SHARED CARE GUIDELINE FOR PRESCRIBING IVABRADINE

INDICATION

This shared care guideline has been prepared to support the transfer of responsibility for prescribing ivabradine from secondary to primary care.

Ivabradine is the first specific heart rate lowering agent. It is selective and specifically inhibits the cardiac pacemaker I_f current, lowering heart rate at concentrations that do not affect other cardiac ionic currents. Specific heart rate lowering with ivabradine reduces myocardial oxygen demand, simultaneously improving oxygen supply.

Ivabradine does not have a negative inotropic effect, preserves ventricular contractility and does not change any major electrophysiological parameters unrelated to heart rate.

This guideline covers use of ivabradine in the indications shown below:

Indication	Comments
Angina	Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in adults with coronary artery disease in normal sinus rhythm and heart rate ≥ 70 bpm. Ivabradine is indicated: • in adults unable to tolerate beta-blockers or with a contra-indication to them OR • in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose
Chronic heart failure	Chronic heart failure – NICE TA 267 states: Ivabradine is recommended as an option for treating chronic heart failure for people with New York Heart Association (NYHA) class II to IV stable 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 • Who are given Ivabradine in combination with standard therapy including beta-blocker therapy, angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists, or when beta-blocker therapy is contraindicated or not tolerated and • With a left ventricular ejection fraction of 35% or less. 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 heart failure team.
POTS/IST	At present there are no approved medicines for the treatment of postural orthostatic tachycardia syndrome (POTS) or inappropriate sinus tachycardia (IST) and therefore, in this circumstance, Ivabradine is prescribed 'off-label'. Treatment must be tailored to each patient, taking into account the cause of their syndrome and their symptoms, since the same medicines can have very different effects on different individuals. In Dorset, ivabradine may be considered as an 'off-label' option for the treatment of POTS or IST when causative factors have been corrected or ruled out and other forms of treatment have failed to control symptoms (i.e. fluid, exercise and compression clothing). In the largest clinical trial of ivabradine in patients with existing heart disease, ivabradine caused a small but important increase in the incidence of heart attacks and death from heart disease. Of course, as stated, this adverse effect of ivabradine has only been seen in patients with existing heart disease and it is not clear if this is relevant to the use of this drug in patients with POTS. The other drugs used in POTS seem to be free of any such problems when used in patients with heart disease.

AREAS OF RESPONSIBILITY FOR SHARED CARE

Patients should be at the centre of any shared care arrangements. Individual patient information and a record of their preferences should accompany shared care prescribing guidelines, where appropriate. Transfer of clinical responsibility to primary care should only be considered where the person's clinical condition is stable or predictable.

Referral to the GP should only take place once the GP has agreed to this in each individual case and the hospital or specialist will continue to provide prescriptions until a successful transfer of responsibilities. The GP should confirm the agreement and acceptance of the shared care prescribing arrangement and confirm that supply arrangements have been finalised. The secondary/tertiary provider must supply an adequate amount of the medication to cover the transition period. The patient should then be told to obtain further prescriptions from the GP.

When clinical responsibility for prescribing is transferred to general practice, it is important that the GP, or other primary care prescriber, is confident to prescribe the necessary medicines. Shared care agreements play a key role in enabling primary care prescribers to prescribe medicines they may not initially be familiar with. Clinical responsibility for prescribing is held by the person signing the prescription, who must also ensure adequate monitoring.

REFERRAL AND INITIATION

Shared Care is only appropriate if it provides the optimum solution for the patient. Patients will only be referred to the GP once the GP has agreed each individual case.

Specialist Responsibilities	
1	To initiate ivabradine in line with local guidance – notifying the GP that ivabradine has been prescribed using the notification of initiation document and clinic letter.
2	To ensure the patient has consented to treatment and is aware if the use of the drug is not for a licensed indication (i.e. it is 'off label').
3	To provide counselling to improve adherence and address any adverse effects (including advice on dosage, frequency, risks and benefits) and ensure that the patient has provided informed consent to treatment
4	Perform baseline monitoring tests: BP, heart rate, ECG, baseline renal and liver function.
5	Patient is provided with contact information for specialist nurse advice during normal working hours.
6	To supply ivabradine for at least the first 4 weeks in cases of angina and heart failure and 3 months for POTS/IST or until the dose is stable, whichever is longer.
7	To advise the patient to report to a healthcare professional any visual disturbances, particularly in the first few weeks of treatment.
8	To advise the patient not to drink grapefruit juice during treatment with ivabradine.
9	Following the initial 4 weeks in angina or heart failure or 3 months in POTS/IST and when the dose is stable, transfer care to the GP using the local transfer of prescribing responsibility document.
10	Provide the GP with relevant specialist contact information should further assistance be required during working hours.
11	To review the patient at the request of GP should any problems arise (side-effects / lack of efficacy)
12	To review the patient once symptoms are stable and annually thereafter, communicating promptly with the GP if treatment is changed.
13	To inform the GP when it is considered appropriate to discontinue treatment.
14	To report any suspected adverse effects to the MHRA: https://yellowcard.mhra.gov.uk/

General Practitioner Responsibilities	
1	Initially to refer the patient to the specialist to ensure use of ivabradine is in line with local guidance.
2	To agree to take over prescribing responsibility when the patient is stable on therapy (at least 4 weeks after initiation in cases of angina and heart failure and 3 months after initiation for POTS/IST) and in line with the transfer of care guidance.
3	To provide on-going prescriptions for ivabradine after the initial 4 weeks/3 months.
4	To carry out monitoring as follows: • monitor heart rate every 12 months (seek advice from the specialist if resting ventricular rate falls below 50bpm). • Manual pulse rhythm check should be performed at every annual review to check for AF. • Review renal and liver function at least annually and more frequently if clinically indicated.
5	Reporting the results of monitoring to the specialist if appropriate.
6	To deal with general health issues of the patient.
7	To avoid or appropriately manage the drug interactions as listed below and in the current BNF.
8	To monitor patient for adverse effects and control of symptoms.
9	To report to and seek advice from the specialist team regarding any concerns, for example: visual or other side-effects, co-morbidities, or lack of efficacy.
10	To advise the specialist if non-adherence is suspected.
11	To seek specialist advice if female patients become pregnant whilst taking ivabradine.
12	To refer back to specialist if the patient's condition deteriorates or treatment failure occurs.
13	To stop treatment on advice of the specialist or immediately if an urgent need to stop treatment arises.
14	To report any suspected adverse effects to the MHRA via the Yellow Card scheme: https://yellowcard.mhra.gov.uk/

Patient's role (or that of carer)	
1	Patients should not consume grapefruit juice during treatment with ivabradine.
2	Report to the specialist or GP if he or she does not have a clear understanding of the treatment
3	Attend appropriate GP and other follow up appointments
4	Share any concerns in relation to treatment with ivabradine, particularly any side effects of concern (including visual disturbances)
5	Use written and other information provided with the medication and by the healthcare team
6	Female patients must seek GP or specialist advice if become pregnant or plan on becoming pregnant.

SUPPORTING INFORMATION

Treatment must be initiated by a cardiology specialist, after careful evaluation of the overall balance of the patient's expected benefits and risks.

The initiating clinician / organisation is responsible for ensuring the patient is provided with a structured support process (including availability of contact numbers for the Ambulatory Cardiac clinic), follow-up and providing a supply of ivabradine for the first 4 weeks of treatment in angina or heart failure or the first 3 months of treatment in POTS/IST or until the dose is stable, whichever is first. During this time, efforts should be made to reinforce adherence and address any adverse effects.

The following points should be noted:

- Ivabradine should only be initiated if the daytime resting heart rate is at least 70bpm
- Down-titrate the dose if resting heart rate decreases persistently below 50bpm during treatment, or if the patient experiences symptoms of bradycardia. The dose can be down-titrated to 2.5mg (half a 5mg tablet) twice daily if necessary
- Monitor patients regularly for atrial fibrillation (AF). If AF occurs, carefully reconsider whether the benefits of continuing ivabradine treatment outweigh the risks
- Do not prescribe ivabradine with other medicines that cause bradycardia, such as verapamil, diltiazem, strong CYP3A4 inhibitors, or betablockers (see drug interactions table below).
- Consider stopping ivabradine if there is no or only limited symptom improvement after 3 months
- Stop Ivabradine treatment if the resting heart rate remains below 50bpm or symptoms of bradycardia persist

Dosage and Administration

Since ivabradine has been studied in a limited number of elderly patients, a lower starting dose of 2.5mg twice daily should be considered for patients aged 75 years or more. If a dose of 2.5mg is to be prescribed, then it should be prescribed as half of a 5mg tablet (tablets are clearly scored) due to a substantial difference in cost.

Chronic stable angina

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.

Chronic heart failure

The usual recommended starting dose of ivabradine for heart failure is 5 mg twice daily. After 2 weeks of treatment, the patient should be reviewed. If the resting heart rate is persistently above 60bpm, the dose should be increased to 7.5mg twice daily. If the resting heart rate is persistently below 50bpm or the patient experiences symptoms of bradycardia (e.g. dizziness, fatigue or hypotension), the dose should be reduced to 2.5mg twice daily. If the resting heart rate is between 50-60bpm, the dose should remain at 5mg twice daily.

POTS/IST

The recommended initial dose is 2.5mg orally twice daily with or without food. The total daily dose is usually 10 mg but can be increased up to a maximum daily dose of 15mg given in 2-4 divided doses and titrated according to response. The initial starting dose should be prescribed as half of a 5mg twice daily due to the substantial difference in cost between the 2.5mg and 5mg tablets.

Adverse effects (incidence, identification, importance and management)

Common (between 1 in 10 and 1 in 100) **or very common** (>1 in 10)	Arrhythmias; atrioventricular block; dizziness; headache; hypertension; Bradycardia AV 1st degree block (ECG prolonged PQ interval) Ventricular extrasystoles Atrial fibrillation Uncontrolled blood pressure Luminous phenomena and vision disorders*
Uncommon (between 1 in 100 and 1 in 1,000)	Abdominal pain; angioedema; constipation; diarrhoea; eosinophilia; hyperuricaemia; hypotension; muscle cramps; nausea; Palpitations supraventricular extrasystoles QT interval prolongation; skin reactions; syncope; vertigo Diplopia Visual impairment Dyspnoea Angioedema Rash Elevated creatinine in blood Asthenia Fatigue

*Visual symptoms are the most common adverse effects 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 of which resolved during or after treatment. Blurred vision also occurs commonly. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs.

Cautions and contra-indications

Cautions

- Patient aged <18 years' old
- Pre-existing cardiac arrhythmia
- Patients with retinitis pigmentosa
- Caution should be exercised when using ivabradine in patients with moderate hepatic impairment. Ivabradine is contraindicated in those with severe hepatic impairment.
- Concurrent heart rate lowering agents
- Severe heart failure (NYHA IV)
- Post CVA (use not recommended immediately after stroke)
- Established renal failure (CrCl <15ml/min)
- Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
- Ivabradine has no or negligible influence on the ability to use machines. A specific study to assess the possible influence of ivabradine on driving performance has been performed in healthy volunteers where no alteration of the driving performance was evidenced. However, in post-marketing experience, cases of impaired driving ability due to visual symptoms have been reported. 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.

Contraindications

- Pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures
- Hypersensitivity to the active substance or to any of the excipients (refer to SPC)
- Daytime resting heart rate < 70bpm at initiation
- Severe hypotension (<90/50mmHg)
- Cardiogenic shock
- Sick sinus syndrome
- Sino-atrial block & 3rd degree AV-block
- Congenital QT syndrome
- Pacemaker dependent* (i.e. heart rate imposed exclusively by the pacemaker)
- Acute Myocardial infarction
- Unstable angina
- Unstable or acute heart failure
- Severe hepatic impairment
- 2nd degree AV-block (use not recommended)
- The use of ivabradine is not recommended immediately after a stroke since no data is available in these situations.
- This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Monitoring requirements and responsibilities

- Monitor heart rate every 3 months (resting ventricular rate must be more than 50bpm to continue treatment). If the heart rate falls persistently below 50 bpm (at rest) and / or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension– This will require a dose reduction or cessation of therapy.
- Manual pulse rhythm check should be performed at every annual review to check for AF, including patients with a history of AF who are currently in sinus rhythm. If AF occurs during treatment ivabradine should be stopped.
- Renal and liver function should be monitored before starting treatment with ivabradine, then at least annually throughout treatment or more frequently if clinically indicated.
- Ensure potassium levels are maintained in range as hypokalemia can increase the risk of arrhythmias and can potentiate bradycardia.

Interactions

Drug/ Drug class	Examples (not exhaustive)	Recommendation
Potent inhibitors of CYP3A4	• Azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole), • HIV protease inhibitors (e.g. ritonavir, nelfinavir), • Macrolide antibiotics (e.g. clarithromycin and erythromycin)	Concomitant use not recommended - may increase ivabradine exposure.
Moderate inhibitors of CYP3A4	• Diltiazem • Verapamil	Concomitant use not recommended - may increase ivabradine exposure.
CYP3A4 inducers	• Rifampicin • Phenytoin • Carbamazepine • Phenobarbital • St. John's wort	Use with caution as may decrease ivabradine exposure. May require closer monitoring and dose adjustment. Use of St John's wort is not recommended.
Drugs which prolong the QT interval	• Amiodarone • Sotalol • Disopyramide • Mefloquine • Quinidine	Concomitant use not recommended - increased risk of ventricular arrhythmias.

Grapefruit juice should be avoided as it can increase exposure to ivabradine.

Peer-reviewed references for product usage

1. Summary of Product Characteristics, Procoralan® Updated March 2022
2. MHRA Drug Safety Update Ivabradine (Procoralan) in the symptomatic treatment of angina: risk of cardiac side effects. https://www.gov.uk/drug-safety-update/ivabradine-procoralan-in-the-symptomatic-treatment-of-angina-risk-of-cardiac-side-effects
3. NICE Clinical Guidance CG126: Stable angina: management (August 2016) https://www.nice.org.uk/guidance/cg126/chapter/1-Guidance
4. NICE TA267 Ivabradine for treating chronic heart failure (November 2012) https://www.nice.org.uk/guidance/ta267

5. Ptaszynski P et al. Metoprolol vs Ivabradine in the treatment of inappropriate sinus tachycardia in patients unresponsive to previous pharmacological therapy. Europace 2013; 15; 116-21
6. Ptaszynski P et al. Ivabradine in the treatment of inappropriate sinus tachycardia in patients after successful catheter ablation of atrioventricular node slow pathway. PACE 2013;36: 42-49
7. Ptaszynski P et al. Ivabradine in combination with metoprolol succinate in the treatment of Inappropriate Sinus tachycardia. J Cardiovasc Pharmacol Therapeutics 2013 18(4);338-344
8. De la Cruz E et al. Long term outcomes in a case series of patients diagnosed of inappropriate sinus tachycardia treated with ivabradine. J Interv Card Electrophysiol. 2013;36 Suppl 1. S91
9. Benezet-Mazuccos J et al. Long term outcomes of ivabradine in inappropriate sinus tachycardia patients. appropriate efficacy or inappropriate patients. PACE 2013;36(7):830-6
10. Adler A et al. Ivabradine for the prevention of inappropriate shocks due to inappropriate sinus tachycardia in patients with an implanted cardioverter defibrillator. Europace 2013;15: 362-365
11. Cappato R et al. Clinical Efficacy of Ivabradine in patients with inappropriate sinus tachycardia: a prospective, randomised, placebo-controlled, double-blind, crossover evaluation. J Am Coll Cardiol. 2012;60: 1323-9
12. Zellerhoff S et al. Ivabradine in patients with inappropriate sinus tachycardia. NaunynSchmied Arch Pharmacol. 2010;382: 483-486
13. Calo L et al. Efficacy of ivabradine administration in patients affected by inappropriate sinus tachycardia. Heart Rhythm 2010;7: 1318-1323
14. Kaplinsky E. Efficacy of Ivabradine in four patients with inappropriate sinus tachycardia: a three month long experience based on electrocardiographic, Holter monitoring, exercise tolerance and quality of life assessments. Cardiology J 2010;17: 166-171
15. Rakovec P. Treatment of inappropriate sinus tachycardia with ivabradine. Wien Klin Wochenschr 2009;121(21-22):715-8

Refer to page 10 of NHS England's guidance on Responsibility for prescribing between Primary & Secondary/Tertiary Care for more information/guidance about taking on prescribing of specialist medicines.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug costs

For ivabradine it is important to be aware of the price difference between the strengths, see below. Where a single dose is 5 mg or 7.5 mg do not use multiples of 2.5 mg tablets due to the cost.

Ivabradine 2.5mg x 56 tablets = £24.81
Ivabradine 5mg x 56 tablets = £7.34
Ivabradine 7.5mg x 56 tablets = £5.92

Prices correct as per May 2022 Drug Tariff online.

Written By	Cardiology Working group	June 2019
Approved By	Dorset Medicines Advisory Group	Jan 2020
Reviewed By	The Cardiology & Anticoagulation Working Group	June 2022
Approved By	Dorset Medicines Advisory Group	July 2022
Date of next review	June 2024 or before, in light of new evidence or information.	