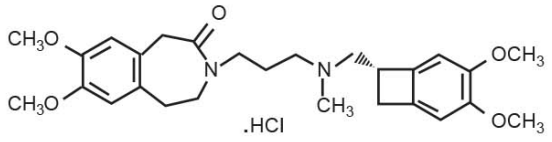
Sivab™
[IVABRADINE]

سِیویب

Film-Coated Tablet 5mg & 7.5mg

DESCRIPTION
Sivab (Ivabradine) is a heart rate lowering agent which acts by selective inhibition of the cardiac pacemaker I_f current. Chemically, Ivabradine hydrochloride is 3-(3-{[((7S)-3,4-Dimethoxybicyclo[4,2,0] octa-1,3,5-trien-7-yl]methyl]methylamino}propyl)-1,3,4,5-tetrahydro-7,8-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

QUALITATIVE & QUANTITATIVE COMPOSITION
Sivab (Ivabradine) is available for oral administration as:

Sivab Tablets 5mg
Each film-coated tablet contains:
Ivabradine Hydrochloride equivalent to Ivabradine…5mg

Sivab Tablets 7.5mg
Each film-coated tablet contains:
Ivabradine Hydrochloride equivalent to Ivabradine…7.5mg

CLINICAL PHARMACOLOGY
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 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 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 by approximately 1 hour and increases plasma exposure by 20% to 30%. It is recommended to take the tablets during meals.

Distribution
Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady state is close to 100 liters.

Metabolism
Ivabradine 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 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.

Special Population
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 in patients with normal hepatic function.

THERAPEUTIC INDICATIONS
Sivab (Ivabradine) Tablets are indicated for the treatment of:

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

Treatment of Coronory Artery Disease (CAD)
The usual recommended starting dose of ivabradine 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 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.

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 in children aged below 18 years have not been established.

ADVERSE REACTIONS
The most common adverse effects seen with ivabradine 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.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS
Ivabradine is contraindicated in patients with:
- Hypersensitivity to ivabradine or to any of the excipient of the product
- Resting heart rate below 60 bpm prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (< 90/50 mm/Hg)
- Severe hepatic impairment
- Sick sinus syndrome
- Sino-atrial block
- Unstable or acute heart failure
- Pacemaker dependent
- Unstable angina
- AV-block 3rd degree
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin, josamycin, telithomycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone.
- Pregnancy, nursing mothers and women of child-bearing potential not using appropriate contraceptive measure.

PRECAUTIONS

- *Cardiac arrhythmias:*
  Ivabradine is not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function. It is recommended to regularly clinically monitor ivabradine treated patients for the occurrence of atrial fibrillation which should also include ECG monitoring if clinically indicated. The risk of developing atrial fibrillation may be higher in chronic heart failure patients treated with ivabradine. Chronic heart failure patients with intraventricular conduction defects and ventricular dyssynchrony should be monitored closely.
- *AV-block of 2nd degree:*
  Ivabradine is not recommended in patients with AV-block of 2nd degree.
- *Low heart rate:*
  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.
- *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.
- *Stroke:*
  The use of ivabradine is not recommended immediately after a stroke.
- *Visual function:*
  Ivabradine influences on retinal function. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.
- *Hypotension:*
  Ivabradine should be used with caution in patients with mild to moderate hypotension
- *Hypertensive patients requiring blood pressure treatment modifications:*
  When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval.
- *Patient with hepatic impairment:*
  Caution should be exercised when using ivabradine in patients with moderate hepatic impairment.

DRUG INTERACTIONS

Concomitant use with Cytochrome P450 3A4 (CYP3A4) inhibitor or inducers:
CYP3A4 inhibitors increase ivabradine plasma concentrations, while inducers decrease them. Increased plasma concentrations of ivabradine 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 with diltiazem and verapamil is not recommended due to the potential for additive heart rate lowering effects.
- *Other moderate CYP3A4 inhibitors:*
  Ivabradine 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 exposure. Therefore, the intake of grapefruit juice should be restricted during the treatment with ivabradine.
- *CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, St John's Wort):*
  Prolonged concomitant administration of these agents with ivabradine may decrease ivabradine 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 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 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.

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 beta-stimulating medicinal products such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.

HOW SUPPLIED

Sivab (Ivabradine) Tablets 5mg are available in blister packs of 14's and 28's.
Sivab (Ivabradine) Tablets 7.5mg are available in blister pack of 14's.

STORAGE

Store at 25°C (Excursions permitted between 15°C to 30°C). Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

Keep out of reach of children

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
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Getz pharma (PVT) LIMITED
www.getzpharma.com
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