# IVACARD™

(As per Innovator's Specification)

## Ivabradine HCl

(Manufacturer Specification)

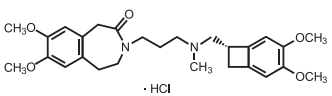
**5**mg & **7.5**mg Film Coated Tablets

**COMPOSITION**

**IVACARD** 5 mg Tablet
Each film coated tablet contains:
Ivabradine as Hydrochloride ..... 5mg
(As per Innovator's Specification)
**IVACARD** 7.5 mg Tablet
Each film coated tablet contains:
Ivabradine as Hydrochloride ..... 7.5mg
(As per Innovator's Specification)

**DESCRIPTION**

**IACARD** (Ivabradine HCl) is a heart rate lowering agent which acts by selective inhibition of the cardiac pacemaker If current. Chemically, Ivabradine HCl is 3-(3-[[((7S)-3,4-Dimethoxybicyclo [4,2,0] octa-1,3,5-trien-7-yl] methyl] methylamino) propyl)-1,3,4,5-tetrahydro7,8-dimethoxy-2H-3-benzazepin-2-one hydrochloride. Its molecular formula is $C_{27}H_{36}N_2O_5$.HCl and the structural formula is:




Ivabradine Hydrochloride

**CLINICAL PHARMACOLOGY**

**Therapeutic Indications:**

**IVACARD** (Ivabradine HCl) is indicated for treatment of:

*Coronary Artery Disease (CAD):*

Symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm, who are unable to tolerate or have a contraindication to beta blockers, or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose and whose heart rate is > 60 bpm.

*Chronic Heart Failure (CHF):*

Symptomatic treatment of chronic heart failure of NYHA Classes II or III and with documented left ventricular ejection fraction (LVEF) ≤ 35% in adult patients in sinus rhythm and with heart rate at or above 77 bpm, in combination with optimal standard chronic heart failure treatment.

**DOSAGE AND ADMINISTRATION**

**IVACARD** (Ivabradine HCl) Tablets must be taken orally twice daily. i.e., once in the morning and once in the evening during meals.

**Treatment of Coronary Artery Disease (CAD):**

The usual recommended starting dose of Ivabradine HCl is 5mg twice daily. After three to four weeks of treatment, the dose may be increased to 7.5mg twice daily depending on the therapeutic response. If, during treatment, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward including the possible dose of 2.5mg twice daily (one half 5mg tablet twice daily). Treatment must be discontinued if heart rate below 50bpm or symptoms of bradycardia persist.

**Treatment of Chronic Heart Failure (CHF):**

The treatment has to be initiated only in patients with stable heart failure. The usual recommended starting dose of Ivabradine HCl is 5mg twice daily. After two weeks of treatment, the dose can be increased to 7.5mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5mg twice daily (one half 5mg tablet twice daily) if resting heart rate is persistently below 50bpm or in case of symptoms related to bradycardia. If heart rate is between 50bpm and 60 bpm, the dose of 5mg twice daily should be maintained. If during treatment, heart rate decreases persistently below 50 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 7.5mg twice daily or 5mg twice daily. If heart rate increases persistently above 60 bpm at rest, the dose can be titrated to the next upper dose in patients receiving 2.5mg twice daily or 5mg twice daily. Treatment must be discontinued if heart rate remains below 50bpm or symptoms of bradycardia persist.

**DRUG INTERACTIONS**

**Drug Interactions Concomitant use with Cytochrome P450 3A4 (CYP3A4) inhibitor or inducers:** CYP3A4 inhibitors increase Ivabradine HCl plasma concentrations, while inducers decrease them. Increased plasma concentrations of Ivabradine HCl may be associated with a risk of excessive bradycardia.

**Moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil) with heart rate reducing properties:** Concomitant use of Ivabradine HCl with diltiazem and verapamil is not recommended due to the potential for additive heart rate lowering effects.

**Other moderate CYP3A4 inhibitors:** Ivabradine HCl can be used with caution if resting heart rate is at or above 60 bpm and heart rate is carefully monitored.

**Grapefruit Juice:** Grapefruit juice increase Ivabradine HCl exposure. Therefore, the intake of grapefruit juice should be restricted during the treatment with Ivabradine HCl.

**CYP3A4 inducers (e.g., rifampicin, barbiturates, phenytoin, St John's Wort):** Prolonged concomitant administration of these agents with Ivabradine HCl may decrease Ivabradine HCl exposure and therefore require an adjustment of dose depending upon the therapeutic response.

**Concomitant use with QT-prolonging medicines:** The concomitant use of cardiovascular (e.g., quinidine, disopyramide, sotalol, amiodarone) or non-cardiovascular (e.g., tricyclic antidepressants, antipsychotics, erythromycin IV, pentamidine, pimozide, mefloquine) QT prolonging medicines with Ivabradine HCl should be avoided since QT prolongation may be exacerbated by heart rate reduction. If combination appears necessary, close cardiac monitoring is needed.

**Concomitant use with Potassium-depleting diuretics:** Hypokalemia can increase the risk of arrhythmia. As Ivabradine HCl 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.

**PREGNANCY**

Pregnancy Category X: Contraindicated in pregnancy.

**LACTATION**

Contraindicated in lactation.

**PEDIATRIC DOSE**

**Pediatric patients less than 40 kg:**

*Starting dose:*

0.05 mg/kg twice daily with food.
Adjust dose at two-week intervals by 0.05 mg/kg based on heart rate.

*Maximum dose:*

0.2 mg/kg (patients 6 months to less than 1 year old)
0.3 mg/kg (patients 1 year old and older),
up to a total of 7.5 mg twice daily.

**Pediatric patients greater than 40 kg:**

*Starting dose:*

2.5 mg twice daily with food.

Adjust dose after two weeks of treatment based on heart rate.
*Maximum dose:*
7.5 mg twice daily.
**Geriatric use:**
Special Population Elderly Patients ≥ 75 years A lower starting dose should be considered for these patients (2.5mg twice daily i.e., one half 5mg tablet twice daily) before up-titration if necessary. Children The safety and efficacy of Ivabradine HCl in children aged below 18 years have not been established.

**ADVERSE REACTIONS**
The most common adverse effects seen with Ivabradine HCl are luminous phenomena in the visual field (Phosphenes). Other adverse reactions include blurred vision, bradycardia, which may be severe and other cardiac arrhythmias, nausea, constipation, diarrhea, headache, dizziness, dyspnea and muscle cramps. Hyperuricemia, eosinophilia and elevated blood creatinine concentrations have been reported.

**CLINICAL PHARMACOLOGY**
**Mechanism of Action:**
Ivabradine HCl is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker If current that controls the spontaneous diastolic depolarization 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 repolarization.
**Pharmacokinetics:**
*Absorption:*
Ivabradine HCl is rapidly and almost completely absorbed after oral administration with peak plasma levels reached in about 1 hour under fasting condition. The absolute bioavailability is around 40%, due to first-pass effect in the gut and liver.
*Effect of Food:*
Food delays the absorption of Ivabradine HCl by approximately 1 hour and increases plasma exposure by 20% to 30%. It is recommended to take the tablets during meals.
*Distribution:*
Ivabradine HCl is approximately 70% plasma protein bound and the volume of distribution at steady state is close to 100 liters.
*Metabolism:*
Ivabradine HCl undergoes extensive metabolism in the liver and gut via the cytochrome P450 isoenzyme CYP3A4 to its main active metabolite N-desmethyl-ivabradine. This is further metabolized to some degree by CYP3A4.
*Excretion:*
The main elimination half-life of Ivabradine HCl is 2 hours in plasma and an effective half-life is 11 hours. The total clearance is about 400mL/min and the renal clearance is about 70mL/min. Metabolites are equally excreted in the feces and urine. About 4% of an oral dose is excreted unchanged in urine.
*Hepatic Impairment:*
In patients with mild hepatic impairment (Child Pugh score up to 7) unbound AUC of Ivabradine HCl and the main active metabolite were about 20% higher in patients with normal hepatic function

**OVERDOSAGE**
**Symptoms:**
Overdosage may lead to severe and prolonged bradycardia.
**Treatment:**
Sever bradycardia should be treated symptomatically in a specialized environment. In the event of bradycardia with poor hemodynamic tolerance, symptomatic treatment including intravenous betastimulating medicinal products such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.

**STORAGE**
Store below 30°C. Protect from light and moisture.
The expiration date refers to the product correctly stored at the required conditions.

**HOW SUPPLIED**
**IVACARD** (Ivabradine HCl) Tablets: 5mg are available in blister packs of 14's.
**IVACARD** (Ivabradine HCl) Tablets: 7.5mg are available in blister packs of 14's.

**TO BE SOLD ON THE PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY.**

**KEEP ALL MEDICINES OUT OF THE REACH OF CHILDREN.**

**PLEASE READ THE CONTENTS CAREFULLY BEFORE USE.**

**THIS PACKAGE INSERT IS CONTINUALLY UPDATED FROM TIME TO TIME.**

Lactose & Gluten Free

# آئیوا کارڈ

(آئیوابراڈین ہائیڈروکلورائیڈ)

5ملی گرام اور 7.5ملی گرام

فلم کوٹڈ گولیاں

## خوراک وہدایات

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 30°C سے کم درجہ حرارت پر، نمی اور روشنی سے محفوظ رکھیں۔

NEXT PHARMACEUTICAL
Manufactured by:
**NEXT Pharmaceutical Products (Pvt.) Ltd.**
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