UNILAB

Ivabradine Valheart®

5 mg & 7.5 mg Film-Coated Tablet

Rx

Anti-Angina

FORMULATION
Each film-coated tablet contains:
Ivabradine (as hydrochloride) ……5 mg or 7.5 mg

PRODUCT DESCRIPTION

5 mg Film-coated Tablet: Pale pinkish orange, rectangular shaped, slightly biconvex film-coated tablet with score line on one side
7.5 mg Film-coated Tablet: Pale pinkish orange, round, slightly biconvex film-coated tablet with beveled edge

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocking agent that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I_f current, resulting in heart rate reduction with no effect on ventricular repolarization or myocardial contractility.

Ivabradine causes a 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. At recommended doses, heart rate reduction is approximately 10 beats per minute (bpm) at rest and during exercise. Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarization.

In clinical studies, ivabradine has reduced heart rate, improved exercise capacity, and decreased the number of anginal attacks in patients with chronic stable angina.

Ivabradine can also inhibit the retinal I_h current. The I_h current, closely resembling the cardiac I_f current, is involved in temporally inhibiting retinal responses to bright light stimuli. Under triggering circumstances (e.g., rapid changes in luminosity), partial blockade of I_h by ivabradine may underlie the luminous phenomena experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field (see **Undesirable Effects**).

PHARMACOKINETICS

Ivabradine is rapidly and almost completely absorbed from the gastrointestinal tract after oral administration. Peak plasma concentrations (C_{max}) are reached within 1 hour under fasting conditions. The absolute oral bioavailability of ivabradine is about 40% due to first-pass metabolism. Ivabradine exhibits linear pharmacokinetics over an oral dose range of 0.5 to 24 mg. Food delays the absorption of ivabradine by approximately 1 hour and increases plasma exposure by 20 to 40%. Ivabradine should be taken with food to reduce individual variability in systemic exposure.

Ivabradine is approximately 70% bound to plasma proteins and the volume of distribution at steady state is about 100 L.

Ivabradine is extensively metabolized in the liver and intestines by oxidation through the cytochrome P450 (CYP) 3A4. The major metabolite is the N-desmethylated derivative (S 18982), which is equipotent to ivabradine and circulates at concentrations of approximately 40% that of ivabradine and is also metabolized by CYP3A4. Ivabradine has low affinity for CYP3A4 and does not modify CYP3A4 substrate metabolism or plasma concentrations. Conversely, potent inhibitors or inducers of CYP3A4 may have a significant effect on plasma concentrations of ivabradine.

Ivabradine plasma concentrations decline with a distribution half-life of 2 hours and an effective half-life of approximately 6 hours.

The total clearance of ivabradine is 24 L/hour and the renal clearance is approximately 4.2 L/hour. About 4% of an oral dose is excreted unchanged in urine. The excretion of metabolites occurs to similar extents via feces and urine.

INDICATIONS

• 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.

• Chronic heart failure

Ivabradine is indicated for the treatment of stable chronic heart failure NYHA II to IV class with systolic dysfunction, in adult patients who are in sinus rhythm with heart rate ≥75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

DOSAGE AND MODE OF ADMINISTRATION

General Dosing Recommendations:

• Ivabradine dosage must be individualized according to patient's heart rate response and closely monitored by a physician.
• Ivabradine tablet must be taken orally twice a day (morning and evening) with meals.

	RECOMMENDED ORAL IVABRADINE DOSE
Chronic Stable Angina	**Adult <75 years old** ⇒ Perform serial heart rate measurements, electrocardiogram (ECG) or ambulatory 24-hour monitoring before initiation or titration of treatment. ***Initial Dose:*** 5 mg twice a day ⇒ After 3 to 4 weeks of treatment, if the patient is still symptomatic, if the initial dose is well tolerated and if resting heart rate remains >60 bpm, the dose may be increased to the next higher dose in patients receiving 2.5 mg twice a day or 5 mg twice a day. ***Maintenance Dose:*** Do not exceed 7.5 mg twice a day ⇒ If there is no improvement in symptoms of angina within 3 months after initiating treatment, ivabradine should be discontinued. ⇒ 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 3 months. ⇒ If, during treatment, heart rate decreases <50 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 a day. After dose reduction, heart rate should be monitored. Treatment must be discontinued if heart rate remains <50 bpm or symptoms of bradycardia persist despite dose reduction.
Chronic Heart Failure	**Adult** ⇒ Initiate treatment only in patients with stable heart failure. ***Usual Initial Dose:*** 5 mg twice a day ⇒ After 2 weeks of treatment, assess the patient and adjust the dose to achieve a resting heart rate between 50 and 60 bpm (refer to Table 1). ⇒ At any time during treatment, the dose may be adjusted as needed depending on the heart rate and tolerability of the patient. ***Maximum Dose:*** 7.5 mg twice a day **Table 1. Dose Adjustments of Ivabradine Based on Resting Heart Rate for Adults** **Heart Rate** / **Dose Adjustment** >60 bpm / Increase dose by 2.5 mg twice a day (maximum dose 7.5 mg twice a day) 50-60 bpm / Maintain dose <50 bpm or signs and symptoms of bradycardia (such as dizziness, fatigue or hypotension) / Decrease dose by 2.5 mg twice a day; if current dose is 2.5 mg twice a day, discontinue therapy. ⇒ Discontinuation of treatment should be considered if despite use of the highest dose (7.5 mg twice a day) for several months, there has been no clear decrease in the patient's resting heart rate. The physician should weigh the benefit of continuing treatment against the risks.
Or as prescribed by a doctor.	

Dosage in Elderly Patients (≥75 years old): Lower initial dose of 2.5 mg twice a day should be considered, before increasing if necessary.

Dosage in Patients with Hepatic Impairment: No dosage adjustment is necessary required in patients with mild or moderate hepatic impairment. Ivabradine is contraindicated in patients with severe hepatic impairment.

Dosage in Patients with Renal Impairment: No dosage adjustment is necessary in patients with creatinine clearance of 15 to 60 mL/min. There are no data available in patients with creatinine clearance below 15 mL/min.

CONTRAINDICATIONS

• Hypersensitivity to ivabradine or to any ingredient in the product
• Resting heart rate below 70 beats per minute prior to treatment
• Cardiogenic shock
• Acute myocardial infarction
• Severe hypotension (<90/50 mmHg)
• Severe hepatic impairment
• Sick sinus syndrome
• Sinoatrial block
• Unstable or acute heart failure
• Pacemaker dependence (heart rate imposed exclusively by the pacemaker)
• Unstable angina
• Third degree atrioventricular (AV) block
• Patients with existing prolonged QT interval (e.g., congenital long QT syndrome)
• Concomitant use with strong CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, oral erythromycin, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone
• Concomitant use with moderate CYP3A4 inhibitors with heart reducing properties (e.g., verapamil or diltiazem)
• Pregnancy and lactation

WARNINGS AND PRECAUTIONS

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).

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.

Cardiac Arrhythmias
Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and likely loses its efficacy when a tachyarrhythmia occurs (e.g., ventricular or supraventricular tachycardia). Ivabradine is therefore not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function.

Atrial fibrillation
In patients treated with ivabradine, the risk of developing atrial fibrillation is increased. It is recommended to regularly clinically monitor 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. Discontinue treatment with ivabradine if atrial fibrillation develops.

Atrial fibrillation has been more common in patients using concomitantly amiodarone or potent class I anti-arrhythmics. Concomitant use of ivabradine and amiodarone should be avoided. If combination is deemed necessary, close cardiac monitoring is required.

Bradycardia and Conduction Disturbances
Bradycardia, sinus arrest, and heart block have occurred with ivabradine. The rate of bradycardia was 6% per patient-year in patients treated with ivabradine (2.7% symptomatic; 3.4% asymptomatic) and 1.3% per patient-year in patients treated with placebo. Risk factors for bradycardia include sinus node dysfunction, conduction defects (e.g., first or second degree AV block, bundle branch block), ventricular dyssynchrony, and use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, amiodarone). Bradycardia may increase the risk of QT prolongation which may lead to severe ventricular arrhythmias, including torsade de pointes, especially in patients with risk factors such as use of QTc prolonging drugs.

Concurrent use of verapamil or diltiazem will increase ivabradine exposure, may themselves contribute to heart rate lowering, and should be avoided.

Avoid use of ivabradine in patients with second degree AV block unless a functioning demand pacemaker is present.

If during treatment, the resting heart rate drops below 50 bpm or the patient experiences symptoms related to bradycardia (e.g., dizziness, fatigue or hypotension), the dose must be titrated downward or treatment must be discontinued. Patients should be informed of signs and symptoms of bradycardia and be advised to contact their physician if these occur.

Chronic Heart Failure
Heart failure must be stable, in terms of clinical conditions and medications, before treatment with ivabradine is considered.

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 Hypertensive Patients
Events of blood pressure inadequately controlled were more frequently reported with ivabradine than with placebo (ivabradine 7.1% versus placebo 6.1%). In hypertensive patients requiring ivabradine treatment, monitor blood pressure regularly and reassess treatment of antihypertensive agents.

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

Hepatic Impairment
Caution should be exercised when using ivabradine in patients with mild or moderate hepatic impairment. Ivabradine is contraindicated in patients with severe hepatic impairment (Child-Pugh C) as it has not been studied in this population and an increase in systemic exposure is anticipated.

Renal Impairment
Caution should be exercised when using ivabradine in patients with severe renal impairment (creatinine clearance <15 mL/min) since there is no available data in these patients.

Visual function
Ivabradine influences retinal function. There is no evidence of a toxic effect of long-term ivabradine treatment on the retina. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.

Cardiac Devices
There is limited data in patients with implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) taking ivabradine. If ivabradine treatment is deemed necessary for these patients, caution and close cardiac monitoring is recommended.

Effects on Ability to Drive and Use Machines
Ivabradine may cause transient luminous phenomena consisting mainly of phosphenes. 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.

INTERACTIONS WITH OTHER MEDICAMENTS

CYP3A4 Inhibitors: Concomitant use with potent CYP3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, oral erythromycin, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir), and nefazodone is contraindicated because of substantial increases in ivabradine exposure and risks of excessive bradycardia.
Concomitant use of ivabradine with moderate CYP3A4 inhibitors with their own heart rate reducing properties (i.e., diltiazem or verapamil) is also contraindicated because of increased ivabradine exposure and additive effects on heart rate. Concomitant use with other moderate CYP3A4 inhibitors (e.g., fluconazole) may be considered at the starting dose of 2.5 mg twice a day and if resting heart rate is above 70 bpm, with monitoring of heart rate.
CYP3A4 Inducers (e.g., St. John's Wort, rifampicin, barbiturates, phenytoin): Concomitant use with a CYP3A4 inducer may decrease ivabradine exposure. Ivabradine may be initiated and titrated with the usual recommended doses. Close heart rate monitoring is recommended if treatment with the CYP3A4 inducer needs to be interrupted, ivabradine dosing may need to be reduced.
QT Prolonging Agents: Concomitant use with cardiovascular QT prolonging agents (e.g., quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone) and non-cardiovascular QT prolonging agents (e.g., pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, intravenous erythromycin) should be avoided since QT prolongation may be exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring (12-lead ECG) is required.
Negative Chronotropes: Concomitant use with drugs that slow heart rate (e.g., digoxin, beta-blockers) increases the risk of bradycardia. Monitor patients taking ivabradine with other negative chronotropes.
Potassium-depleting Diuretics (e.g., furosemide, hydrochlorothiazide, indapamide): Hypokalemia can increase the risk of arrhythmia. As ivabradine may cause bradycardia, the resulting combination of hypokalemia and bradycardia is a predisposing factor to the onset of severe arrhythmias, especially in patients with long QT syndrome, whether congenital or substance-induced.
Grapefruit Juice: Coadministration with grapefruit juice increased ivabradine exposure by 2-fold. Therefore, grapefruit juice should be avoided during treatment with ivabradine.
Other Drugs: Coadministration of ivabradine did not result in a clinically significant interaction with proton pump inhibitors (omeprazole, lansoprazole), sildenafil, HMG-CoA reductase inhibitors (simvastatin), dihydropyridine calcium channel blockers (amlodipine, lacidipine), aspirin, and warfarin.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: There are no adequate and well-controlled studies of ivabradine in pregnant women. However, embryo-fetal toxicity and cardiac teratogenic effects were observed in fetuses of pregnant rats treated during organogenesis at exposures 1 to 3 times the human exposures ($AUC_{0\text{-}24hr}$) at the maximum recommended human dose (MRHD). Therefore, ivabradine is contraindicated during pregnancy.

Lactation: It is not known if ivabradine is distributed in human milk. However, animal studies have shown that ivabradine is distributed into milk in rats. Therefore, ivabradine is contraindicated during breastfeeding.

Elderly: Ivabradine has only been studied in a limited number of patients ≥75 years of age. A lower starting dose is recommended in these patients.

Children: The safety and efficacy of ivabradine in pediatric patients below 18 years of age have not been established.

UNDESIRABLE EFFECTS

The most frequently reported adverse effects with ivabradine include luminous phenomena (phosphenes) and bradycardia. These adverse effects are dose-dependent and related to the pharmacological effect of the drug. The luminous phenomena (phosphenes) reported with ivabradine are described as a transiently enhanced brightness in a limited area of visual field, halos, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency). Phosphenes generally become apparent within the first 2 months of treatment and are described as intermittent events triggered by sudden variations in light intensity. These events are of mild to moderate intensity and resolve spontaneously during treatment or are reversible after discontinuation of treatment.

Blood and lymphatic system disorders: Eosinophilia
Metabolism and nutrition disorders: Hyperuricemia, hypokalemia
Nervous system disorders: Dizziness, headache (generally during the first month of treatment), syncope, transient ischemic attack
Eye disorders: Blurred vision, diplopia, photophobia, visual brightness, visual color distortions, visual disturbance, visual impairment
Ear and labyrinth disorders: Vertigo, positional vertigo, tinnitus
Cardiac disorders: Acute myocardial infarction/myocardial infarction, atrial fibrillation, atrial flutter, AV block (second and third degree), bundle branch block (left, right, bilateral), cardiac arrhythmias, cardiac valve incompetency, first degree AV block (ECG prolonged PQ interval), palpitations, sick sinus syndrome, sinus bradycardia, sinoatrial block, supraventricular extrasystoles, torsade de pointes, ventricular extrasystoles, ventricular fibrillation, ventricular tachycardia
Vascular disorders: Hypertension, hypotension, intermittent claudication, orthostatic hypotension, inadequately controlled blood pressure
Respiratory, thoracic and mediastinal disorders: Dyspnea
Gastrointestinal disorders: Abdominal pain, constipation, diarrhea, nausea
Skin and subcutaneous tissue disorders: Angioedema, erythema, pruritus, rash, urticaria
Musculoskeletal and connective tissue disorders: Arthralgia, muscle cramps, muscle spasms
General disorders and administration site conditions: Asthenia, fatigue, malaise, peripheral coldness, sudden cardiac death
Investigations: ECG prolonged QT interval, elevated blood creatinine, decreased heart rate (asymptomatic bradycardia)

OVERDOSE AND TREATMENT

Overdose with ivabradine may lead to severe and prolonged bradycardia. Severe bradycardia should be treated symptomatically in a specialized environment. In the event of bradycardia with poor hemodynamic tolerance, temporary cardiac pacing may be required. Supportive treatment, including intravenous fluids, atropine, and intravenous agents such as isoproterenol, may be considered.

STORAGE CONDITIONS

Store at temperatures not exceeding 30°C.
Keep the product out of reach and sight of children.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at +632-8-**UNILAB**-1 (+632-8-**864522**-1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

AVAILABILITY

Ivabradine (Valheart®) 5 mg Film-Coated Tablet, In Blister Pack of 14's (Box of 56's)
Ivabradine (Valheart®) 7.5 mg Film-Coated Tablet, In Blister Pack of 14's (Box of 56's)

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Trusted Quality Healthcare

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Ivabradine (Valheart®) 5 mg Film-Coated Tablet: DRP-11478
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