Oxford University Hospitals NHS Trust

NHS
Oxfordshire
Clinical Commissioning Group

AMB C

Ivabradine for Heart Failure

Amber Continuation Guideline

This guideline provides prescribing and monitoring guidance for ivabradine therapy for heart failure. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF. There is a separate shared care protocol for ivabradine in stable angina available here

Specialist HF Team responsibilities (OUH HF Team and OH HF Team) prior to transfer of prescribing

Since the NICE TA 267 in 2012[1], experience with ivabradine therapy has become more widespread and it is acceptable practice for the hospital heart failure (OUH HF) team to initiate therapy in the out-patient or in-patient setting and then the GP to continue prescribing. It is also acceptable for the community (OH) heart failure team to initiate therapy following MDT discussion at OUH.

The HF team:

- To discuss ivabradine treatment with the patient and ensure the decision to start treatment is agreed between the patient and the HF team. The OUH HF team should be satisfied that the patient understands the information supplied and the importance of adhering to treatment.
- To contact the patient's GP and community HF nurse (CHFN) formally, by letter or email to request transfer of care and outline the amber continuation guidelines.
- To initiate ivabradine therapy and continue prescribing for the first month of therapy.
- To review patient within 4 weeks to ensure stability and to consider up-titration of ivabridine, with review thereafter if indicated. This again will be formally communicated with the GP and HF team by letter or email.
- To ensure the patient understands the nature and complications of ivabradine therapy and their role in reporting adverse effects promptly, either to the HF team or the GP.
- To liaise with the GP regarding changes in disease management, drug dose and missed clinic appointments.
- Be available to give advice to GP and patient at any time throughout treatment (see Back-up Information and Advice section, page 3).

GP responsibilities summary

- To prescribe ivabradine according to amber continuation guideline.
- To advise the HF team of any clinical changes or adverse effects where appropriate.
- To monitor for adverse effects as detailed in the amber continuation guideline.
- Be aware of any specific drug interactions with ivabradine when prescribing new drugs.

Patient responsibilities

- Ensure they bring a list of current medication to every hospital out-patient visit as appropriate.

- Report any adverse effects to their GP and/or HF team. All patients are provided with HF team contact details to facilitate this.
- Attend for regular monitoring as requested by GP / HF team.

Background for Use

Ivabradine is a pure heart rate lowering agent which selectively and specifically inhibits the cardiac pacemaker I_f current that controls the spontaneous diastolic depolarisation in the sino atrial node, thereby lowering heart rate and decreasing myocardial oxygen consumption. Ivabradine does not affect myocardial contractility or atrioventricular conduction. Ivabradine is licensed for the symptomatic treatment of chronic stable angina and the treatment of chronic heart failure[2].

Supporting Information

The aim of treatment for heart failure patients is to improve life expectancy, quality of life and also to avoid or reduce hospitalisation. The NICE TA 267 recommends ivabradine as a treatment option for patients with chronic heart failure, who meet all the following criteria:

- New York Heart Association (NYHA) class II to IV stable chronic heart failure with systolic dysfunction
- In sinus rhythm with a resting heart rate of 75 bpm or more
- Left ventricular ejection fraction of 35% or less
- In combination with standard therapy including beta-blocker therapy, angiotensin-converting enzyme (ACE) inhibitors and aldosterone antagonists, or when beta-blocker therapy is contra-indicated or not tolerated

In addition ivabradine should only be initiated after patient has been optimised on standard therapy and stabilised on this therapy for a period of at least 4 weeks[1].

Contraindications and Precautions

Contraindications (for full details see BNF or SPC)	Cautions (for full details see BNF or SPC)
• Bradycardia – resting heart rate below 60 bpm • Sick sinus syndrome • Sino-atrial block or 2nd or 3rd degree AV block • Congenital QT syndrome • Cardiogenic shock and acute MI • Severe hypotension (blood pressure below 90/50 mmHg) • Severe hepatic insufficiency • Unstable or acute heart failure • Unstable angina • Within 4 weeks of CVA • Combination with potent CYP3A4 inhibitors (see below under drug interactions) • Pregnancy and breast feeding • Atrial fibrillation	• Pre-existing cardiac arrhythmias • Severe renal impairment – creatinine clearance below 15ml/min • Moderate hepatic insufficiency • Concurrent heart rate lowering agents (see below under drug interactions) • Post CVA • Retinitis pigmentosa

BNF = British National Formulary; SPC = Summary of Product Characteristics

Dosage

HF team to prescribe for first month and to monitor commencement and up-titration of therapy. Starting dose is 5mg twice daily or 2.5mg twice daily if patient is over 75 years of age (note resting heart rate should be above 75 bpm or above before initiating ivabradine for heart failure). Review within 4 weeks:

- If resting heart rate is between 50 and 60 bpm maintain starting dose
- If resting heart rate is above 60bpm consider increasing dose to 7.5mg twice daily (or 5mg twice daily if initial starting dose is 2.5mg twice daily)
- If resting heart rate is less than 50 bpm consider dose reduction or cessation of therapy:
    - If during treatment the heart rate is persistently below 50 bpm at rest continuation may be considered if the heart rate remains below 50 bpm but the patient is well and free of symptoms. Advice may be sought from the patient's consultant/specialist prescriber.
    - If during treatment the heart rate is persistently below 50 bpm at rest and the patient experiences symptomatic bradycardia e.g. dizziness, fatigue or hypotension, the dose must be titrated downward including the use of 2.5mg twice daily (one half 5mg tablet twice daily).
    - If treatment requires a dose reduction, the patient should be reviewed after one week when heart rate should be monitored and symptoms reassessed. If symptomatic bradycardia persists, treatment must be discontinued.
- HF team to formally transfer prescribing to GP once patient on optimal dose.

Time to Response
Effects on heart rate will occur during first few days of therapy, reaching a maximum effect after approximately 2 weeks. Beneficial effects on outcome in heart failure were seen within first 3 months of therapy in the SHIFT study[3].

Pre-Treatment Assessment by HF team and monitoring during up-titration phase by GP:
Prior to initiation and before and after each dose titration the following should be monitored:

- Blood pressure
- Heart rate
- ECG (if history of arrhythmias)
- Renal function if known to have history of moderate to severe renal impairment

Ongoing Monitoring by GPs
Once the patient is stabilised on ivabradine ongoing monitoring by the GP should include:

- Heart rate and blood pressure if changes in dosage or as appropriate during routine appointments.
- Routine renal function and electrolyte monitoring every 6 months (as per general heart failure standard of care)

More frequent monitoring should be undertaken if clinically indicated or following advice from HF team (OUH or OH).

Actions to be taken (for full details of side effects see BNF and SPC)

The in-patient HF team or community HF nurses may be contacted for advice regarding tolerability, side effects or potential complications of ivabradine therapy anytime during treatment. Patients may also be referred back to OUH HF team if necessary. See Back-up information and advice for contact details.

Side Effects	Actions to be taken
Bradycardia	If resting heart rate drops below 50 bpm, reduce ivabradine dose to next level, e.g. if patient taking 5mg twice daily reduce to 2.5mg twice daily. If patient is already on the lowest dose of 2.5mg twice daily, and the bradycardia is persistent and symptomatic discontinue treatment.
Arrhythmias	If the patient develops any symptoms of arrhythmias: palpitations, irregular pulse, do ECG monitoring and discuss with OUH HF team. If patient develops

	atrial fibrillation during ivabradine therapy please discontinue treatment. Ivabradine is not recommended in patients with 2nd degree AV-block.
Hypotension	If patient develops severe hypotension (less than 90/50mmHg) – discuss with OUH HF team, consider discontinuing treatment if dosage adjustments of other drugs to raise blood pressure are not appropriate.
Renal Impairment	If patient develops significant renal impairment, eGFR less than 30ml/min, ivabradine can be continued but with caution. Contact OUH HF team as appropriate if further advice needed due to deteriorating renal function.
Hepatic impairment	Discontinue if patient develops severe hepatic impairment. Ivabradine is extensively metabolized by CYP3A4 in the liver and gut.
Visual disturbances	Ivabradine may cause luminous phenomena (phosphenes) this may cause problems for patients for example night-time driving. Reduction in dosage will reduce this side effect, if particularly troublesome. Treatment should be discontinued if there is any unexpected deterioration in visual function
Headache	Common during first few weeks of therapy, reassure patient this side effect should subside

Ivabradine is a black triangle drug – any adverse effect must be reported to the MHRA using the yellow card system and via the local incident reporting system.

Notable Drug Interactions (Refer to BNF and SPC)

Drug / Drug class	Recommendation – for full details see BNF and SPC
Cardiovascular QT prolonging agents e.g. amiodarone, sotalol, quinidine and disopyramide Non-cardiovascular QT prolonging agents e.g. mefloquine, pimozide, pentamidine	Avoid concurrent use of ivabradine with any medication which can prolong QT interval (QT prolongation may be exacerbated by heart rate reduction).
Ketoconazole, itraconazole, HIV protease inhibitors, clarithromycin, and erythromycin	Avoid concomitant use of potent CYP3A4 inhibitors with ivabradine (increased plasma concentrations of ivabradine).
Diltiazem and verapamil	Avoid concomitant use of heart rate lowering and moderate CYP3A4 inhibitor calcium channel blockers (increased plasma concentrations of ivabradine and additional heart rate reduction)
Fluconazole	Concomitant use of moderate CYP3A4 inhibitors with ivabradine should be used with caution, recommend starting dose of 2.5mg twice daily
Grapefruit juice	Avoid grapefruit juice with ivabradine.
Potassium depleting diuretics e.g. furosemide, bumetanide, thiazides	Hypokalaemia can increase the risk of arrhythmias. As ivabradine can cause bradycardia, the combination of hypokalaemia and bradycardia is a risk for severe arrhythmias. Monitor potassium closely, especially when diuretic doses are increased and supplement potassium as appropriate.
Rifampicin, phenytoin, carbamazepine	Concomitant use of CYP3A4 inducers may reduce ivabradine plasma levels. Dosage adjustments may be necessary.
St John's Wort	Avoid use with ivabradine as significant reductions in ivabradine concentrations with concomitant use.

Back-up Information and Advice

Contact the heart failure team: telephone 01865 223067 or email heartfailure.nurse@ouh.nhs.uk

The community HF team can also be contacted for advice during treatment: telephone 01865 904006 or email oxfordhealth.communityheartfailure@nhs.net

References

1. NICE TA 267: Ivabradine for the treatment of patients with chronic heart failure. November 2012.
2. Procoralan. Summary of Product characteristics accessed via eMC, last updated 01 2018.
3. Swedberg et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010; Vol 376: 875-885.