breast-feeding, and choose for another way of feeding their child.
Fertility: Studies in rats have shown no effect on fertility in males and females.

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. . 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.

SIDE EFFECTS:
Like all medicines, this medicine can cause side effects, although not everybody gets them. If you experience the following serious side effect stop taking Ivabradine Tablets and seek medical help immediately:
Swollen face, tongue or throat, difficulty in breathing or swallowing (angioedema) – this occurs uncommonly (may affect up to 1 in 100 people).
The most common adverse reactions with this medicine are dose dependent and related to its mode of action.

Very common (may affect more than 1 in 10 people):
Luminous visual phenomena (brief moments of increased brightness, most often caused by sudden changes in light intensity). They can also be described as a halo, coloured flashes, image decomposition or multiple images. They generally occur within the first two months of treatment after which they may occur repeatedly and resolve during or after treatment.

Common (may affect up to 1 in 10 people):
Modification in the heart functioning (the symptoms are a slowing down of the heart rate). They particularly occur within the first 2 to 3 months of treatment initiation.

Other side effects have also been reported:

Common (may affect up to 1 in 10 people):
Headache, dizziness, blurred vision (cloudy vision), irregular rapid contraction of the heart, abnormal perception of heartbeat and uncontrolled blood pressure.

Uncommon (may affect up to 1 in 100 people):
Fainting, double vision, impaired vision, spinning sensation (vertigo), palpitations and cardiac extra beats, low blood pressure, difficulty breathing (dyspnoea), feeling sick (nausea), constipation, diarrhoea, abdominal pain, skin rash, muscle spasms, feeling of tiredness, feeling of weakness, changes in laboratory parameters: an excess of eosinophils (a type of white blood cell), high blood levels of uric acid, elevated creatinine in blood (a breakdown product of muscle), abnormal ECG heart tracing.

STORAGE CONDITIONS AND OTHER INFORMATION
• Keep this medicine out of the sight and reach of children.
• Do not use this medicine after the expiry date which is stated on the carton and on the blister after EXP. The expiry date refers to the last day of that month.
• This medicine does not require any special storage conditions.

PRESENTATION:
Ivable 5mg tablet is available in blister packs of 14's & 28's.
Ivable 7.5mg tablet is available in blister packs of 14's & 28's.

ہدایات:
- خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
- دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
- صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کریں۔ • بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.,
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Art no: 626

Ivable®

(IVABRADINE)

5mg & 7.5mg Tablets

ایوابِل

(ایوابریڈِن)

۵ ملی گرام اور ۷.۵ ملی گرام گولیاں

Ivable Tablet 5mg
Each film coated tablet contains:
Ivabradine Hydrochloride (Mfg. Specs) Eq. to
Ivabradine ..... 5 mg.
Product complies as per *Innovator's Specifications.

Ivable Tablet 7.5mg
Each film coated tablet contains:
Ivabradine Hydrochloride (Mfg. Specs) Eq. to
Ivabradine ..... 7.5 mg.
Product complies as per *Innovator's Specifications.

EFFECTS OF THIS MEDICINE
Symptomatic treatment of chronic stable angina pectoris
Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 bpm. Ivabradine is indicated:
Treatment of chronic heart failure
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 ≥ 75 bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

CLINICAL PHARMACOLOGY:
Pharmacodynamics:
Pharmacotherapeutic group: hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blockers.
The main pharmacodynamic property of ivabradine in humans is a specific dose dependent reduction in heart rate. Analysis of heart rate reduction with doses up to 20 mg twice daily indicates a trend towards a plateau effect which is consistent with a reduced risk of severe bradycardia below 40 bpm. At usual recommended doses, heart rate reduction is approximately 10 bpm at rest and during exercise. This leads to a reduction in cardiac workload and myocardial oxygen consumption.

Pharmacokinetics:
Absorption/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 delayed absorption by approximately 1 hour, and increased 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 and Protein Binding:
Ivabradine is approximately 70% plasma protein bound and the volume of distribution at steady-state is close to 100 l in patients.

Metabolism:
Ivabradine is extensively metabolised by the liver and the gut by oxidation through cytochrome P450 3A4 (CYP3A4) only. The major active metabolite is the N-desmethylated derivative with an exposure about 40% of that of the parent compound.

Elimination:
Ivabradine is eliminated with a main half-life of 2 hours (70-75% of the AUC) in plasma and an effective half-life of 11 hours. About 4% of an oral dose is excreted unchanged in urine.

POSOLOGY:
Usual dose:
Treatment of chronic stable angina pectoris:
The starting dose of Ivabradine should not exceed 5 mg twice daily in patients aged below 75 years. The maintenance dose should not exceed 7.5 mg twice daily.

Treatment of chronic heart failure:
The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily (one half 5 mg tablet twice daily).

Elderly:
In patients aged 75 years or more, a lower starting dose should be considered (2.5 mg twice daily i.e. one half 5 mg tablet twice daily) before up-titration if necessary.

Renal impairment:
No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min.

Hepatic impairment:
No dose adjustment is required in patients with mild hepatic impairment. Caution should be exercised when using ivabradine in patients with moderate hepatic impairment. Ivabradine is contraindicated for use in patients with severe hepatic insufficiency.

Paediatric population:
The safety and efficacy of ivabradine in the treatment of chronic heart failure in children aged below 18 years have not yet been established.

METHOD OF ADMINISTRATION ORAL USE:
Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals.

Overdose:
Symptoms: Overdose may lead to severe and prolonged bradycardia.
Management: Severe bradycardia should be treated symptomatically in a specialised environment. In the event of bradycardia with poor haemodynamic tolerance, symptomatic treatment including intravenous beta-stimulating medicinal products such as isoprenaline may be considered. Temporary cardiac electrical pacing may be instituted if required.

Missed Dose:
If you forget to take a dose of Ivabradine Tablets, take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose.

Other medicines and Ivabradine Tablets
Dose adjustment of Ivabradine Tablets or monitoring should be required:

• QT prolonging medicines to treat either heart rhythm disorders or other conditions:

- quinidine, disopyramide, sotalol, ibutilide, amiodarone (to treat heart rhythm disorders)
- bepridil (to treat angina pectoris)
- certain types of medicines to treat anxiety, schizophrenia or other psychoses (such as pimozide, ziprasidone, sertindole)
- anti-malarial medicines (such as mefloquine or halofantrine)
- pentamidine (an antiparasitic medicine)
- cisapride (against the gastro-oesophageal reflux)
- intravenous erythromycin (an antibiotic)
- fluconazole (an antifungal medicine)
- rifampicin (an antibiotic)
- barbiturates (for difficult sleeping or epilepsy)
- phenytoin (for epilepsy)
- Hypericum perforatum or St John's Wort (herbal treatment for depression)
- Some types of diuretics which may cause decrease in blood potassium level, such as furosemide, hydrochlorothiazide, indapamide(used to treat oedema, high blood pressure).

PRECAUTIONS WHILE TAKING THIS MEDICINE
Patients with hypotension
Ivabradine is contra-indicated in patients with severe hypotension (blood pressure < 90/50 mmHg).
Atrial fibrillation - Cardiac arrhythmias
Heart rate reduction, as caused by ivabradine, may exacerbate QT prolongation, which may give rise to severe arrhythmias, in particular Torsade de pointes.
Hypertensive patients requiring blood pressure treatment modifications
In the SHIFT trial more patients experienced episodes of increased blood pressure while treated with ivabradine (7.1%) compared to patients treated with placebo (6.1%). These episodes occurred most frequently shortly after blood pressure treatment was modified, were transient, and did not affect the treatment effect of ivabradine.

SPECIAL WARNINGS:
Measurement of heart rate
Given that the heart rate may fluctuate considerably over time, serial heart rate measurements, ECG or ambulatory 24-hour monitoring should be considered when determining resting heart rate before initiation of ivabradine treatment and in patients on treatment with ivabradine when titration is considered. This also applies to patients with a low heart rate, in particular when heart rate decreases below 50 bpm.

Cardiac arrhythmias
Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and likely loses its efficacy when a tachyarrhythmia occurs (e.g. ventricular or supraventricular tachycardia). Ivabradine is therefore not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function.
Patients should be informed of signs and symptoms of atrial fibrillation and be advised to contact their physician if these occur. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.
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 a low heart rate
Ivabradine must not be initiated in patients with a pre-treatment resting heart rate below 70 beats per minute. 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.

Stroke
The use of ivabradine is not recommended immediately after a stroke since no data is available in these situations.

Visual function
Ivabradine influences retinal function. There is no evidence of a toxic effect of long-term ivabradine treatment on the retina. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.

Pregnancy and breast-feeding:

***Women of childbearing potential*:** Women of child-bearing potential should use appropriate contraceptive measures during treatment.
***Pregnancy*:** There are no or limited amount of data from the use of ivabradine in pregnant women. Studies in animals have shown reproductive toxicity. These studies have shown embryotoxic and teratogenic effects. The potential risk for humans is unknown. Therefore, ivabradine is contra-indicated during pregnancy.

***Breast-feeding*:** Women that need treatment with Ivabradine should stop