Biocon

Ivabradine Tablets

BRADIA™-5 œÌQrË-5

COMPOSITION:
BRADIA-5
Each film-coated tablet contains ivabradine hydrochloride equivalent to ivabradine 5 mg

PHARMACEUTICAL FORM:
Film-coated tablets containing 5 mg of ivabradine. (equivalent to 5.390 mg ivabradine as hydrochloride)

INDICATION:
Symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm. 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 and whose heart rate is > 60 bpm.

DOSE AND METHOD OF ADMINISTRATION:
The usual recommended starting dose of ivabradine is 5 mg twice daily. After three to four weeks of treatment, the dose may be increased to 7.5 mg twice daily depending on the therapeutic response.

If, during treatment, heart rate falls persistently 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 possible dose of 2.5 mg twice daily (one half 5 mg tablet twice daily). Treatment must be discontinued if heart rate below 50 bpm or symptoms of bradycardia persists.

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

Special population:
- Elderly
  Based on published information, ivabradine has been studied in a limited number of patients aged 75 years or more, a lower starting dose should be considered for these patients (2.5 mg twice daily i.e. one half 5 mg tablet twice daily) before up-titration if necessary.
- Renal insufficiency
  No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min (see pharmacokinetic properties). No data are available in patients with creatinine clearance below 15 ml/min. Ivabradine should therefore be used with precaution in this population.
- 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 contra-indicated for use in patients with severe hepatic insufficiency, since it has not been studied in this population and a large increase in systemic exposure is anticipated.
- Children and adolescents

Ivabradine is not recommended in children and adolescents as the efficacy and safety of ivabradine have not been studied in these populations.

CONTRAINDICATIONS:
- Hypersensitivity to ivabradine or to any of the excipients
- Resting heart rate below 60 beats per minute prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (< 90/50 mmHg)
- Severe hepatic insufficiency
- Sick sinus syndrome
- Sino-atrial block
- Heart failure patients with NYHA functional classification III-IV due to a lack of data
- Pacemaker dependent
- Unstable angina
- AV-block of 3rd degree
- Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone.
- Pregnancy, lactation.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE:
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.
  It is recommended to regularly clinically monitor ivabradine treated patients for the occurrence of atrial fibrillation (sustained or paroxysmal), which should also include ECG monitoring if clinically indicated (e.g. in case of exacerbated angina, palpitations, irregular pulse).
- Use in patients with AV-block of 2nd degree
  Ivabradine is 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 60 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 other antianginal therapies
  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. Additional efficacy of ivabradine in combination with dihydropyridine calcium channel blockers has not been established.
- Chronic heart failure
  Heart failure must be appropriately controlled before considering ivabradine treatment. The use of ivabradine is contra-indicated in heart failure patients with NYHA functional classification III-IV, and should be used with caution in heart failure patients with NYHA functional classification I-II.
- 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. 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
  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 < 90/50 mmHg).
- 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. 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
  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.

DRUG INTERACTIONS:

Pharmacodynamic interactions
- Concomitant use not recommended
  QT prolonging medicinal products
- Cardiovascular medicinal products (e.g. quinidine, disopyramide, bepridil, sotalol, ibutilide, amiodarone).
- Non cardiovascular medicinal products (e.g. pimozide, ziprasidone, sertindole, mefloquine, halofantrine, pentamidine, cisapride, erythromycin IV).

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 (see Special warnings and special precautions for use).

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, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone is contra-indicated The potent CYP3A4 inhibitors ketoconazole (200 mg once daily) and josamycin (1 g 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 5 bpm. The concomitant use of ivabradine with these medicinal products is not recommended.
- Concomitant use with precautions
- Moderate CYP3A4 inhibitors: The concomitant use of ivabradine with other moderate CYP3A4 inhibitors (e.g. fluconazole) may be considered at the starting dose of 2.5 mg twice daily and if resting heart rate is above 60 bpm, with monitoring of heart rate.

- Grapefruit juice: Ivabradine exposure was increased by 2-fold following co-administration with grapefruit juice. Therefore the intake of grapefruit juice should be restricted during the treatment with ivabradine.

- 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 10 mg 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.

- Other concomitant use
  Specific drug-drug interaction studies have shown no clinically significant effect of the following medicinal products on pharmacokinetics and pharmacodynamics of ivabradine: proton pump inhibitors (omeprazole, lansoprazole), sildenafil, HMG CoA reductase inhibitors (simvastatin), dihydropyridine calcium channel blockers (amlodipine, lacidipine), digoxin and warfarin. In addition there was no clinically significant effect of ivabradine on the pharmacokinetics of simvastatin, amlodipine, lacidipine, on the pharmacokinetics and pharmacodynamics of digoxin, warfarin and on the pharmacodynamics of aspirin.

In pivotal phase III clinical trials performed with ivabradine the following medicinal products were not restricted and therefore were routinely combined with ivabradine with no evidence of safety concerns: Angiotensin converting enzyme inhibitors, angiotensin II antagonists, diuretics, short and long acting nitrates, HMG CoA reductase inhibitors, fibrates, proton pump inhibitors, oral antidiabetics, aspirin and other anti-platelet agents.

PREGNANCY AND LACTATION:
There are no adequate data concerning the use of ivabradine in pregnant women. Animal reproduction studies have shown embryo-toxic and teratogenic effects. The potential risk for humans is unknown. Therefore, ivabradine is contra-indicated during pregnancy.
Animal studies indicate that ivabradine is excreted in milk. Therefore, ivabradine is contra-indicated in breast-feeding women.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:
According to studies performed to assess the possible influence of ivabradine on driving performance in healthy volunteers, no alteration of the driving performance was evidenced. Ivabradine has no influence on the ability to drive and use machines. However, 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.

UNDESIRABLE EFFECTS:
Ivabradine has been studied in clinical trials involving nearly 5,000 participants. Approximately 2,900 patients have been treated with ivabradine in phase II-III studies.

The most common undesirable effects with ivabradine were dose dependent and related to the pharmacological effect of the medicinal product.
The following adverse reactions have been reported during clinical trials and are ranked using the following frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

The following adverse effects or events have been reported during clinical trials:
Eye disorders: (Very common)
- Luminous phenomena (phosphenes): Reported by 14.5% of patients, described as a transient enhanced brightness in a limited area of the visual field. They are usually triggered by sudden variations in light intensity. The onset of phosphenes is generally within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity. All phosphenes resolved during or after treatment, of which a majority (77.5%) resolved during treatment. Less than 1% of patients changed their daily routine or discontinued the treatment in relation with phosphenes.

Cardiovascular disorders:
Common
Bradycardia was reported by 3.3% of patients particularly within the first 2 to 3 months of treatment initiation. 0.5% of patients experienced a severe bradycardia below or equal to 40 bpm.
- AV 1st degree block
- Ventricular extra systoles

Uncommon

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• Palpitations, supraventricular extra systoles

Gastrointestinal disorders:
(Uncommon)
• Nausea
• Constipation
• Diarrhea

General disorders:
(Not known)
• Malaise, possibly related to bradycardia

Skin and subcutaneous tissue disorders (Not known)
Rash, Erythema, Pruritus

OVERDOSE
Overdose may lead to severe and prolonged bradycardia
Severe bradycardia should be treated symptomatically in a specialized environment. In the event of bradycardia with poor hemodynamic tolerance, symptomatic treatment including intravenous beta stimulating agents 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.
Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker I, 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 repolarisation.

Ivabradine can interact also with the retinal current I, which closely resembles cardiac I, . 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, 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
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 (see undesirable effects).

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. Ivabradine does not influence intracardiac conduction, contractility (no negative inotropic effect) or ventricular repolarisation:

• in clinical electrophysiology studies, ivabradine had no effect on atrioventricular or intraventricular conduction times or corrected QT intervals;
• in patients with left ventricular dysfunction (left ventricular ejection fraction (LVEF) between 30 and 45%), ivabradine did not have any deleterious influence on LVEF.

The antianginal and anti-ischaemic efficacy of Ivabradine was studied in five double-blind randomised trials (three versus placebo, and one each versus atenolol and amlodipine). These trials included a total of 4,111 patients with chronic stable angina pectoris, of whom 2,617 received ivabradine.

Ivabradine 5 mg twice daily was shown to be effective on exercise test parameters within 3 to 4 weeks of treatment. Efficacy was confirmed with 7.5 mg twice daily. In particular, the additional benefit over 5 mg twice daily was established in a reference-controlled study versus atenolol: total exercise duration at trough was increased by about 1 minute after one month of treatment with 5 mg twice daily and further improved by almost 25 seconds after an additional 3-month period with forced titration to 7.5 mg twice daily. In this study, the antianginal and anti-ischaemic benefits of ivabradine were confirmed in patients aged 65 years or more. The efficacy of 5 and 7.5 mg twice daily was consistent across studies on exercise test parameters (total exercise duration, time to limiting angina, time to angina onset and time to 1mm ST segment depression) and was associated with a decrease of about 70% in the rate of angina attacks. The twice-daily dosing regimen of ivabradine gave uniform efficacy over 24 hours.

In a 725-patients randomised placebo-controlled study, ivabradine did not show additional efficacy on top of amlodipine at the trough of drug activity (12 hours after oral intake) while an additional efficacy was shown at peak (3-4 hours after oral intake).

Ivabradine efficacy was fully maintained throughout the 3- or 4-month treatment periods in the efficacy trials. There was no evidence of pharmacological tolerance (loss of efficacy) developing during treatment nor of rebound phenomena after abrupt treatment discontinuation. The antianginal and anti-ischaemic effects of ivabradine were associated with dose-dependent reductions in heart rate and with a significant decrease in rate pressure product (heart rate x systolic blood pressure) at rest and during exercise. The effects on blood pressure and peripheral vascular resistance were minor and not clinically significant.

A sustained reduction of heart rate was demonstrated in patients treated with ivabradine for at least one year (n = 713). No influence on glucose or lipid metabolism was observed.

The antianginal and anti-ischaemic efficacy of ivabradine was preserved in diabetic patients (n = 457) with a similar safety profile as compared to the overall population.

Pharmacokinetic properties
Under physiological conditions, ivabradine is rapidly released from tablets and is highly water-soluble (>10 mg/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 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
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.

• 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. The metabolism of this active metabolite also involves CYP3A4. Ivabradine has low affinity for CYP3A4, shows no clinically relevant CYP3A4 induction or inhibition and is therefore unlikely to modify CYP3A4 substrate metabolism or plasma concentrations. Inversely, potent inhibitors and inducers may substantially affect ivabradine plasma concentrations.

• 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. 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 - 24 mg.

• 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 insufficiency: 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: 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. Data are insufficient to draw conclusions in patients with moderate hepatic impairment. No data are available in patients with severe hepatic impairment.

• 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 15-20 mg twice daily. At higher doses, the decrease in heart rate is no longer proportional to ivabradine plasma concentrations and tends to reach a plateau. High exposures to ivabradine that may occur when ivabradine is given in combination with strong CYP3A4 inhibitors may result in an excessive decrease in heart rate although this risk is reduced with moderate CYP3A4 inhibitors.

PRECLINICAL SAFETY DATA:
Accordind to published information Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential.
SHELF LIFE
Please refer to the expiry date on foil

STORAGE AND PRECAUTIONS
Store in a cool and dry place. Protect from moisture

PRESENTATION
Blister pack of 10 Tablets
INSTRUCTIONS FOR USE AND HANDLING
No special requirement
FOR FURTHER DETAILS, PLEASE CONTACT:

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