidine (obat antiparasit)
  - Cisapride (melawan refluks gastro-esofagus)
- Beberapa jenis diuretik yang dapat menyebabkan penurunan kadar kalium darah, seperti furosemide, hidroklorotiazida, indapamide (digunakan untuk mengobati edema, tekanan darah tinggi).

CORALAN dengan makanan dan minuman
Hindari jus jeruk bali selama pengobatan dengan CORALAN.

Kehamilan dan menyusui
Jangan mengonsumsi CORALAN jika Anda sedang hamil atau berencana untuk memiliki bayi (lihat "Jangan mengonsumsi CORALAN").
Jika Anda sedang hamil dan telah mengonsumsi CORALAN, bicarakan dengan dokter Anda.
Jangan mengonsumsi CORALAN jika Anda dapat hamil kecuali Anda menggunakan tindakan kontrasepsi yang dapat diandalkan (lihat "Jangan mengonsumsi CORALAN").
Jangan mengonsumsi CORALAN jika Anda menyusui (lihat "Jangan mengonsumsi CORALAN"). Bicaralah dengan dokter Anda jika Anda sedang menyusui atau berniat untuk menyusui karena menyusui harus dihentikan jika Anda mengonsumsi CORALAN.
Jika Anda sedang hamil atau menyusui, berpikir Anda mungkin hamil atau berencana untuk memiliki bayi, mintalah saran dari dokter atau apoteker Anda sebelum minum obat ini.

Mengemudi dan menggunakan mesin
CORALAN dapat menyebabkan fenomena visual bercahaya sementara (kecerahan sementara di bidang penglihatan, lihat "Kemungkinan efek samping"). Jika ini terjadi pada Anda, berhati-hatilah saat mengemudi atau menggunakan mesin pada saat mungkin ada perubahan intensitas cahaya yang tiba-tiba, terutama saat mengemudi di malam hari.

CORALAN mengandung laktosa

Jika Anda telah diberitahu oleh dokter Anda bahwa Anda memiliki intoleransi terhadap beberapa gula, hubungi dokter Anda sebelum minum obat ini.

3. BAGAIMANA ATURAN MINUM CORALAN

Selalu minum obat ini persis seperti yang dikatakan dokter atau apoteker Anda. Periksa dengan dokter atau apoteker Anda jika Anda tidak yakin.
CORALAN harus diminum saat makan.

Jika Anda sedang dirawat untuk angina pektoris stabil
Dosis awal tidak boleh melebihi satu tablet CORALAN 5 mg dua kali sehari. Jika Anda masih memiliki gejala angina dan jika Anda telah mentolerir dosis 5 mg dua kali sehari dengan baik, dosisnya dapat ditingkatkan. Dosis pemeliharaan tidak boleh melebihi 7,5 mg dua kali sehari. Dokter Anda akan meresepkan dosis yang tepat untuk Anda. Dosis yang biasa adalah satu tablet di pagi hari dan satu tablet di malam hari. Dalam beberapa kasus (misalnya jika Anda lanjut usia), dokter Anda mungkin meresepkan setengah dosis yaitu, satu setengah 5 mg tablet CORALAN 5 mg (setara dengan 2,5 mg ivabradine) di pagi hari dan setengah tablet 5 mg di malam hari.
Jika tidak ada perbaikan gejala angina dalam waktu 3 bulan setelah memulai pengobatan, pengobatan dengan ivabradine sebaiknya dihentikan.

Jika Anda sedang dirawat karena gagal jantung kronis
Dosis awal yang direkomendasikan adalah satu tablet CORALAN 5 mg dua kali sehari, meningkat jika perlu menjadi satu tablet CORALAN 7,5 mg dua kali sehari. Dokter Anda akan memutuskan dosis yang tepat untuk Anda. Dosis yang biasa adalah satu tablet di pagi hari dan satu tablet di malam hari. Dalam beberapa kasus (misalnya jika Anda lanjut usia), dokter Anda mungkin meresepkan setengah dosis yaitu, satu setengah 5 mg tablet CORALAN 5 mg (setara dengan 2,5 mg ivabradine) di pagi hari dan setengah tablet 5 mg di malam hari.

Jika Anda mengonsumsi lebih banyak CORALAN daripada yang seharusnya:
Dosis besar CORALAN bisa membuat Anda merasa sesak napas atau lelah karena jantung Anda terlalu melambat. Jika ini terjadi, segera hubungi dokter Anda.

Jika Anda lupa mengonsumsi CORALAN:
Jika Anda lupa minum dosis CORALAN, minum dosis berikutnya pada waktu biasa. Jangan minum dosis ganda untuk menebus dosis yang terlupakan.
Kalender yang tercetak pada blister yang berisi tablet akan membantu Anda mengingat kapan terakhir kali Anda minum tablet CORALAN.

Jika Anda berhenti mengonsumsi CORALAN:
Karena pengobatan angina atau gagal jantung kronis biasanya seumur hidup, Anda harus berdiskusi dengan dokter Anda sebelum menghentikan produk obat ini.
Jika Anda berpikir bahwa efek CORALAN terlalu kuat atau terlalu lemah, bicarakan dengan dokter atau apoteker Anda.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter atau apoteker Anda.

4. KEMUNGKINAN EFEK SAMPING

Seperti semua obat, obat ini dapat menyebabkan efek samping, meskipun tidak semua orang mendapatkannya.

Frekuensi kemungkinan efek samping yang tercantum di bawah ini ditentukan menggunakan konvensi berikut:
Sangat umum: dapat mempengaruhi lebih dari 1 dari 10 orang
umum: dapat mempengaruhi hingga 1 dari 10 orang
Jarang terjadi: dapat mempengaruhi hingga 1 dari 100 orang
Langka: dapat mempengaruhi hingga 1 dari 1.000 orang
Sangat jarang: dapat mempengaruhi hingga 1 dari 10.000 orang
Tidak diketahui: frekuensi tidak dapat diperkirakan dari data yang tersedia

Efek samping yang paling umum dengan obat ini tergantung pada dosis dan terkait dengan cara kerjanya:

Sangat umum:
Fenomena visual bercahaya (saat-saat singkat peningkatan kecerahan, paling sering disebabkan oleh perubahan intensitas cahaya yang tiba-tiba). Efek samping juga dapat digambarkan sebagai lingkaran cahaya, kilatan berwarna, dekomposisi gambar atau beberapa gambar. Efek samping umumnya terjadi dalam dua bulan pertama pengobatan setelah itu dapat terjadi berulang kali dan sembuh selama atau setelah pengobatan

Umum:
Modifikasi fungsi jantung (gejalanya adalah melambatnya detak jantung). Efek samping terutama terjadi dalam 2 hingga 3 bulan pertama inisiasi pengobatan.

Efek samping lainnya juga telah dilaporkan:

Umum:
Kontraksi jantung yang cepat tidak teratur, persepsi detak jantung yang tidak normal, tekanan darah yang tidak terkontrol, sakit kepala, pusing dan penglihatan kabur (penglihatan keruh).

Jarang:
Palpitasi dan detak jantung ekstra, merasa mual (mual), sembelit, diare, sakit perut, sensasi berputar (vertigo), kesulitan bernapas (dispnea), spasme otot, perubahan parameter laboratorium : kadar asam urat darah tinggi, kelebihan eosinofil (sejenis sel darah putih) dan peningkatan kreatinin dalam darah (produk pemecahan otot), ruam kulit, angioedema (seperti wajah bengkak, lidah atau tenggorokan, kesulitan bernapas atau menelan), tekanan darah rendah, pingsan, perasaan lelah, perasaan lemah, pelacakan jantung EKG abnormal, penglihatan ganda, gangguan penglihatan.

Langka:
Urtikaria, gatal, kulit memerah, merasa tidak enak badan.

Sangat jarang:
Detak jantung tidak teratur.

Pelaporan efek samping
Jika Anda mendapatkan efek samping, bicarakan dengan dokter atau apoteker Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam selebaran ini.

Anda juga dapat melaporkan keluhan efek samping atau kondisi tidak nyaman secara langsung melalui *e-mail* PT. Darya-Varia Laboratoria Tbk dengan alamat pv@darya-varia.com, atau melalui *call center* PT. Servier Indonesia dengan No. Telp. 021-57903940 atau disampaikan berupa tulisan melalui kontak kami di situs www.servier.co.id.

Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut tentang keamanan obat ini.

5. BAGAIMANA CARA MENYIMPAN CORALAN

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tertera pada karton dan blister setelah 'EXP'. Tanggal kedaluwarsa mengacu pada hari terakhir bulan itu.

Obat ini tidak memerlukan kondisi penyimpanan khusus.

Jangan membuang obat apa pun melalui air limbah atau limbah rumah tangga. Tanyakan kepada apoteker Anda cara membuang obat yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. ISI DARI KEMASAN CORALAN DAN INFORMASI LEBIH LANJUT

Apa yang terkandung dalam CORALAN

- Zat aktif:
  CORALAN 5 mg: satu tablet berlapis film mengandung 5 mg ivabradine (setara dengan 5.390 mg ivabradine sebagai hidroklorida).
  CORALAN 7,5 mg: satu tablet berlapis film mengandung 7,5 mg ivabradine (setara dengan 8,085 mg ivabradine sebagai hidroklorida).
- Bahan lain dalam inti tablet adalah: laktosa monohidrat, magnesium stearate, pati jagung, maltodekstrin, silika anhidrat koloid, dan dalam lapisan tablet: hipromelosa, titanium dioksida, makrogol 6000, gliserol, magnesium stearate, oksida besi kuning, oksida besi merah.

Seperti apa bentuk dan isi kemasan CORALAN

Tablet CORALAN 5 mg adalah tablet berlapis film lonjong berwarna salmon yang dicetak di kedua sisi, diukir dengan "5" di satu sisi dan  di sisi lain.
Tablet CORALAN 7,5 mg adalah tablet berlapis film berwarna salmon, segitiga, yang diukir dengan "7,5" di satu sisi dan  di sisi lainnya.

Kemasan

CORALAN 5 mg No. Reg: DKI1668601317A1
Dus, 4 blister @ 14 tablet salut selaput

CORALAN 7,5 mg No. Reg DKI1668601317B1
Dus, 4 blister @ 14 tablet salut selaput

DISETUJUI OLEH BPOM: 04/09/2025 ID REG: EREG10008712500179 - EREG10008712500180

HARUS DENGAN RESEP DOKTER

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Les Laboratoires Servier Industrie
Gidy - France

Didaftarkan oleh:
PT. Darya-Varia Laboratoria Tbk
Bogor – Indonesia

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DDMMYY

DISETUJUI OLEH BPOM: 04/09/2025 ID REG: EREG10008712500179 - EREG10008712500180