Ivabradine (Procoralan®) ▼ AMBER 0

For the symptomatic treatment of chronic stable angina or chronic heart failure

Information for prescribers - to be read in conjunction with the SPC

Background
Heart rate is regulated normally by spontaneous activity in pacemaker cells in the sinoatrial (SA) node. Early in diastole the negative membrane potential of SA node cells activates a cation channel giving rise to an inward current, the If current, which contributes to depolarisation of SA node cells which in turn leads to action potential firing. Ivabradine selectively blocks the If channel thus slowing the diastolic depolarisation of the SA node resulting in a reduction in heart rate both at rest and during exercise. Myocardial contractility and atrioventricular conduction are not affected.

Angina
Ivabradine is recommended for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm:
- who have a resting heart rate of at least 70bpm and a contra-indication or intolerance to beta blockers or calcium channel blockers or
- in combination with beta-blockers where symptoms are not controlled with an optimal beta-blocker dose and heart rate is at least 70bpm (if calcium channel blocker not tolerated/contra-indicated or
- in combination with a dihydropyridine calcium channel blocker (e.g. slow release nifedipine, amlodipine or felodipine) where symptoms are not controlled and beta blockers are not tolerated/contra-indicated
- Prescribers should consider stopping ivabradine if there is no or only limited symptom improvement after 3 months.

Heart Failure
- Ivabradine is recommended within its marketing authorisation for people:
  - with New York Heart Association (NYHA) class II to IV chronic heart failure with systolic dysfunction AND
  - who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more AND
  - when given in combination with standard therapy including: maximum tolerated dose of a beta-blocker, ACE inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or there is true intolerance (symptomatic low BP or unstable asthma).
- **Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimal standard therapy with angiotensin-converting enzyme (ACE) inhibitors, beta-blockers and aldosterone antagonists.**
- Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team
- Following initiation, dose titration and monitoring should be carried out by a heart failure specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

Dosage and Administration
- Patients should be advised to take the tablets during meals to avoid variation in bioavailability.
- **Down titrate the dose to 2.5mg twice daily if the heart rate drops below 50 bpm or the patient experiences symptoms of bradycardia that persist. If the resting heart rate remains below 50 beats per minute or symptoms of bradycardia persist, stop treatment.**

Chronic Stable Angina
The recommended starting dose is 5mg twice daily.
After three to four weeks the dose may be increased to a maximum of 7.5mg twice daily depending on therapeutic response.
In patients aged over 75 years a starting dose of 2.5mg twice daily (one half 5mg tablet twice daily) should be considered.

Chronic Stable Heart Failure
- The recommended starting dose is 5mg twice daily.
• After two weeks, 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) if resting heart rate is persistently below 50 bpm or if there are symptoms of bradycardia.
• If the heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.
• 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 2.5 mg twice daily or 5 mg twice daily.

Monitoring
It is recommended to regularly monitor heart rate and assess for the occurrence of atrial fibrillation (sustained or paroxysmal).

Contraindications and Cautions for Use
Ivabradine is contraindicated in:
• patients with a pre-treatment resting heart rate below 70bpm
• severe hypotension (<90/50 mmHg)
• unstable angina
• Sick sinus syndrome
• severe hepatic insufficiency
• unstable or acute heart failure
• acute MI
• immediately post CVA
• sino-atrial block or 2nd or 3rd degree AV-block.
• Pregnancy or lactation and women of child-bearing potential not using contraceptive measures
• Patients on potent CYP3A4 inhibitors (see below)

Ivabradine is not effective in the treatment or prevention of cardiac arrhythmias and should not be used in patients with AF or other cardiac arrhythmias that interfere with sinus node function.

Chronic heart failure patients with intraventricular conduction defects (bundle branch block left, bundle branch block right) and ventricular dyssynchrony should be monitored closely.

Side Effects
In clinical trials the most frequently reported adverse events were visual symptoms and bradycardia.

Luminous phenomena (phosphenes) described as a transient enhanced brightness in a limited area of the visual field, were reported by 14.5% of patients. These are usually triggered by sudden variations in light intensity. Patients should be warned of this effect, particularly with regard to driving at night. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs
Other possible side effects are AV 1st degree block (ECG prolonged PQ interval), ventricular extrasystoles, headache, dizziness and uncontrolled BP.

Drug Interactions
• QT prolonging medicines: The concomitant use of QT prolonging medicines should be avoided since QT prolongation may be exacerbated by heart rate reduction.
• Cytochrome P450 3A4 inhibitors: Ivabradine is metabolised by CYP3A4 and is a very weak inhibitor of this enzyme. The concomitant use of potent CYP3A4 inhibitors e.g. macrolide antibiotics, HIV protease inhibitors, ketoconazole and itraconazole, is contraindicated due to the risk of excessive bradycardia with increased plasma concentrations of ivabradine.
• The concurrent use of rate-limiting calcium channel blockers e.g. verapamil, diltiazem is contra-indicated.
• Potassium-depleting diuretics: hypokalaemia increases the risk of arrhythmia. Ivabradine may cause bradycardia, the combination of hypokalaemia and bradycardia is a predisposing factor to the onset of severe arrhythmias. Concomitant use with caution.
• AF is more common in patients using amiodarone or potent class I anti-arrhythmics concomitantly.
• Patients should be advised to avoid grapefruit juice & avoid the intake of St John's Wort.

This is not an exhaustive list of side effects, cautions, contra-indications or interactions please refer to the BNF or Summary of Product Characteristics for more information.

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