Ivabradine ▼

- Initiated as an adjunct therapy in the treatment of stable chronic heart failure in patients inadequately controlled or intolerant of first-line therapies
- Initiated as monotherapy or adjunct therapy in the treatment of chronic stable angina in patients inadequately controlled or intolerant of first-line therapies

This document supports the use and transfer of an agent which is classified as **AMBER**.
It is intended for completion by specialist in order to give Primary Care prescribers a clear indication of the reason for recommending an **AMBER** medication together with suggested criteria for its subsequent continuation or discontinuation. This RICaD should be provided as a supplement to the specialist's clinical letter.

Patient details		**GP details**		**Specialist details**	
Name		**GP name**	**Dr**	**Specialist name**	
PID		**GP address**		**I confirm that this patient is eligible to receive ivabradine under the restrictions listed below**	
DOB				**Signature**	
Patient address				**Date**	
				Contact details	

Rationale for Choice

Relevant Diagnosis:	Chronic heart failure (NICE TA 267)	Chronic stable angina (NICE CG 126)
Agreed Indication(s) for inclusion in the BSSE APC Formulary:	Ivabradine is indicated in patients in patients with chronic heart failure with NYHA II-IV class with systolic dysfunction, in patients with sinus rhythm and whose heart rate > or = 75 beats per minute (bpm), in combination with standard therapy including beta blocker therapy or when a beta-blocker therapy is contra-indicated or not tolerated	Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 bpm. Ivabradine is indicated: - in adults unable to tolerate or with a contra-indication to the use of beta-blockers - or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

Diagnosis:	Chronic heart failure (NICE TA 267)	Chronic stable angina (NICE CG 126)
Reason why ivabradine has been chosen in preference to drugs without Formulary restrictions:	For specialist initiation by a heart failure specialist with access to a multidisciplinary team in line with NICE TA 267 states ivabradine is an option for patient ○ who has New York Heart Association (NYHA) II to IV stable chronic heart failure with systolic dysfunction ☐ ○ who are in sinus rhythm with a heart rate of 75 beats per minute (bpm) or more ☐ ○ who are given ivabradine in combination with standard therapy (including beta-blocker therapy, ACE inhibitors and aldosterone antagonists) OR when beta-blocker therapy is not tolerated or contraindicated ☐ ○ with a left ventricular ejection fraction ≤ 35% ☐	For specialist initiation with access to a multidisciplinary team Ivabradine is an option as • monotherapy if the person cannot tolerate beta blockers and calcium channel blockers or both are contraindicated ☐ • as adjunct therapy in patients whose symptoms are not controlled and the other option (calcium channel blocker or beta blocker) is contraindicated or not tolerated ☐ Do not offer a third anti-anginal drug to people whose stable angina is controlled with two anti-anginal drugs. Consider adding a third anti-anginal drug only when: • the person's symptoms are not satisfactorily controlled with two anti-anginal drugs ☐ and • the person is waiting for revascularisation or revascularisation is not considered appropriate or acceptable ☐

Special precautions	**Contraindications**
	• Hypersensitivity to the active substance or to any of the excipients listed
	  • In heart failure:- Do not initiate if heart rate below 75 beats per minute (bpm)
	  • In stable angina:- Do not initiate if heart rate below 70 beats per minute (bpm)
	  • Resting heart rate below 70 beats per minute (bpm) prior to treatment
	• Cardiogenic shock
	• Acute myocardial infarction
	• Severe hypotension (< 90/50 mmHg)
	• Severe hepatic insufficiency
	• Sick sinus syndrome
	• Sino-atrial block
	• Unstable or acute heart failure
	• Pacemaker dependent (heart rate imposed exclusively by the pacemaker)
	• Unstable angina
	• AV-block of 3rd degree
	• Congenital QT syndrome
	• Combination with strong cytochrome P450 3A4 inhibitors such as azole antifungals (ketoconazole, itraconazole), macrolide antibiotics (clarithromycin, erythromycin *per os*, josamycin, telithromycin), HIV protease inhibitors (nelfinavir, ritonavir) and nefazodone
	• Combination with verapamil or diltiazem which are moderate CYP3A4 inhibitors with heart rate reducing properties
	• Pregnancy, lactation and women of child-bearing potential not using appropriate contraceptive measures
	Caution (As per BNF online May 15- for more information please see SmPC)
	  • monitor regularly for atrial fibrillation (consider benefits and risks of continued treatment if atrial fibrillation occurs)
	  • atrial fibrillation or other arrhythmias (treatment ineffective)
	  • monitor for bradycardia, especially after any dose increase, and discontinue if resting heart rate persistently below 50 beats per minute (bpm) or continued symptoms of bradycardia despite dose reduction
	  • *for angina*, consider stopping if there is no or limited symptom improvement after 3 months
	  • intraventricular conduction defects
	  • hypotension (avoid if severe)
	  • retinitis pigmentosa
	  • elderly	

Pre-treatment test results	n/a	

Guidance on initiation (to be completed by the specialist)

Diagnosis:	Chronic heart failure (NICE TA 267)	Chronic stable angina (NICE CG 126)
Initiation dose:	The treatment has to be initiated only in patient with stable heart failure. It is recommended that the treating physician should be experienced in the management of chronic 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 beats per minute (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. Prescribing responsibility will transfer to GPs once the patient is stable on ivabradine.	It is recommended that the decision to initiate or titrate treatment takes place with the availability of serial heart rate measurements, ECG or ambulatory 24-hour monitoring. 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 beats per minute (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. If there is no improvement in symptoms of angina within 3 months after start of treatment, treatment of ivabradine should be discontinued. In addition, 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.
Stable dose for continuation in primary care	Specialist to complete	Specialist to complete
MHRA advice:		Only increase the dose to 7.5 mg twice daily after 3 to 4 weeks of treatment and if the 5 mg dose is well tolerated but insufficient. Carefully monitor the effect of a dose increase on heart rate.
Additional info:	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 (bpm)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.	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 (one half 5 mg tablet twice daily). After dose reduction, heart rate should be monitored.
	Treatment must be discontinued if heart rate remains below 50 beats per minute (bpm) or symptoms of bradycardia persist despite dose reduction.	
	Ivabradine▼is a black triangle drug. All suspected adverse effects should be reported to the CHM www.yellowcard.gov.uk	
	SmPC can be accessed at http://emc.medicines.org.uk	
Monitoring:	No specific/ mandatory monitoring required. However heart rate should be monitored at routine appointments as dose modification may be required.	
		MHRA Advice – Dec 2014 Monitor patients regularly for atrial fibrillation. If atrial fibrillation occurs, carefully reconsider whether the benefits of continuing ivabradine treatment outweigh the risks

Suggested Criteria for Continuation or Discontinuation(to be completed by the specialist)

<table>
<tr><th colspan="3">Assessment of Efficacy</th></tr>
<tr><td>Diagnosis:</td><td>Chronic heart failure (NICE TA 267)</td><td>Chronic stable angina (NICE CG 126)</td></tr>
<tr><td>Frequency:</td><td>Around once a month initially (via initiating prescriber) until symptom control and appropriate dose titration has been achieved.

Initial dose titration should be carried out by the Heart Failure Nurses or specialist unless the patient has access to a GP with a specialist interest in heart failure.</td><td>Around once a month initially (at GP surgery) until symptom control has been achieved.</td></tr>
<tr><td>Location:</td><td colspan="2">During admission and on review at follow up out-patient appointments</td></tr>
<tr><td>Method:</td><td colspan="2">Routine out-patient clinical review.</td></tr>
<tr><td>Continuation Criteria</td><td colspan="2">To continue as tolerated by the patient in accordance with heart rate and appropriate dose titration</td></tr>
<tr><td rowspan="2">Discontinuation Criteria</td><td colspan="2">Treatment must be discontinued if heart rate falls below 50 beats per minute (bpm) or symptoms of bradycardia persist, severe side effects or intolerance to the medication. Main reported side effects include bradycardia (see notes above in guidance on initiation section), headache, dizziness, visual disturbances including phosphenes and blurred vision.

Less common side effects include: nausea, constipation, diarrhoea, palpitations</td></tr>
<tr><td></td><td><u>MHRA Advice – Dec 2014</u>
Consider stopping ivabradine if there is no or only limited symptom improvement after 3 months</td></tr>
<tr><td rowspan="2">Follow up action</td><td colspan="2">No specific monitoring required</td></tr>
<tr><td></td><td><u>MHRA Advice – Dec 2014</u>
Monitor patients regularly for atrial fibrillation. If atrial fibrillation occurs, carefully reconsider whether the benefits of continuing ivabradine treatment outweigh the risks</td></tr>
<tr><td>Shared Care read code</td><td colspan="2">In the patients notes, using the appropriate Read Code listed below, denote that the patient is receiving treatment under a shared care agreement/RICaD

<table>
<tr><th>GP Prescribing System</th><th>Read Code</th><th>Description</th></tr>
<tr><td>EMIS and Vision</td><td>8BM5.00</td><td>Shared care prescribing</td></tr>
<tr><td>SystmOne</td><td>XaB58</td><td>Shared care</td></tr>
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