Ivaset®

(Ivabradine)

Highnoon

COMPOSITION
Ivaset 5mg Tablet:
Each film-coated tablet contains: Ivabradine (as HCl) 5mg
Ivaset 7.5mg Tablet:
Each film-coated tablet contains: Ivabradine (as HCl) 7.5mg

DESCRIPTION
Ivabradine is a pure heart rate lowering agent, a selective and specific inhibitor of the cardiac pacemaker I_f current that regulates heart rate.

MECHANISM OF ACTION
Ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker I_f current, which regulates heart rate. Studies indicate cardiac effects to be most pronounced in the sinoatrial (SA) node, but prolongation of the AH interval and PR interval prolongation were also noted. There was no effect on ventricular repolarization and no effects on myocardial contractility.
It can also inhibit the retinal current I_h which closely resembles cardiac I_f. Under triggering circumstances (e.g., rapid changes in luminosity), partial inhibition of I_h by Ivabradine underlies the luminous phenomena experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field.

PHARMACOKINETICS
Ivabradine is almost completely absorbed after oral doses, but bioavailability is about 40% because of first-pass metabolism. Peak plasma concentrations occur after 1 hour in the fasting state, but this is delayed by 1 hour by food and the extent of absorption increased by 20 to 30%. Ivabradine is about 75% bound to plasma proteins. Ivabradine undergoes extensive metabolism in the liver and gut via the cytochrome P450 isoenzyme CYP3A4 to its main active metabolite N-desmethyl- ivabradine (S-18982). This is further metabolized to some degree by CYP3A4. Ivabradine has a plasma elimination half- life of 2 hours and an effective half-life of 11 hours. Its metabolites are excreted to a similar extent in the urine and faeces. About 4% of dose appears in the urine as the parent drug. Animal studies indicate that Ivabradine is distributed into the breast milk.

INDICATIONS
- Reduce the risk of hospitalization for worsening heart failure in adult 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.
- Treatment of stable symptomatic heart failure due to dilated cardiomyopathy (DCM) in paediatric patients aged 6 months and older, who are in sinus rhythm with an elevated heart rate.

DOSAGE AND ADMINISTRATION
The recommended starting dose of Ivabradine is 5 mg twice daily with food. Assess patient after two weeks and adjust dose to achieve a resting heart rate between 50 and 60 beats per minute (bpm). Thereafter, adjust dose as needed based on resting heart rate and tolerability. The maximum dose is 7.5 mg twice daily.
In patients with a history of conduction defects or other patients in whom bradycardia could lead to hemodynamic compromise, initiate therapy at 2.5 mg twice daily before increasing the dose based on heart rate.

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 **< 50 BPM OR SIGNS AND SYMPTOMS OF BRADYCARDIA**	Maintain dose Decrease dose by 2.5 mg (given twice daily); if current dose is 2.5 mg twice daily, discontinue therapy

Recommended Dosage Paediatric Patients 6 Months of Age and Older Weighing Less than 40 kg
The recommended starting dose of Ivabradine in paediatric patients 6 months of age and older and weighing less than 40 kg is 0.05 mg/kg twice daily with food.
Assess patient at two-week intervals and adjust dose by 0.05 mg/kg to target a heart rate (HR) reduction of at least 20%, based on tolerability. The maximum dose is 0.2 mg/kg twice daily for patients 6 months to less than 1 year old, and 0.3 mg/kg twice daily for patients 1 year old and older, up to a total of 7.5 mg twice daily.
If a dose of Ivabradine is missed or spit out, do not give another dose to make up for the missed or spit out dose. Give the next dose at the usual time.

Paediatric Patients Weighing 40kg and Greater
The recommended starting dose of Ivabradine tablets in paediatric patients weighing more than 40 kg is 2.5 mg twice daily with food. Assess patient at two-week intervals and adjust dose by 2.5 mg to target a heart rate (HR) reduction of at least 20%, based on tolerability. The maximum dose is 7.5 mg twice daily. Dose Reduction for Bradycardia If bradycardia develops, reduce the dose to the previous titration step. In patients who develop bradycardia at the recommended initial dosage, consider reducing the dosage to 0.02 mg/kg twice daily.

CONTRAINDICATIONS
It is contraindicated in patients with:
- Known hypersensitivity to ivabradine or any of the excipients.
- Clinically significant hypotension.
- Acute compensated heart failure.
- Severe hepatic impairment.
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present.
- Clinically significant bradycardia.
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker).
- Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitor.

ADVERSE REACTIONS
The reported adverse effect are; atrial fibrillation, bradycardia , conduction disturbances, eosinophilia, hyperuricaemia, headache, dizziness, bradycardia, syncope, luminous phenomena (phosphenes), blurred vision, diplopia, visual impairment, vertigo, bradycardia, AV 1st degree block (ECG prolonged PQ interval), palpitations, hypotension, possibly related to bradycardia, dyspnoea, nausea, constipation, diarrhoea, abdominal pain, angioedema, rash, erythema, pruritus, urticaria, muscle spasms, asthenia, fatigue, malaise, elevated creatinine in blood, hypertension, torsade de pointes, ventricular fibrillation and ventricular tachycardia.

DRUG INTERACTION
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.
- Avoid concomitant use of CYP3A4 inducers when using Ivabradine . Examples of CYP3A4 inducers include St. John's wort, rifampicin, barbiturates, and phenytoin.
- 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.
- Pacemakers in Adults Ivabradine dosing is based on heart rate reduction, targeting a heart rate of 50 to 60 beats per minute in adults. Patients with demand pacemakers set to a rate ≥ 60 beats per minute cannot achieve a target heart rate < 60 beats per minute.
- The use of Ivabradine is not recommended in patients with demand pacemakers set to rates ≥ 60 beats per minute.

WARNING AND PRECAUTIONS
Fetal Toxicity
Ivabradine may cause fetal toxicity when administered to a pregnant woman. Embryo-fetal toxicity and cardiac teratogenic effects could occur.
Females of reproductive potential should be advised to use effective contraception when taking Ivabradine.
Atrial Fibrillation
Ivabradine increases the risk of atrial fibrillation including in the systolic heart failure. Regularly monitor cardiac rhythm. Discontinue Ivabradine if atrial fibrillation develops.

Bradycardia and Conduction Disturbances
Adult Patients
Bradycardia, sinus arrest, and heart block have occurred 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
The use of Ivabradine is not recommended immediately after a stroke.
Ivabradine has not been studied in patients with Wolf Parkinson White syndrome.
Ivabradine should also be used with caution in patients with NYHA Class IV- severe functional status, hypertrophic cardiomyopathy and coexisting coronary artery disease.
Ivabradine should not be commenced peri-operatively due to limited safety data.

USE IN SPECIFIC POPULATIONS
Pregnancy
Ivabradine may cause foetal harm when administered to a pregnant woman. 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 foetus

Disease-associated Maternal and/or Embryo-foetal 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.

Lactation
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.
Females and Males of Reproductive Potential

Contraception
Females Ivabradine may cause foetal harm, based on animal data. Advise females of reproductive potential to use effective contraception during Ivabradine treatment.

Paediatric Use
The safety and effectiveness of Ivabradine have been established in paediatric patients (age 6 months to less than 18 years old)
The safety and efficacy of Ivabradine have not been established in patients less than 6 months of age.
Bradycardia and first-degree heart block were observed in paediatric patients treated with Ivabradine. Asymptomatic and symptomatic bradycardia were observed in paediatric patients treated with Ivabradine. Dose titration may be considered.

Geriatric Use
No pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population. However, Ivabradine has only been studied in a limited number of patients ≥ 75 years of age.

Hepatic Impairment
No dose adjustment is required 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
No dosage adjustment is required for patients with creatinine clearance 15 to 60 mL/min. No data are available for patients with creatinine clearance below 15 mL/min.

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

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in a dry place. Protect from light.

PRESENTATION
Ivaset 5mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.
Ivaset 7.5mg Tablets: Alu. Alu. Blister Pack of 2 x 7's.

ایواسیٹ®

(ایوابراڈین)

خوراک و ہدایات:
صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

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TITLIS PHARMA (PVT) LTD
528-A, Sundar Industrial Estate,
Raiwind Road, Lahore, Pakistan.

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