Oxford University Hospitals NHS
NHS Trust

NHS
Oxfordshire
Clinical Commissioning Group

Shared Care Protocol: Use of ivabradine as add on therapy for symptomatic treatment of patients with stable angina

This protocol provides prescribing and monitoring guidance for ivabradine therapy. 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 an Amber Continuation guideline available for the treatment of heart failure with ivabradine.

Shared Care Responsibilities
Shared care assumes communication and agreement between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Specialists must contact GPs as soon as decision is made to commence treatment with ivabradine to ensure adequate time for full communication, support and agreement to be made. Specialists must retain prescribing until the patient's clinical condition is stable or predictable.

Specialist OUH Cardiologist:
Since the NICE Clinical guideline for the management of stable angina, clinical experience with the use of ivabradine has become more widespread[1]. Ivabradine may be initiated by an OUH cardiologist (consultant or registrar) or consultant nurse in the in-patient or out-patient setting:

- To discuss ivabradine treatment with the patient and ensure the decision to start treatment is agreed between the patient and the prescriber. The cardiologist/consultant nurse should be satisfied that the patient understands the information supplied and the importance of adhering to treatment.
- To contact GP formally, by letter or email to request shared care and outline shared care protocol criteria.
- To initiate ivabradine therapy and prescribe for the first month of therapy, or until uptitration is complete and dose stabilised
- To discuss follow-up plan with the GP.
- To uptitrate ivabradine therapy
- Ensure the patient understands the need for, nature and complications of ivabradine therapy and their role in reporting adverse effects promptly, either to the cardiology 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

- To prescribe ivabradine according to shared care protocol.
- To advise the cardiologist/consultant nurse of any clinical changes or adverse effects.
- Monitor for adverse effects as detailed in shared care protocol.
- Be aware of any specific drug interactions with ivabradine when prescribing new drugs.

Patient

- Ensure they bring a list of current medication to every hospital visit.
- Report any adverse effects to their GP and/or cardiology team.
- Attend for regular monitoring as requested by GP /cardiology 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].

Treatment of angina is based on a step-wise increment of treatment options with beta blockers or calcium channel blockers offered as first-line treatment. If either a beta or calcium channel blocker does not control symptoms consider switching to the other option or using both drugs together. If use of either beta blockers or calcium channel blockers in combination or in single use are not tolerated, or do not control symptoms a third line agent may be considered either as monotherapy (if either are not tolerated) or as add-on therapy. Third line agents include: long-acting nitrate, nicorandil, ivabradine or ranolazine. To date there are no large randomized trials that address treatment strategies in patients with chronic angina who are refractory to more than two anti-anginal agents[1].

Supporting Information

Ivabradine is licensed for the symptomatic treatment of chronic stable angina in the following patients:

- Adults in normal sinus rhythm with heart rate of 70 bpm or greater
- Adults who are unable to tolerate or have a contra-indication to the use of beta-blockers, or
- In combination with beta-blockers in patients inadequately controlled with optimal beta-blocker dosage[2].

In clinical practice ivabradine will be restricted to those patients who have tried a combination of at least two or more anti-anginal therapies (at adequate doses) and have on-going symptoms.

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	• 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

Ivabradine is initiated and prescribed for the first month, or until uptitration is complete and dose stabilised by secondary care:

- Initial dosage is 5mg twice daily in patients below 75 years of age.
- Consider a starting dose of 2.5mg twice daily in patients over 75 years of age.

Up-titration:

- After 3 to 4 weeks of treatment if the patient is still symptomatic and if the initial dose is well tolerated, the dose may be increased to 7.5mg twice daily.

- If the starting dose was 2.5mg twice daily, then uptitrate to 5mg twice daily. After a minimum of 3 to 4 weeks, the dosage may be further upitrated to 7.5mg twice daily if treatment is tolerated.
- Dosage should only be uptitrated if resting heart rate is above 60 bpm.
- The maintenance dose should not exceed 7.5mg twice daily.

If, during treatment the heart rate decreases to below 50 bpm at rest or the patient experiences symptoms related to bradycardia e.g. dizziness, fatigue or hypotension, the dose must be titrated downward including the use of 2.5 mg twice daily (one half 5mg tablet twice daily). After dose reduction, the patient should be reviewed after one week when heart rate should be monitored (serial heart rate measurements, ECG or ambulatory 24-hour monitoring) and symptoms reassessed. Treatment must be discontinued if the heart rate is below 50 bpm and symptoms of bradycardia persist.
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.

Time to Response / discontinuation of treatment
Ivabradine should be discontinued if the symptoms of angina do not improve within 3 months of starting ivabradine therapy[2].

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

- Frequent heart rate monitoring or serial heart rate measurements
- Blood pressure
- 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 (with reference to symptoms and timing of reviews) during routine appointments.
- If the patient develops AF or other arrhythmia carry out an ECG and contact cardiologist for advice: discontinuation of therapy may be appropriate (see below)

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

The OUH cardiologist, consultant nurse or SpR on call may be contacted for advice regarding tolerability, side effects or potential complications of ivabradine therapy anytime during treatment. 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 a cardiologist. If patient develops atrial fibrillation during ivabradine therapy please discontinue treatment. 2nd degree AV-block Ivabradine is not recommended in patients with. In the Signify study, in patients with symptomatic angina, there was a small but significant increase in combined risk of cardiovascular death or non-fatal heart attack in the ivabradine group compared to placebo. However participants in the study were given higher doses of ivabradine than currently recommended, but this did not fully explain the findings[3].
Hypotension	If patient develops severe hypotension (less than 90/50mmHg) – consider discontinuing treatment if dosage adjustments of other drugs to raise blood pressure are not appropriate.
Renal Impairment	If patient develops significant renal impairment, CrCl less than 15ml/min, ivabradine can be

	continued but with caution. Contact cardiologist as appropriate if further advice needed due to deteriorating renal function.
Hepatic impairment	Discontinue if patient develops severe hepatic impairment (SPC describes as Child Pugh score B and C). 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.
The MHRA issued a warning on the risks of cardiac side effects when ivabradine is used for the symptomatic treatment of angina see[4]: https://www.gov.uk/drug-safety-update/ivabradine-carefully-monitor-for-bradycardia

Notable Drug Interactions (Refer to BNF and SPC for full details)

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 verapamil and diltiazem due to risks of bradycardia (additional heart rate lowering effect and moderate CYP3A4 inhibition leading to increased plasma concentrations of ivabradine).
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 SpR on call through the JR switchboard: 0300 304 7777 and ask for bleep 4205. Alternatively email the cardiologist / consultant nurse who initiated or recommended ivabradine therapy via email or telephone as per contact details in referral letter/email.

References

1. NICE Clinical Guideline CG126: Stable angina management, updated August 2016
2. Procoralan. Summary of Product characteristics accessed via eMC, last updated 07 Jun 2016.
3. Fox et al. NEJM 2014; 371: 1091-1099
4. Ivabradine in the symptomatic treatment of angina: risk of cardiac side effects, accessed via: https://www.gov.uk/drug-safety-update/ivabradine-procoralan-in-the-symptomatic-treatment-of-angina-risk-of-cardiac-side-effects