IVADIN
(IVABRADINE)

آئیواڈِن

COMPOSITION

Ivabradine 5mg
Each film coated tablet contains
5mg Ivabradine equivalent to 5.39mg Ivabradine as hydrochloride.
Ivabradine 7.5mg
Each film coated tablet contains
7.5mg Ivabradine equivalent to 8.085mg Ivabradine as hydrochloride.
(As per innovator's Specs.)

DESCRIPTION

Ivadin contains Ivabradine which is a hyperpolarization-activated cyclic nucleotide-gated channel blocker that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the If-current (If), resulting in heart rate reduction with no effect on ventricular repolarization and no effects on myocardial contractility. The chemical name for Ivabradine is 3-(3-{[(7S)-3,4-Dimethoxybicyclo[4.2.0]octa-1,3,5-trien-7-yl)methyl] Tmethyl amino} propyl)-1,3,4,5-tetrahydro-7,8-dimethoxy-2H-3-benzazepin-2-one, hydrochloride. The molecular formula is $C_{27}H_{36}N_2O_5$, HCl.

CLINICAL PHARMACOLOGY

Mechanism of Action
Ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker If current, which regulates heart rate.
The cardiac effects are most pronounced in the sinoatrial (SA) node, but prolongation of the AH interval occurrs on the surface ECG, as has PR interval prolongation. There is no effect on ventricular the retinal current I_h: I_h is involved in curtailing retinal responses to bright light stimuli. Under repolarization and no effects on myocardial contractility. Ivabradine can also inhibit triggering circumstances (e.g., rapid changes in luminosity), partial inhibition 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.
Pharmacodynamics
Ivabradine causes a dose-dependent reduction in heart rate. The size of the effect is dependent on the baseline heart rate (i.e., greater heart rate reduction occurs in subjects with higher baseline heart rate). At recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. Analysis of heart rate reduction vs. dose indicates a plateau effect at doses > 20 mg twice daily.
Ivabradine does not have negative inotropic effects. Ivabradine increases the uncorrected QT interval with heart rate slowing but does not cause rate-corrected prolongation of QT.
Pharmacokinetics
Absorption
Following oral administration, peak plasma Ivabradine concentrations are reached in approximately 1 hour under fasting conditions. The absolute oral bioavailability of Ivabradine is approximately 40% because of first-pass elimination in the gut and liver. Food delays absorption by approximately 1 hour and increases plasma exposure by 20% to 40%. Ivabradine should be taken with meals.
Ivabradine is approximately 70% plasma protein bound, and the volume of distribution at steady state is approximately 100 L.
Distribution
Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady state is close to 100 l in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5 mg twice daily is 22 ng/ml (CV=29%). The average plasma concentration is 10 ng/ml (CV=38%) at steady state.
Metabolism
The pharmacokinetics of Ivabradine are linear over an oral dose range of 0.5 mg to 24 mg. Ivabradine is extensively metabolized in the liver and intestines by CYP3A4-mediated oxidation. The major metabolite is the N-desmethylated derivative (S 18982), which is equipotent to Ivabradine and circulates at concentrations approximately 40% that of Ivabradine. The N desmethylated derivative is also metabolized by CYP3A4. Ivabradine plasma levels decline with a distribution half-life of 2 hours and an effective half-life of approximately 6 hours.
Elimination
The total clearance of Ivabradine is 24 L/h, and renal clearance is approximately 4.2 L/h, with ~
4% of an oral dose excreted unchanged in urine. The excretion of metabolites occurs to a similar extent via feces and urine.

Pharmacokinetics in special populations
Elderly
No pharmacokinetic differences (AUC or Cmax) have been observed between elderly (≥ 65 years) or very elderly (≥ 75 years) patients and younger patients.

Hepatic Impairment
In patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment, the pharmacokinetics of Ivabradine are similar to that in patients with normal hepatic function. No data are available in patients with severe hepatic impairment (Child-Pugh C).
Renal Impairment
Renal impairment (creatinine clearance from 15 to 60 mL/min) has minimal effect on the pharmacokinetics of Ivabradine. No data are available for patients with creatinine clearance below 15 mL/min.
Pediatrics
The pharmacokinetics of Ivabradine has not been investigated in patients < 18 years of age.

INDICATIONS

Ivabradine is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

DOSAGE AND ADMINISTRATION

Adult dosage
The recommended starting dose of Ivabradine is 5 mg twice daily with meals. Assess patient after two weeks and adjust dose to achieve a resting heart rate between 50 and 60 beats per minute (bpm) as shown in the table below. Thereafter, adjust dose as needed based on resting heart rate and tolerability. The maximum dose is 7.5 mg twice daily.

Heart Rate	Dose Adjustment
> 60 bpm	Increase dose by 2.5 mg (given twice daily) up to a maximum dose of 7.5 mg twice daily
50-60 bpm	Maintain dose
< 50 bpm or signs and symptoms of bradycardia	Decrease dose by 2.5 mg (given twice daily); if current dose is 2.5 mg twice daily, discontinue therapy

CONTRAINDICATIONS

Ivabradine is contraindicated in patients with:
• Acute decompensated heart failure
• Blood pressure less than 90/50 mmHg
• Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand
• Resting heart rate less than 60 bpm prior to treatment
• Severe hepatic impairment
• Pacemaker dependence (heart rate maintained exclusively by the pacemaker)
• Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors

WARNING AND PRECAUTIONS

Fetal Toxicity
Ivabradine may cause fetal toxicity when administered to a pregnant woman. Use of effective contraception is advised while using Ivabradine for women of child bearing potential.
Atrial Fibrillation
Ivabradine increases the risk of atrial fibrillation. Regularly monitor cardiac rhythm. Discontinue Ivabradine if atrial fibrillation develops.
Bradycardia and Conduction Disturbances
Bradycardia, sinus arrest, and heart block may occur with Ivabradine. Risk factors for bradycardia include sinus node dysfunction, conduction defects (e.g., 1st or 2nd degree atrioventricular 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 2nd degree atrioventricular block, unless a functioning demand pacemaker is present.
Visual function
Ivabradine influences retinal function. Caution should be exercised in patients with retinitis pigmentosa.
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. Ivabradine has no influence on the ability to use machines.

ADVERSE REACTIONS

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
Uncommon: Diplopia, Visual impairment
Ear and labyrinth disorders
Uncommon: Vertigo
Cardiac disorders
Common: Bradycardia, AV 1st degree block (ECG prolonged PQ interval), Ventricular extrasystoles, Atrial fibrillation
Uncommon: Palpitations, supraventricular extrasystoles
Very rare: AV 2nd degree block, AV 3rd degree block, Sick sinus syndrome
Vascular disorders
Common: Uncontrolled blood pressure
Uncommon: Hypotension, possibly related to bradycardia
Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea
Gastrointestinal disorders
Uncommon: Nausea, Constipation, Diarrhoea, Abdominal pain
Skin and subcutaneous tissue disorders
Uncommon: Angioedema, Rash
Rare: Erythema, Pruritus, Urticaria
Musculoskeletal and connective tissue disorders
Uncommon: Muscle spasms
General disorders and administration site conditions
Uncommon: Asthenia and fatigue possibly related to bradycardia
Rare: Malaise, possibly related to bradycardia

DRUG INTERACTIONS

Cytochrome P450-Based Interactions
Ivabradine is primarily metabolized by CYP3A4. Concomitant use of CYP3A4 inhibitors increases Ivabradine plasma concentrations, and use of CYP3A4 inducers decreases them. Increased plasma concentrations may exacerbate bradycardia and conduction disturbances. The concomitant use of strong CYP3A4 inhibitors is contraindicated. Examples of strong CYP3A4 inhibitors include azole antifungals (e.g., itraconazole), macrolide antibiotics (e.g., clarithromycin, telithromycin), HIV protease inhibitors (e.g., nelfinavir), and nefazodone.
Avoid concomitant use of moderate CYP3A4 inhibitors when using Ivabradine. Examples of moderate CYP3A4 inhibitors include diltiazem, verapamil, and grapefruit juice.
Negative Chronotropes
Most patients receiving Ivabradine will also be treated with a beta-blocker. The risk of bradycardia increases with concomitant administration of drugs that slow heart rate (e.g., digoxin, amiodarone, beta-blockers). Monitor heart rate in patients taking Ivabradine with other negative chronotropes. Concomitant use of Ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is contraindicated.
Pacemakers
Ivabradine dosing is based on heart rate reduction, targeting a heart rate of 50 to 60 beats per minute. The use of Ivabradine is not recommended in patients with demand pacemakers set to rates ≥ 60 beats per minute.
Interaction with QT prolongation products
The concomitant use of cardiovascular (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone 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
Use of Grapefruit juice
Grapefruit juice may increase the concentrations of Ivabradine hence it is advised to not take grapefruit juice when using Ivabradine

USE IN SPECIAL POPULATIONS

Pregnancy
There are no adequate and well-controlled studies of Ivabradine in pregnant women to inform any drug-associated risks. Advise a pregnant woman of the potential risk to the fetus.
Disease-associated maternal and/or embryo/fetal risk
Stroke volume and heart rate increase during pregnancy, increasing cardiac output, especially during the first trimester. Pregnant patients with left ventricular ejection fraction less than
35% on maximally tolerated doses of beta-blockers may be particularly heart-rate dependent for augmenting cardiac output. Therefore, pregnant patients who are started on Ivabradine, especially during the first trimester, should be followed closely for destabilization of their congestive heart failure that could result from heart rate slowing.
Monitor pregnant women with chronic heart failure in 3rd trimester of pregnancy for preterm birth.
Nursing mother
There is no information regarding the presence of Ivabradine in human milk, the effects of Ivabradine on the breastfed infant, or the effects of the drug on milk production. Because of the potential risk to breastfed infants from exposure to Ivabradine, breastfeeding is not recommended.
Pediatrics
Safety and effectiveness in pediatric patients have not been established.
Elderly
No pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients.
Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment while caution is advised for use in patients with moderate hepatic impairment. Ivabradine is contraindicated in patients with severe hepatic impairment (Child-Pugh C) as no data is available and an increase in systemic exposure is anticipated.
Renal impairment
No dosage adjustment is required for patients with creatinine clearance greater than 15 mL/min. No data are available for patients with creatinine clearance below 15 mL/min.

OVER DOSAGE
Overdose may lead to severe and prolonged bradycardia which should be treated symptomatically. In the event of bradycardia with poor hemodynamic tolerance, temporary cardiac pacing may be required. Supportive treatment including intravenous (IV) fluids, atropine, and IV beta-stimulating agents such as isoproterenol may be considered.

PRESENTATION
Ivabradine 5mg : Pack of 14's tablets.
Ivabradine 7.5mg : Pack of 14's tablets.

INSTRUCTIONS
Use as advised by the physician.
Keep all medicines out of the reach of children.
To be sold on the prescription of a registered medical practitioner only.
Protect from light, heat and moisture.
Store below 30°C.
For suspected adverse drug reaction, report at
pharmacovigilance@pharmevo.biz

For more information on our products
call PharmAssist helpline 0800-82222
Monday to Friday 9:00 am to 6:00 pm
or email us at : pharmassist@pharmevo.biz

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Industrial Zone, Port Qasim,
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