13-07-2021
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Rhytab® Tablets

(Ivabradine Hydrochloride)

QUALITATIVE AND QUANTITATIVE COMPOSITION

Rhytab® Tablet 5mg
Each film coated tablet contains:
Ivabradine Hydrochloride MS
eq. to Ivabradine.....5mg

Rhytab® Tablet 7.5mg
Each film coated tablet contains:
Ivabradine Hydrochloride MS
eq. to Ivabradine..... 7.5mg

PHARMACEUTICAL FORM

Tablet

CLINICAL PARTICULARS

Therapeutic Indications:

Symptomatic treatment of Chronic Stable Angina Pectoris: 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:

- In adults unable to tolerate or with a contra-indication to the use of beta-blockers
- Or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

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.

POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

Symptomatic Treatment of Chronic Stable Angina Pectoris: It is recommended that the decision to initiate or titrate treatment takes place with the availability of serial heart rate measurements, ECG or ambulatory 24-hour monitoring.

Starting dose should not exceed 5mg twice daily in patients aged below 75 years. After three to four weeks of treatment, if the patient is still symptomatic, if initial dose is well tolerated resting heart rate remains above 60 bpm, dose may be increased to next higher dose in patients receiving 2.5mg twice daily or 5mg twice daily. Maintenance dose should not exceed 7.5mg twice daily.

If there is no improvement in symptoms of angina within 3 months, treatment of ivabradine should be discontinued. In addition, discontinuation of treatment should be considered if there is only limited symptomatic response and when there is no clinically relevant reduction in resting heart rate within three months.

If, during treatment, heart rate decreases below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension, the dose must be titrated downward including the lowest dose of 2.5mg twice daily (one half 5mg tablet twice daily). After dose reduction, heart rate should be monitored. Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dose reduction.

Treatment of Chronic Heart Failure: Treatment has to be initiated only in patient with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic heart failure.

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 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

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 to the next lower dose in patients receiving 7.5mg twice daily or 5mg twice daily. If heart rate increases persistently above 60 beats per minute at rest, the dose can be up 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 50 bpm or symptoms of bradycardia persist.

Special Population

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

Renal impairment: No dose adjustment is required.

Hepatic impairment: No dose adjustment is required in patients with mild hepatic impairment. Caution should be exercised in patients with moderate hepatic impairment. Contra-indicated for use in patients with severe hepatic insufficiency.

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

METHOD OF ADMINISTRATION:

Tablets must be taken orally twice daily, i.e. once in the morning and once in the evening during meals.

CONTRAINDICATIONS:

- Hypersensitivity to the active substance or to any of the excipients
- Cardiogenic shock
- Severe hypotension (< 90/50 mmHg)
- Sick sinus syndrome / Sino-atrial block
- Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
- AV-block of 3rd degree
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin per os, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone
- Combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties
- Pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures
- Resting heart rate below 70 beats per minute prior to treatment
- Acute myocardial infarction
- Severe hepatic insufficiency
- Unstable or acute heart failure
- Unstable angina

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Special Warnings:

Lack of benefit on clinical outcomes in patients with symptomatic chronic stable angina pectoris: Indicated only for symptomatic treatment of chronic stable angina pectoris because ivabradine has no benefits on cardiovascular outcomes (e.g. myocardial infarction or cardiovascular death).

Measurement of heart rate: 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.

Cardiac arrhythmias: Not effective in the treatment or prevention of cardiac arrhythmias. Not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function. If atrial fibrillation develops during treatment, 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 AV-block of 2nd degree: Not recommended in patients with AV-block of 2nd degree.

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 if heart rate below 50 bpm 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 contraindicated.

Chronic Heart Failure: Should be used with caution in heart failure patients with NYHA functional classification IV.

Stroke: Not recommended immediately after a stroke.

Visual function: Ivabradine influences 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.

Precautions for Use:

Patients with hypotension: Ivabradine should be used with caution in patients with mild to moderate hypotension.

Atrial fibrillation-Cardiac arrhythmias: No evidence of risk of (excessive) bradycardia on return to sinus rhythm when pharmacological cardioversion is initiated in patients treated with ivabradine. However, in the absence of extensive data, non-urgent DC-cardioversion should be considered 24 hours after the last dose of ivabradine.

Use in patients with congenital QT syndrome or treated with QT prolonging medicinal products: 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. 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: When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTIONS:

Pharmacodynamic interactions:

Concomitant use not recommended: 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

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exacerbated by heart rate reduction. If the combination appears necessary, close cardiac monitoring is needed.
Concomitant use with precaution: Potassium-depleting diuretics (thiazide diuretics and loop 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.

Pharmacokinetic Interactions:
Cytochrome P450 3A4 (CYP3A4): Ivabradine is metabolised by CYP3A4 only and it is a very weak inhibitor of this cytochrome. Increased plasma concentrations of ivabradine may be associated with the risk of excessive bradycardia.
Contraindication 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. Increased ivabradine mean plasma exposure by 7 to 8 fold.
Moderate CYP3A4 inhibitors: 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 5 bpm. The concomitant use of ivabradine with these medicinal products is contraindicated.
Concomitant use not recommended: Ivabradine exposure was increased by 2-fold following the co-administration, therefore, the intake of grapefruit juice should be avoided.
Concomitant use with precautions: 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 70 bpm, with monitoring of heart rate. CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, hypericum perforatum [St. John's Wort]) may decrease ivabradine exposure and activity. The intake of St. John's Wort should be restricted during the treatment with ivabradine.
Paediatric population: Interaction studies have only been performed in adults.

FERTILITY, PREGNANCY AND LACTATION:
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. The potential risk for humans is unknown. Therefore, ivabradine is contra-indicated during pregnancy.
Breast-feeding: Ivabradine is contra-indicated during breast-feeding. Women that need treatment with ivabradine should stop breast-feeding.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
Ivabradine has no influence on the ability to use machines.

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.
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, ***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 extra systoles, Atrial fibrillation. In the SIGNIFY study atrial fibrillation was observed in 5.3% of patients taking ivabradine compared to 3.8% in the placebo group, ***Uncommon:*** Palpitations, Supraventricular extra systoles,
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:*** Rash, Angioedema, ***Rare:*** Erythema, Pruritus, Urticaria
Musculoskeletal and connective tissue disorders: ***Uncommon:*** Muscle cramps
General disorders and administration site conditions: ***Uncommon:*** Asthenia, possibly related to bradycardia
Fatigue, possibly related to bradycardia: ***Rare:*** Malaise, possibly related to bradycardia
Investigations: ***Uncommon:*** Elevated creatinine in blood, ECG prolonged QT interval

OVERDOSE:
Overdose may lead to severe and prolonged bradycardia. 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.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Cardiac therapy, other cardiac preparations. **ATC code:** C01EB17.

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 depolarisation in the sinus node and regulates heart rate.
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. Under triggering circumstances (e.g. rapid changes in luminosity), partial inhibition of I_h by ivabradine underlies the luminous phenomena that may be occasionally experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in a limited area of the visual field.

PHARMACOKINETIC PROPERTIES:
Absorption and Bioavailability: Rapidly and almost completely absorbed after oral administration with a peak plasma level reached in about 1 hour under fasting condition with absolute bioavailability of 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: Approximately 70% plasma protein bound and the volume of distribution at steady-state is close to 100 litre in patients. The maximum plasma concentration following chronic administration at the recommended dose of 5mg twice daily is 22 ng/ml (CV=29%). The average plasma concentration is 10 ng/ml (CV=38%) at steady-state.
Biotransformation: 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 (S 18982) with an exposure about 40% of that of the parent compound. The metabolism of this active metabolite also involves CYP3A4.
Elimination: Eliminated with a main half-life of 2 hours (70-75% of the AUC) in plasma and an effective half-life of 11 hours. The total clearance is about 400 ml/min and the renal clearance is about 70 ml/min. Excretion of metabolites occurs to a similar extent via faeces and urine. About 4% of an oral dose is excreted unchanged in urine.
Linearity/non linearity: The kinetics of ivabradine is linear over an oral dose range of 0.5 – 24mg.

SPECIAL POPULATIONS:
Elderly: No pharmacokinetic differences (AUC and Cmax) have been observed between elderly (≥ 65 years) or very elderly patients (≥ 75 years) and the overall population.
Renal impairment: The impact of renal impairment (creatinine clearance from 15 to 60 ml/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: No data are available in patients with severe hepatic impairment.
Paediatric population: The pharmacokinetic profile in paediatric chronic heart failure patients aged 6 months to less than 18 years is similar to the pharmacokinetics described in adults when a titration scheme based on age and weight is applied.
Pharmacokinetic/pharmacodynamic (PK/PD) relationship: PK/PD relationship analysis has shown that heart rate decreases almost linearly with increasing ivabradine and S 18982 plasma concentrations for doses of up to 15-20mg twice daily.

SHELF LIFE
See expiry on the pack.

AVAILABILITY
Rhytab® tablet 5mg in a pack of 14's
Rhytab® tablet 7.5mg in a pack of 14's

INSTRUCTIONS
Dosage: As advised by the physician.
To be sold on the prescription of registered medical practitioner.
Keep out of reach of children. Avoid exposure to heat, light and humidity.
Store between 15 to 30°C. Improper storage may deteriorate the medicine.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg. Lic. No. 000072

راھئے ٹیب® ٹیبلٹ

(ایوابراڈین ہائیڈروکلورائیڈ)

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو گرمی، روشنی اور نمی سے محفوظ ۱۵ سے ۳۰ ڈگری
سینٹی گریڈ کے درمیان میں رکھیں ورنہ دوا خراب ہو جائیگی

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