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Medicines Optimisation

Ivabradine prescribing guideline

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1. 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.

Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team, as recommended in the NICE TAG (2012)and SIGN 147 (2016) . Dose titration and monitoring should be carried out by a heart failure specialist and multidisciplinary team or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse.

2. Assess suitability for treatment

Consider in symptomatic patients (NYHA class II-IV) with LVEF ≤ 35%, in sinus rhythm and with a resting heart rate ≥ 75 bpm and are already stabilised on optimally treated standard therapy including beta-blocker therapy, ACE inhibitors (or ARB if not tolerated) and MRAs, or when beta-blocker therapy is contraindicated or not tolerated.

Ivabradine should only be initiated in patients who have been stable for at least 4 weeks on maximally tolerated standard therapy.

3. Initiation and Monitoring of Ivabradine

Start with a dose of 5 mg bd (or if aged ≥ 75 years, consider 2.5 mg bd initially, and titrate as appropriate).

Following initiation, dose titration and monitoring should be carried out by a cardiac specialist, or in primary care by either a GP with a special interest in heart failure or a heart failure specialist nurse. It is recommended to regularly monitor heart rate and assess for the occurrence of atrial fibrillation (sustained or paroxysmal).

After two weeks of treatment:

- If resting heart rate is persistently above 70 bpm, increase to 7.5 mg bd, or
- If resting heart rate is persistently below 50 bpm or if symptoms related to bradycardia (such as dizziness, fatigue or hypotension), decrease to 2.5 mg bd.
- If resting heart rate is between 50 and 70 bpm, the dose of 5 mg bd should be maintained.
- Monitor heart rate, blood pressure and clinical status.

- Prescribers should consider stopping ivabradine if there is no or only limited symptom improvement after 3 months.

4. Specialist heart failure nurse

1. To up – titrate ivabradine in accordance with the SPC to the optimum effective and tolerated dose.
2. To liaise with the GP for transfer of prescribing of ivabradine in stabilised patients once the ivabradine dose has been optimised.
3. Monitor heart rate every three months and re-assess if resting ventricular rate falls below 50bpm.
4. Reduce dose or stop if resting heart rate decreases persistently below 50 bpm at rest or the patient experiences symptoms related to bradycardia.
5. Arrange an ECG if resting heart rate ≤ 45 bpm to exclude heart block.
6. Stop if develops persistent atrial arrhythmias.
7. Monitor concordance with therapy.
8. Review treatment if there are significant side-effects, if there is no benefit of treatment or if symptoms deteriorate

5. General practitioner

1. Where appropriate, to continue to prescribe ivabradine for stable patients.
2. To follow monitoring instructions from specialist care
3. To follow heart failure monitoring advice as specified in the NICE Quality Standard 9 relating to heart failure, i.e. 6 monthly clinical reviews or more frequently if indicated.
4. Monitor heart rate at review or if clinically warranted, and notify specialist if resting ventricular rate falls below 50bpm.
5. To deal with general health issues of the patient.
6. Monitor concordance with therapy.
7. Refer to the specialist if there are significant side-effects, if there is no benefit of treatment or if symptoms deteriorate.
8. To be responsive to urgent requests for review should patient circumstances change.
9. To ensure the patient continues to give informed consent to all treatments.
10. To report adverse events to MHRA (Yellow card): www.yellowcard.gov.uk
11. To ensure patient is compliant with heart failure therapies.

6. Problem Solving

Ivabradine can cause visual disturbances, especially where sudden variations in light intensity may occur. Patient should be advised regarding driving, especially when driving at night and when operating machinery. Visual symptoms are usually transient, and resolve during the first few months of treatment, but in the event of patient discomfort, ivabradine could be stopped.

7. Drug Interactions

These are potential drug interactions:

- Avoid concomitant use of drugs that might prolong the QT interval.
- Ivabradine is metabolised by CYP3A4 and therefore other drugs affecting this system should be avoided (e.g. antifungals, macrolide antibiotics). Diltiazem, verapamil and sotalol should all be avoided.
- Ivabradine exposure can be increased by grapefruit juice, intake of grapefruit juice should be restricted during the treatment with ivabradine.

8. Contra-indications and cautions for use

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.

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
- Severe (NYHA IV) 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.
- Chronic retinal diseases, including retinitis pigmentosa
- 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

9. 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, such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone 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.
- 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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Appendix One: Abbreviations

Abbreviation	Definitions