Prescribing Information Document
Ivabradine for treating chronic heart failure and stable angina.

1. Introduction

The document aims to support prescribing of ivabradine in adults with heart failure and stable angina across Herts and West Essex ICS.

HWE ICS approved indications for use:

Ivabradine is recommended as an option for treating **chronic heart failure** for people in line with the recommendations from NICE TA267

- 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. 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.

Ivabradine is recommended for use for **symptomatic management of chronic stable angina** as a second line treatment choice to reduce angina frequency and improve exercise tolerance in those who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, calcium channel blockers and long-acting nitrates. (First line treatments are considered as beta-blockers and calcium channel blockers). Ivabradine should be initiated by secondary care specialist.

2. Criteria for transfer of prescribing to primary care

The following must apply before the GP is asked to accept on-going prescribing responsibility for ivabradine.

For heart failure management: Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team. 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.

Prescribing may be transferred to primary care once the patient is on a stable dose and heart rate is stable.

For management of stable angina: Ivabradine should be initiated by secondary care specialist. The decision to initiate or titrate treatment takes place with the availability of serial heart rate measurements, ECG or ambulatory 24-hour monitoring.

If there is no improvement in symptoms of angina within 3 months after start of treatment, ivabradine should be discontinued. Discontinuation should be considered if there is only limited symptomatic response and when there is no clinically relevant reduction in resting heart rate within three months.

Prescribing may be transferred to primary care once the patient has been stabilised on a dose, heart rate is stable and symptomatic improvement has been established.

Off-label/ unlicenced use to remain with the specialist.

3. Areas of responsibility

Specialist Responsibilities	
1.	Initiate ivabradine in patients with heart failure in line with criteria recommended in NICE TA267 or for patients with stable angina as a second line as listed above (see 'HWE ICS approved indications for use')
2.	Perform baseline monitoring tests: BP, heart rate, ECG, baseline renal and liver function.
3.	Discuss treatment with ivabradine with the patient including; - counselling points; *to include but not limited to:* • *Advise on dosage and frequency.* • *Advise on common side effects with the patient/ carer and symptoms the patient may experience.* *Advise patient to report to a healthcare professional any visual disturbances, particularly in the first few weeks of treatment.* *Advise patient on symptoms related to bradycardia such as dizziness, fatigue or hypotension.* *Advise the patient of signs and symptoms of atrial fibrillation.* • *Advise patient not to drink grapefruit juice during treatment with ivabradine as it can increase exposure to ivabradine.* - Ongoing requirement for monitoring/review - Patients or their carers should be advised to seek help if side effects are suspected.
4.	Prescribe ivabradine prior to transferring prescribing to primary care. (see 'Criteria for transfer of prescribing to primary care')
5	Ensure that patient/carer is informed and made aware of their responsibilities (see 'Patient/carer responsibilities').
6.	At the point of requesting the transfer of prescribing to primary care, to provide advice to Primary Care prescribers which includes but is not limited to the following: - Clear diagnosis and information that has been discussed with patient and carer - Dosing regime - Additional monitoring requirements (if different to standard ongoing monitoring detailed in primary care prescriber responsibilities below) - Stopping/escalation (re-referral) criteria - Specialist team contact details for GPs to obtain advice and support

GP/ Primary care prescriber responsibilities	
1.	Review the request from the specialist and consider if sufficient information has been provided to take on the responsibility for prescribing ivabradine in adult patients, patient is on a stabilised dose and indication is according to the agreed licensed indications for use.
2.	Prescribe ivabradine at the dose advised by the specialist team.
3.	Monitor heart rate and manual pulse rhythm annually in stable patients* Where irregular pulse is detected, consider ECG and/or seek advice from specialist team. (See further information below: side effects on atrial fibrillation and cardiac arrythmia's) Where resting ventricular rate falls below 50bpm, seek advice from specialist if required and adjust dose as required during treatment. (see 'Further information' below on dose, dose down titration and cessation of treatment and monitoring. More frequent monitoring may be required when heart rate decreases below 50bpm and after dose changes) <u>Concomitant disease monitoring as required</u>:

	For patients with heart failure; monitor in line with standard monitoring guidance detailed in NICE guidance 'chronic heart failure in adults; diagnosis and management' or as otherwise indicated as part of the patients care and treatment plan.
4.	Check for possible drug interactions when newly prescribing or stopping concurrent medication.
5.	Refer the patient back to secondary/specialist care during pregnancy, if there is no ongoing benefit of treatment and symptoms/the patient's condition deteriorates.
6.	Seek advice from the specialist team regarding any concerns, for example: visual or other side-effects or lack of efficacy.
7.	To deal with general health issues of the patient.

Patient/Carer responsibilities	
1.	Report to their specialist if they do not have a clear understanding of, or have any concerns with their treatment.
2.	Inform the GP if pregnant or planning a pregnancy while on treatment with ivabradine.
3.	Report any adverse effects or worsening of condition to the GP and/or specialist whilst taking ivabradine.
4.	Attend review appointments with specialist and primary care as requested.

4. Further information

For full details, please refer to the current individual drug Summary of Product Characteristics (SPC) and BNF. Further information also available on cks.nice.org and MHRA safety alert (dec 2014)

Treatment in heart failure:

The treatment can be initiated only in patients with stable heart failure. The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, 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 in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension. If heart rate is between 50 and 60 bpm, the dose of 5 mg twice daily should be maintained.

If **during treatment**, heart rate decreases persistently below 50 beats per minute (bpm) at rest or the patient experiences symptoms related to bradycardia, the dose must be titrated downward to the next lower dose in patients receiving 7.5 mg twice daily or 5 mg twice daily. 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.
Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist.

Symptomatic treatment of chronic stable angina:

Do not start ivabradine if the resting heart rate is below 70 beats per minute.

Patients aged 74years or under: The starting dose of ivabradine should not exceed 5 mg twice daily in patients aged below 75 years. After three to four weeks of treatment, if the patient is still symptomatic, if the initial dose is well tolerated and if resting heart rate remains above 60 bpm, the dose may be increased to the next higher dose in patients receiving 2.5 mg twice daily or 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.
Patients aged 75years or over: Initially 2.5 mg twice daily, increased if necessary to 7.5 mg twice daily.

If there is no improvement in symptoms of angina within 3 months after start of treatment, treatment of ivabradine should be discontinued. Discontinuation of treatment should be considered if there is only limited symptomatic response and when there is no clinically relevant reduction in resting heart rate within three months.

If, **during treatment**, heart rate decreases 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 lowest dose of 2.5 mg twice daily. After dose reduction, heart rate should be monitored*.

Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dose reduction.

***Monitoring heart rate**

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. This also applies to patients with a low heart rate, in particular when heart rate decreases below 50 bpm, or after dose reduction.

Contra-indications and cautions:

refer to SPC for complete and up to date list of contraindications.

Side effects:

refer to SPC for complete and up to date list of side effects.

Of particular note:	**Action to take**
Atrial fibrillation Cardiac arrhythmias	Discuss with specialist to review benefits and risks of ivabradine (MHRA safety alert, 2014) Seek advice from specialist
Bradycardia *Of note; reported particularly in first 2-3months of treatment initiation*	Follow dosing advice on dose down titration and cessation of treatment. Discontinue if resting heart rate persistently below 50 beats per minute or continued symptoms of bradycardia despite dose reduction. If required, seek advice from specialist
Eye disorders (blurred vision, phosphenes) *Of note: usually starting within the first 2 months of treatment and resolving either on continued treatment or on stopping treatment.*	Discuss treatment continuation with patient
Other common side effects Headache: common but is usually transient and resolves within the first month of treatment. Uncontrolled blood pressure: The SHIFT trial reported that more patients experienced episodes of increased blood pressure while treated with ivabradine (7.1%) compared to patients treated with placebo (6.1%). These episodes occurred most frequently shortly after blood pressure treatment was modified, were transient, and did not affect the treatment effect of ivabradine. When treatment modifications are made in chronic heart failure patients treated with ivabradine blood pressure should be monitored at an appropriate interval	

People taking ivabradine should be advised to be careful when driving or using machines at times when there could be sudden changes in light intensity (especially when driving at night) if they experience luminous phenomena.

NB: hypokalaemia - Ensure potassium levels are maintained in range as hypokalaemia can increase the risk of arrhythmias. This may be particularly important in patient who are on potassium depleting diuretics (thiazide and loop diuretics). As ivabradine may cause bradycardia, the resulting combination of hypokalaemia and bradycardia is a predisposing factor to the onset of severe arrhythmias, especially in patients with long QT syndrome, whether congenital or substance-induced

Drug interactions:

refer to SPC for complete and up to date list of side effects.

Interactions of particular note:

MHRA safety alert, 2014

''do not prescribe ivabradine with other medicines that cause bradycardia, such as verapamil, diltiazem, or strong CYP3A4 inhibitors''.

Potent CYP3A4 inhibitors (such as azole antifungals, macrolide antibiotics and protease inhibitors) concomitant administration is **contraindicated**, as they may increase the plasma concentration of ivabradine, increasing the risk of bradycardia.

Combination **with verapamil or diltiazem** which are moderate CYP3A4 inhibitors with heart rate reducing properties is contra-indicated. The use of other moderate CYP3A4 inhibitors may be considered at a lower starting dose of 2.5 mg twice daily and if resting heart rate is above 70 bpm, with monitoring of heart rate.

CYP3A4 inducers (e.g. rifampicin, barbiturates, phenytoin, St John's Wort may decrease ivabradine exposure and activity and concomitant use of CYP3A4 inducing medicinal products may require an adjustment of the dose of ivabradine. SPC notes that the intake of St John's Wort should be restricted during the treatment with ivabradine.

Avoid concomitant use of **drugs prolonging QT interval** (e.g. amiodarone, sotalol, disopyramide, mefloquine, quinidine) due to increased risk of ventricular arrhythmias.

5. References

1) Electronic Medicines Compendium, SPC ivabradine, accessed via medicines.org.uk (accessed March 2024)
2) Ivabradine for treating chronic heart failure, NICE TA267; published 2012 (link)
3) Chronic heart failure in adults: diagnosis and management, NICE CG106, published Sept 2018 (link)
4) Stable angina: management, NICE CG126, published 2011, last update Aug 2016 (link)
5) 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes, European Heart Journal (2020) 41, 407-477
6) NICE CKS, Ivabradine (December 2023), accessed via https://cks.nice.org.uk/topics/angina/prescribing-information/ivabradine/ (accessed March 2024)
7) Ivabradine (Procoralan) in the symptomatic treatment of angina: risk of cardiac side effects, Drug safety update December 2014, accessed via https://www.gov.uk/drug-safety-update (accessed March 2024)

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