APPROVED SPC

For

CORALAN

Date Approved: April 2017
Registration No.:

Confidential Information

Coralan 5 mg: A39/7.1.4/0410

Coralan 7,5 mg: A39/7.1.4/0411

Coralan 5 mg and 7,5 mg

SCHEDULING STATUS: **S3**

PROPRIETARY NAME AND DOSAGE FORM:

Coralan 5 mg, film-coated tablet.

Coralan 7,5 mg, film-coated tablet.

COMPOSITION:

Each **Coralan 5 mg** tablet contains 5,390 mg of ivabradine hydrochloride corresponding to 5 mg of ivabradine base.

Each **Coralan** 7,5 mg tablet contains 8,085 mg of ivabradine hydrochloride corresponding to 7,5 mg of ivabradine base.

The excipients in the tablet core are: lactose monohydrate, magnesium stearate, maize starch, maltodextrin, colloidal anhydrous silica, and in the tablet coating: hypromellose, titanium dioxide (E171) (CI 77891), macrogol 6 000, glycerol, magnesium stearate, yellow iron oxide (E172) (CI 77492), red iron oxide (E172) (CI 77491).

Contains sugar (lactose 63,91 mg for the 5 mg tablet and 61,215 mg for the 7,5 mg tablet).

CATEGORY AND CLASS:

A 7.1.4 Vasodilators – coronary and other medicines used in angina pectoris.

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Ivabradine is a 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, myocardial contractility or ventricular repolarisation.

In experimental models the adaptability of myocardial contractility, cardiac output, mean coronary blood flow velocity and vascular resistance observed during exercise is preserved.

In animal models used to mimic exercise-induced ischaemia that causes angina pectoris in humans, ivabradine reduces myocardial ischaemia and myocardial contractility dysfunction induced by stunning.

The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. At recommended doses, heart rate reduction is approximately 10 beats per minute (bpm) at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption. Analysis of heart rate reduction indicates a trend towards a plateau effect at higher doses.

Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarisation:

- in clinical electro-physiology studies, ivabradine had no effect on atrioventricular or intraventricular conduction times or corrected QT intervals.

Pharmacokinetic properties:

Under physiological conditions, ivabradine is released from tablets and is highly 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:

About 90 % of ivabradine is absorbed after oral administration, with a peak plasma level reached in about 0,75 – 1,5 hours. The absolute bioavailability of ivabradine tablets is around 40 %, due to first-pass effect. Food delays absorption by about 1 hour and increases plasma exposure by 20 – 30 %.

Distribution:

Ivabradine is approximately 70 % plasma protein bound and the volume of distribution at steady-state is close to 100 litres in patients. The maximum plasma concentration following

chronic administration at the recommended dose of 5 mg twice daily is 22 ng/ml. The average plasma concentration is 10 ng/ml 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), and its exposure is about 40 % of that of the parent compound, with similar pharmacokinetic and pharmacodynamic properties. The metabolism of this active metabolite also involves CYP3A4.

Ivabradine has low affinity for CYP3A4, shows no sign of enzyme induction or inhibition and is therefore unlikely to modify CYP3A4 substrate metabolism or plasma concentrations. Inversely, strong inhibitors and inducers of CYP3A4 may substantially affect ivabradine plasma concentrations. (see INTERACTIONS).

Elimination:

Ivabradine is eliminated with a plasma half-life of 2 hours. The total clearance is about 400 ml/min and the renal clearance is about 70 ml/min. Excretion of metabolites and little amounts of unchanged compounds occurs to a similar extent via faeces and urine.

Linearity/non-linearity:

The kinetics of ivabradine are linear.

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.

Renal impairment:

In patients with renal insufficiency (15 – 60 ml/min), no specific dosage adjustment is required since this condition has no significant impact on ivabradine clearance.

Hepatic impairment:

No specific dosage adjustment is required in patients with mild liver dysfunction (Child Pugh score less than 7). The use of ivabradine is not recommended in patients with moderate liver dysfunction (limited data, see WARNINGS AND SPECIAL PRECAUTIONS) and is contraindicated in severe liver dysfunction (no data available see CONTRAINDICATIONS).

INDICATIONS:

Symptomatic treatment of chronic stable angina pectoris:

Coralan is indicated for the symptomatic treatment of chronic stable angina pectoris, in patients with normal sinus rhythm and heart rate ≥ 70 bpm, as monotherapy or in combination with beta-blockers.

Treatment of chronic heart failure:

Coralan is indicated in adults in sinus rhythm with mild to moderate (NYHA II & III class) symptomatic heart failure whose heart rate is ≥ 77 bpm to reduce cardiovascular events (cardiovascular mortality or hospitalisation for worsening heart failure), in combination with standard therapy including beta-blockers or when beta-blockers are contraindicated or not tolerated.

CONTRAINDICATIONS:

Pregnancy and lactation, as Coralan® has shown to be teratogenic in animal reproductive studies (see HUMAN REPRODUCTION).

- Known hypersensitivity to ivabradine or any of the excipients of **Coralan**
- 3rd degree AV Block
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
- Resting heart rate below 70 bpm prior to treatment
- Severe hypotension (< 90/50 mmHg)
- Cardiogenic shock
- Unstable or acute heart failure
- Acute coronary syndrome

- Unstable angina pectoris
- Use in patients with congenital long QT syndrome or in patients treated with QT prolonging medicines should be avoided (see WARNINGS AND SPECIAL PRECAUTIONS)
- In combination with strong cytochrome P450 inhibitors such as azole antifungals, macrolide antibiotics, HIV protease inhibitors (see INTERACTIONS)
- Concomitant use of St. John's Wort
- **Coralan** is not recommended in patients with moderate liver dysfunction (limited data in these populations) and is contraindicated in severe liver dysfunction (no data)
- Combination with verapamil or diltiazem, which are moderate CYP3A4 inhibitors with heart-rate reducing properties (see INTERACTIONS)
- Women of childbearing potential not using appropriate contraceptive measures (see HUMAN REPRODUCTION)
- Concomitant use of grapefruit juice is not recommended (see INTERACTIONS).

Concomitant use with QT-prolonging medicines:

The concomitant use of cardiovascular (quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone) or non-cardiovascular (tricyclic antidepressant, antipsychotics, erythromycin IV, pentamidine, pimozide, mefloquine) QT-prolonging medicines with **Coralan** should be avoided since QT-prolongation may be exacerbated by heart rate reduction.

- **Coralan** has not been studied in patients with rapid conduction disorders i.e. WPW.
- Cardiac dysrhythmias:
- sick sinus syndrome
- sino-atrial block.

Stroke:

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

Use in patients with AV-block of 2nd degree:

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

WARNINGS AND SPECIAL PRECAUTIONS:

Coralan treatment should be discontinued if the symptoms of angina pectoris do not improve with 3 months of **Coralan** treatment.

Lack of benefit on clinical outcomes in patients with symptomatic chronic stable angina pectoris:

Coralan is indicated only for symptomatic treatment of chronic stable angina pectoris, because **Coralan** has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death).

Measurement of heart rate:

Given that the heart rate may fluctuate considerably over time, serial heart rate measurements, ECG or ambulatory 24-hour monitoring is recommended when determining resting heart rate before initiation of **Coralan** treatment, and in patients on treatment with **Coralan** when titration is considered. This also applies to patients who develop a low heart rate on treatment with **Coralan**, in particular when heart rate decreases below 50 bpm, or after dose reduction (see DOSAGE AND DIRECTIONS FOR USE).

Chronic heart failure:

Heart failure must be stable before considering **Coralan** treatment.

Use in patients with a low heart rate:

Coralan must not be initiated in patients with a pre-treatment resting heart rate below 70 beats per minute (see CONTRAINDICATIONS).

If, during **Coralan** treatment, heart rate decreases below 50 bpm at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward or discontinued. Treatment must be discontinued if heart rate below 50 bpm persists. (see DOSAGE AND DIRECTION FOR USE).

Combination with other anti-angina medications:

Concomitant use of **Coralan** with heart rate reducing calcium channel blockers such as verapamil or diltiazem is contraindicated (see CONTRAINDICATIONS and INTERACTIONS).

Additional efficacy of **Coralan** in combination with dihydropyridine calcium channel blockers has not been established.

Use in patients with congenital QT syndrome or in patients treated with QT-prolongation medicines:

Since **Coralan** reduces heart rate it should be avoided in patients with congenital QT syndrome or treated with QT-prolongations medicines. If the combination appears necessary, close cardiac monitoring is needed.

Heart rate reduction, as caused by **Coralan,** may exacerbate QT-prolongation, which may give rise to severe dysrhythmias, in particular *Torsade de pointes*.

Cardiac dysrhythmias:

Coralan is not effective in the treatment or prevention of cardiac dysrhythmias and likely loses its efficacy when a tachy-dysrhythmia occurs (i.e. ventricular or supra-ventricular tachycardia).

Coralan is not recommended in patients with atrial fibrillation or with other cardiac dysrhythmias that interfere with sinus node function.

In patients treated with **Coralan** the risk of developing atrial fibrillation is increased (see SIDE EFFECTS). Atrial fibrillation has been more common in patients concomitantly using amiodarone or potent class I anti-dysrhythmics.

It is recommended to regularly clinically monitor **Coralan** treated patients for the occurrence of atrial fibrillation (sustained of paroxysmal), which should also include ECG monitoring if clinically indicated (i.e. in case of exacerbated angina, palpitations or irregular pulse).

Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their doctor if these occur.

If atrial fibrillation develops during treatment, the balance of benefits and risks of continued **Coralan** treatment should be carefully reconsidered.

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

Visual function:

Ivabradine influences on retinal function. 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.

Wolf-Parkinson-White-syndrome:

Coralan has not been studied in patients with Wolf-Parkinson-White-syndrome (see CONTRAINDICATIONS).

Moderate to severe liver dysfunction:

Coralan is not recommended in patients with moderate liver dysfunction since there is limited data in these populations and is contraindicated in severe liver dysfunction (see CONTRAINDICATIONS).

Aortic and/or Mitral valvular disease*:*

Due to the lack of data, **Coralan** is not recommended in patients with severe aortic and/or mitral valvular disease.

Concomitant use with cytochrome P450 3A4 (CYP3A4) inhibitors or inducers:

- **Strong CYP3A4 inhibitors:**

  As these agents significantly increase **Coralan** plasma concentrations, their concomitant use with **Coralan** is contraindicated (see CONTRAINDICATIONS).

- **Moderate CYP3A4 inhibitors:**

  As these agents increase **Coralan** plasma concentrations, their concomitant use with **Coralan** may require a downward titration of the dose of **Coralan** depending on heart rate (see INTERACTIONS).

- **CYP3A4 inducers:**

As these agents decrease **Coralan** plasma concentrations, their prolonged concomitant use with **Coralan** may require an upward titration of the dose of **Coralan** depending on the therapeutic response. In this case, heart rate monitoring is recommended when discontinuing CYP3A4 inducers (also see INTERACTIONS).

Hypertension requiring blood pressure treatment modifications:

As patients treated with **Coralan** may experience episodes of increased blood pressure, blood pressure should be monitored at appropriate intervals (see SIDE EFFECTS).

Patients with hypotension:

Limited data are available in patients with mild to moderate hypotension, and **Coralan** should therefore be used with caution in these patients.

Coralan is contraindicated in patients with severe hypotension (blood pressure < 90/50 mmHg) (see CONTRAINDICATIONS).

Lactose:

Coralan tablets contain lactose.

Patients with rare hereditary problems of galactose intolerance e.g. galactasaemia, Lapp lactase deficiency, or glucose-galactose malabsorption or fructose intolerance should not take **Coralan**.

Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

Effects on ability to drive and use machines:

Coralan may cause transient visual symptoms consisting mainly of phosphenes. The possible occurrence of such visual symptoms should be taken into account when driving or using machines in situations where sudden variations in light intensity may occur.

INTERACTIONS:

Pharmacokinetic interactions:

Cytochrome P450 3A4 (CYP3A4):

Coralan is metabolised by cytochrome P450 3A4 (CYP3A4) and is a weak inhibitor of this cytochrome. Therefore, **Coralan** is unlikely to influence the metabolism and plasma concentrations of other CYP3A4 substrates.

CYP3A4 inhibitors and inducers are liable to interact with **Coralan** and to influence its metabolism and pharmacokinetics.

Drug-drug interaction studies have established that CYP3A4 inhibitors, increase **Coralan** plasma concentrations, while inducers decrease them. Increased plasma concentrations of **Coralan** may be associated with excessive bradycardia (see CONTRAINDICATIONS).

Concomitant use contraindicated:

The concomitant use of potent CYP3A4 inhibitors such as azole antifungals (ketoconazole, ictraconozole), macrolide antibiotics (clarithromycin, erythromycin taken orally, josmycin, telithromycin), HIV protease inhibitors (including nelfinavir, ritonavir) is contraindicated (see CONTRAINDICATIONS).

The potent CYP3A4 inhibitors ketoconazole (200 mg once daily) and josamycin (1 g twice daily) increased the mean plasma exposure of **Coralan** by 7 to 8 fold.

Moderate CYP3A4 inhibitors:

Specific interaction studies in healthy volunteers and patients have shown that the combination of **Coralan** with diltiazem and verapamil resulted in an increased ivabradine exposure (2 to 3 fold increase in AUC) with an additional heart rate reduction of 5 bpm. The concomitant use of ivabradine with these medicines is contraindicated (see CONTRAINDICATIONS).

Concomitant use not recommended:

Grapefruit juice: **Coralan** 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 caution:

The concomitant use of **Coralan** with **other moderate CYP3A4 inhibitors** (i.e. fluconazole) may be considered at the starting dose of 2,5 mg twice daily and if resting heart rate is above 70 bpm, while monitoring heart rate.

CYP3A4 metabolism inducers such as rifampicin, barbiturates, phenytoin and *Hypericum perforatum* (St. John's Wort):

Prolonged concomitant use of these agents with ivabradine may decrease ivabradine exposure and activity and therefore require an upward titration of the dose of **Coralan**.

The combination of **Coralan** 10 mg twice daily with St. John's Wort was shown to reduce the area under the curve (AUC) of ivabradine by 50 %. The intake of St. John's Wort is contraindicated (see CONTRAINDICATIONS).

Other concomitant use:

Specific interaction studies have shown no clinically significant pharmacokinetic or pharmacodynamic interactions between **Coralan** and any of the following: digoxin, HMG CoA reductase inhibitors (statins), proton pump inhibitors (e.g. omeprazole, lansoprazole), dihydropyridine calcium channel blockers (nifedipine, amlodipine, lacidipine), aspirin and warfarin.

In pivotal phase III clinical trials the following medicines were frequently combined with **Coralan** with no evidence of safety concerns: angiotensin converting enzyme inhibitors,

angiotensin II antagonists, beta-blockers, diuretics, anti-aldosterone, calcium channel blockers (e.g. nifidipine), short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics (including: biguanides, sulphonylureas, alpha-glucosidases inhibitors, DPP-4 inhibitors, glitazones (thiazolidinediones), aspirin and other anti-platelet agents.

Pharmacodynamic interactions:

Concomitant use not recommended:

QT-prolonging medicines:

- Cardiovascular QT-prolonging medicines (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone).
- Non cardiovascular QT-prolonging medicines (e.g. pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin). The concomitant use of cardiovascular and non-cardiovascular QT-prolonging medicines with **Coralan** should be avoided since QT-prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is required.

Concomitant use with precaution:

Potassium-depleting diuretics (thiazide diuretics and loop diuretics):

Hypokalaemia can increase the risk of dysrhythmia. As **Coralan** may cause bradycardia, the resulting combination of hypokalaemia and bradycardia is a predisposing factor to the onset of severe dysrhythmias, especially in patients with long QT syndrome, whether congenital or substance induced (see CONTRAINDICATIONS).

HUMAN REPRODUCTION:

Animal reproduction studies have shown embryotoxic and teratogenic effects at doses similar to those used in humans.

Animal studies indicate that ivabradine is excreted in milk. Therefore, Coralan is contraindicated during pregnancy and lactation (see CONTRAINDICATIONS).

Women of childbearing potential:

Women of childbearing potential should use appropriate contraceptive measures during treatment (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

Symptomatic treatment of chronic stable angina pectoris:

It is recommended that the decision to initiate or titrate treatment takes place using serial heart rate measurements, ECG or ambulatory 24-hour monitoring.

The starting dose of **Coralan** in patients below 75 years of age should not exceed 5 mg twice daily. After two 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 a maximum of 7,5 mg twice daily depending on the therapeutic response. If there is no improvement in symptoms of angina within 3 months after start of treatment,

treatment of **Coralan** should be discontinued (see WARNINGS AND SPECIAL PRECAUTIONS).

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 bpm at rest or the patient experiences symptoms related to bradycardia, such as dizziness, fatigue or hypotension, the dosage 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 WARNINGS AND SPECIAL PRECAUTIONS). Treatment must be discontinued if the heart rate remains below 50 bpm or symptoms of bradycardia persist, despite dose reduction.

Treatment of chronic heart failure:

The recommended starting dose of ivabradine is 5 mg twice daily in patients below 75 years of age. After two weeks of treatment, the dose can be increased to a maximum of 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, the heart rate decreases persistently to 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 the heart rate increases persistently to above 60 beats per minute at rest, the dose can be up titrated to the next higher 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 WARNINGS AND SPECIAL PRECAUTIONS).

Method of administration:

Coralan tablets must be taken orally twice daily, i.e. once in the morning and once in the evening. **Coralan** tablets should be taken with food.

Special populations:

Elderly patients:

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.

Patients with renal impairment:

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

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

Patients with hepatic impairment:

No dose adjustment is required in patients with mild hepatic impairment.

Coralan is not recommended in patients with moderate hepatic insufficiency, since there is limited data and is contraindicated for use in patients with severe hepatic insufficiency, since it has not been studied in this population (see CONTRAINDICATIONS).

Paediatric population:

The safety and efficacy of **Coralan** in children aged below 18 years have not yet been established.

SIDE EFFECTS:

Coralan has been studied in clinical trials involving nearly 45 000 patients. The side effects associated with the use of **Coralan** are the following according to the MedDRA system organ class and frequencies: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1 000, < 1/100); rare (≥ 1/10 000, < 1/1 000); very rare (< 1/10 000).

The most common adverse events with **Coralan**, luminous phenomena (phosphenes) (± 15 %) and bradycardia (± 3,3 %), are dose dependant and are related to the pharmacological effect of the medicine.

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

The following adverse events were reported post marketing:

Nervous system disorders	Syncope, possibly related to bradycardia
Eye disorders	Visual impairment
	Diplopia
Vascular disorders	Hypotension, possibly related to bradycardia
Gastrointestinal disorders	Abdominal pain
Skin and subcutaneous tissue disorders	Angioedema
	Rash
	Erythema
	Pruritus
	Urticaria
General disorders and administration site conditions	Asthenia, possibly related to bradycardia
	Fatigue, possibly related to bradycardia
	Malaise, possibly related to bradycardia

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 described as a halo, image decomposition (stroboscopic and kaleidoscopic), coloured bright lights, or multiple images (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. Less 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 and 0,5 % of patients experienced a severe bradycardia below or equal to 40 bpm.

In patients with angina pectoris, artrial fibrillation developed in about 5 % of patients treated with **Coralan**.

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 atrial fibrillation developed in 4,86 % of ivabradine treated patients compared to 4,08 % in controls.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Symptoms:

In overdose, side effects will be exacerbated and exaggerated (see SIDE EFFECTS). Overdose may lead to severe and prolonged bradycardia, which should be treated symptomatically in a specialised environment.

Management:

In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment including intravenous beta-stimulating agents such as dobutamine may be considered.

Temporary cardiac electrical pacing may be instituted if required.

IDENTIFICATION:

Coralan 5 mg: salmon-coloured, rod-shaped, film-coated tablet scored on both edges, engraved with “5” on one face and  on the other face.

Coralan 7,5 mg: salmon-coloured, triangular, film-coated tablet engraved with “7,5” on one face and  on the other face.

PRESENTATION:

Aluminium/PVC blister strips with 56 tablets in cartons.

STORAGE INSTRUCTIONS:

Store at or below 30 °C.

Keep out of reach of children.

REGISTRATION NUMBER:

Coralan 5 mg: A39/7.1.4/0410

Coralan 7,5 mg: A39/7.1.4/0411

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Servier Laboratories SA (Pty) Ltd

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1686

DATE OF PUBLICATION OF THE PACKAGE INSERT:

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Namibia Details

Coralan 5 mg: 08/7.6/0163 (NS2)

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