Prescribing ivabradine for patients with chronic heart failure due to left ventricular dysfunction

Ivabradine is also licensed for the treatment of chronic stable angina. Guidance on the prescribing of ivabradine for this indication can be found at www.swlmcg.nhs.uk

Ivabradine (Procoralan®) is a pure heart-rate lowering agent licensed for use in heart failure. Data from the SHIFT study demonstrated that heart rate reduction using ivabradine in selected patients with chronic heart failure can significantly reduce hospitalisations due to worsening heart failure, whilst also preventing heart failure and cardiovascular related death.

In South London, ivabradine should be considered as an option in line with its licensed indication and supporting NICE guidance (TA267, 2012). Use is only recommended if all the following criteria are met:

- Left ventricular systolic dysfunction with an ejection fraction of ≤35% and NYHA class II-IV
- On maximum tolerated dose of both ACE inhibitor (or ARB) and beta-blocker (unless contraindicated); and an aldosterone antagonist
- In sinus rhythm, with a resting heart rate ≥ 75 beats per minute (bpm)

The MHRA issued new advice for health professionals on the prescribing of ivabradine in chronic stable angina, but many of the points apply equally in the setting of heart failure, in particular:

- monitor patients regularly for atrial fibrillation. If atrial fibrillation occurs, carefully reconsider whether the benefits of continuing ivabradine treatment outweigh the risks
- the recommended starting dose is 5 mg twice daily
- do not exceed the maximum maintenance dose of 7.5 mg twice daily
- down-titrate the dose if resting heart rate decreases persistently below 50 beats per minute or if the patient experiences symptoms of bradycardia. The dose can be down-titrated to 2.5 mg twice daily if necessary
- stop ivabradine treatment if the resting heart rate remains below 50 beats per minute or symptoms of bradycardia persist

Ivabradine should only be initiated after a stabilisation period of 4 weeks on optimised standard therapy with ACE inhibitors, beta-blockers and aldosterone antagonists.

- Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary team. Dose titration and monitoring should be carried out by a heart failure specialist in primary or secondary care, such as a GP with a special interest in heart failure or a heart failure specialist nurse
- Responsibility for the prescribing of ivabradine may be transferred to the GP when the dose of ivabradine is optimised (i.e. heart rate controlled to between 50-60bpm or on maximum ivabradine dose) and the patient is considered stable.

Contra-indications

- Hypersensitivity to the active substance or to any of the excipients
- Resting heart rate <70bpm at initiation
- Sick sinus syndrome
- Sino-atrial block & 3rd degree AV-block
- Congenital QT syndrome
- Pacemaker dependent patients* (i.e. where heart rate is maintained exclusively by the pacemaker)
- Severe Hypotension (BP < 90/50mmHg)
- Cardiogenic shock and acute MI
- Unstable or acute heart failure
- Severe hepatic impairment
- Unstable angina
- Pregnancy and lactation
- [Note drug interactions below]

*Ivabradine is suitable for use in patients with specialist pacing devices under cardiology supervision.

Cautions

- Pre-existing cardiac arrhythmias
- Concurrent heart rate lowering agents
- Mild to moderate hypotension
- Severe heart failure (NYHA IV)
- Post-CVA (use not recommended immediately after a stroke)
- Retinitis pigmentosa
- Moderate hepatic impairment
- Established renal failure (CrCl<15ml/min)

This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
Ivabradine is not recommended in patients with atrial fibrillation (AF) or other cardiac arrhythmias that interfere with sinus node function; as it is unlikely to be effective in this circumstance. It is recommended that all patients prescribed ivabradine are regularly monitored for the occurrence of AF (sustained or paroxysmal), including in patients with a history of AF who are currently in sinus rhythm. If AF occurs during treatment, ivabradine should be stopped.

**Initiation and dose titration:**
Obtain baseline BP and pulse rate before initiation and after each dose change.
- **Ivabradine is usually initiated at a dose of 5mg twice daily.**
  - After 3 to 4 weeks the dose may be increased to 7.5mg twice daily if the heart rate remains >60bpm and greater symptom control is required.
  - If the patient is elderly (>75 years) or 5mg twice daily is not tolerated, the dose can be reduced to 2.5mg twice daily.

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.

**Monitoring**
If the heart rate falls persistently below 50 beats per minute (at rest) and / or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension - reduce the dose:
- from 7.5mg twice daily to 5mg twice daily; or
- from 5mg twice daily to 2.5mg twice daily (half a 5 mg tablet twice daily).
- Discontinue treatment if heart rate remains below 50bpm or symptoms of bradycardia persist after dose reduction.

**Side effects (for full details see BNF or SPC)**
Visual symptoms are the most common adverse effect reported. Luminous phenomena were reported in 14.5% of patients and therefore new patients should be warned about this potential side effect. Phosphenes generally begin to occur 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. Blurred vision also occurs commonly. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs.
Other common side effects (occurring in between 1 in 10 and 1 in 100 patients) include headache and dizziness, bradycardia, 1st degree AV block and ventricular extrasystoles and uncontrolled blood pressure.

*Ivabradine is a black triangle drug - any adverse effect must be reported to the MHRA and via the local incident reporting system*

**Drug Interactions (for full details see BNF or SPC)**

**Drug / Drug class**
Strong inhibitors of CYP3A4 such as:
- Azole-antifungotics (e.g., ketoconazole, itraconazole, voriconazole and posaconazole),
- HIV protease inhibitors (e.g. ritonavir),
- Macrolide antibiotics (e.g. clarithromycin and erythromycin)

Moderate inhibitors of CYP3A4 such as diltiazem and verapamil

CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John’s wort)

Drugs which prolong the QTc (e.g. Amiodarone, sotalol, disopyramide and mefloquine)

**Recommendation**
Concomitant use not recommended - may increase ivabradine exposure

Concomitant use not recommended - may increase ivabradine exposure

Use with caution as may decrease ivabradine exposure.
May require closer monitoring and dose adjustment.
Use of St John’s wort is not recommended.

Concomitant use not recommended - increased risk of ventricular arrhythmias

**Additional advice to patients**
Patients should be advised not to consume grapefruit juice during treatment with ivabradine

References