IVATAB Tablets

(Ivabradine Hydrochloride)

ایواٹیب گولیاں

(ایوابراڈین ہائیڈروکلورائیڈ)

COMPOSITION:
Each film coated tablet contains:
Ivabradine Hydrochloride eq. to Ivabradine ... 5mg or 7.5mg. [Mfg. Specs. NQ.]

PHARMACOLOGICAL PROPERTIES: Mechanism of action: Ivabradine is a pure heart rate lowering agent, acts 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. 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.

Pharmacokinetics: Under physiological conditions, Ivabradine is rapidly released from tablets and is highly water soluble (>10mg/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 delays absorption by approximately 1 hour, and increases plasma exposure by 20 to 30%. The intake of the tablet during meals is recommended in order to decrease intra-individual variability in exposure.
Distribution: Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady state is close to 100 Litres in patients.
Biotransformation: Ivabradine is extensively metabolized 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.
Elimination: Ivabradine is eliminated with a main half life of 2 hours in plasma and an effective half life of 11 hours. The total clearance is about 400ml/min and the renal clearance is about 70ml/min.

SPECIAL POPULATIONS: Elderly: No pharmacokinetic differences (AUC and C_{max}) have been observed between elderly (65 years) or very elderly patients (75 years) and the overall population.
Renal insufficiency: The impact of renal impairment (creatinine clearance from 15 to 60ml/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).
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.

INDICATIONS: Treatment of coronary artery disease: Symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm. **IVATAB Tablet** (Ivabradine) is indicated in adults unable to tolerate or with a contra-indication to the use of β-blockers or in combination with β-blockers in patients inadequately controlled with an optimal β-blocker dose and whose heart rate is >60bpm.

Treatment of chronic heart failure: IVATAB Tablet (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 ≥75bpm, in combination with standard therapy including β-blocker therapy or when β-blocker therapy is contra-indicated or not tolerated.

CONTRA-INDICATIONS: Hypersensitivity to the active substance or to any of the excipients; Resting heart rate below 60 bpm prior to treatment; Cardiogenic shock; Acute myocardial infarction; Severe hypotension (<90/50mmHg); 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.

POSOLOGY AND METHOD OF ADMINISTRATION: IVATAB Tablet (Ivabradine) must be taken orally twice daily, i.e. once in the morning and once in the evening during meals. The usual recommended starting dose of **IVATAB Tablet** (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 50bpm at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the possible dose of 2.5mg twice daily (half 5mg tablet twice daily). Treatment must be discontinued if heart rate below 50bpm or symptoms of bradycardia persist.
Special population: Ederly: In patients aged 75 years or more, a lower starting dose should be considered for these patients (2.5mg twice daily i.e. half 5mg tablet twice daily) before up-titration if necessary.
Pediatric population: The safety and efficacy of **IVATAB Tablet** (Ivabradine) in children aged below 18 years have not yet been established.

OVERDOSE: Overdose may lead to severe and prolonged bradycardia. Symptomatic treatment and temporary cardiac electrical pacing may be instituted if required.

SPECIAL WARNINGS: 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. 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.

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Use in patients with a low heart rate: Ivabradine must not be initiated in patients with a pre-treatment resting heart rate below 60bpm. The dose must be titrated downward or treatment discontinued if resting heart rate below 50bpm or symptoms of bradycardia persist.
Combination with calcium channel blockers: Concomitant use of Ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is not recommended. No safety issue has been raised on the combination of Ivabradine with nitrates and dihydropyridine calcium channel blockers such as amlodipine.
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 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.

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 contra-indicated in patients with severe hypotension (blood pressure < 90/50mmHg).
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.
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. If the combination appears necessary, close cardiac monitoring is needed.

INTERACTIONS: Pharmacodynamic interactions: Concomitant use not recommended: QT prolonging medicinal products; Cardiovascular QT prolonging medicinal 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.

Pharmacokinetic interactions: Cytochrome P450 3A4 (CYP3A4): Ivabradine is metabolized 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.
Contra-indication 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 contra-indicated. The potent CYP3A4 inhibitors ketoconazole (200mg once daily) and josamycin (1g twice daily) increased Ivabradine mean plasma exposure by 7 to 8 fold.
Concomitant use not recommended: 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 5bpm. The concomitant use of Ivabradine with these medicinal products is not recommended.
Concomitant use with precautions:
(1) Moderate CYP3A4 inhibitors: the concomitant use of Ivabradine with other moderate CYP3A4 inhibitors (e.g. fluconazole) may be considered at the starting dose of 2.5mg twice daily and if resting heart rate is above 60bpm, with monitoring of heart rate. (2) Grapefruit juice: Ivabradine exposure was increased by 2 fold following the co-administration with grapefruit juice. Therefore the intake of grapefruit juice should be restricted during the treatment with Ivabradine. (3) 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 10mg 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.

PREGNANCY AND LACTATION: Studies in animals have shown reproductive toxicity. Therefore, Ivabradine is contra-indicated during pregnancy.
Breastfeeding: Animal studies indicate that Ivabradine is excreted in milk. Therefore, Ivabradine is contra-indicated during breast feeding.

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.

UNDESIRABLE EFFECTS: The most common adverse reactions with Ivabradine, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product.

INSTRUCTIONS: Store below 30°C. Protect from light and moisture. Keep out of the reach of children.

PRESENTATION: IVATAB 5mg Tablets are available in pack size of 28's.
IVATAB 7.5mgTablets are available in pack size of 14's.

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔ ہدایات: ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔ گرمی، روشنی اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

PHARMA
Manufactured by:
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