Ivabradine (Procoralan®) for chronic heart failure –
Shared Care Guideline

The information contained in this guideline is issued on the understanding that it is accurate using the resources available at the time of issue. For further information please refer to the relevant Summary of Product Characteristics http://www.medicines.org.uk/EMC/medicine/17188/SPC/Procoralan/ or contact a member of the Cardiology or Pharmacy Departments.

Therapeutic Use
Indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is ≥ 75bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.

Criteria for Patient Selection
Patient must fulfil the following criteria recommended by 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.’

Absolute contra-indications (as per licensed information)
• Hypersensitivity to the active substance or to any of the excipients
• Resting heart rate below 60 beats per minute prior to treatment (but note NICE recommendation above)
• Cardiogenic shock
• Acute myocardial infarction
• Severe hypotension (<90/50mmHg)
• 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
• 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
• Pregnancy or lactation

Dosage and administration
• Ivabradine is available as 5mg and 7.5mg film-coated, scored tablets.
• An MHRA Drug Safety Update was issued in June 2014 following emerging evidence from the SIGNIFY trial (ivabradine vs placebo in adults with coronary heart disease) that ivabradine showed a small but significant increase in the combined risk of cardiovascular death and non-fatal myocardial infarction in a subgroup with symptomatic angina of CCS class II or more. The dose of ivabradine used in SIGNIFY was higher than the licensed dose. The increased cardiovascular risk appears to be associated with a target heart rate below 60bpm. The MHRA has issued the following advice:
The starting dose of ivabradine is 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.

- Carefully monitor patients for bradycardia or its symptoms (eg, dizziness, fatigue, hypotension).
- Down-titrate the dose if resting heart rate decreases persistently below 50 bpm or if the patient experiences symptoms of bradycardia. The dose can be down-titrated to 2.5 mg twice daily if necessary.
- Stop ivabradine treatment if the resting heart rate remains below 50 bpm or symptoms of bradycardia persist.
- 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.
- Avoid concomitant use of ivabradine with heart rate-reducing calcium channel blockers such as verapamil or diltiazem.

- Review the treatment of patients currently using ivabradine where appropriate.

### Side Effects

- **Very common:** visual disturbances such as luminous phenomena (phosphenes).
- **Common:** headache (generally during the first month of treatment), dizziness (possible related to bradycardia), blurred vision, bradycardia, AV 1st degree block (ECG prolonged PQ interval), ventricular extrasystoles, uncontrolled blood pressure.

### Drug Interactions

These are potential drug interactions:

- Avoid concomitant use of drugs that might prolong the QT interval.
- Ivabradine is metabolised by CYP3A4 and therefore other drugs affecting this system should be avoided (e.g. antifungals, macrolide antibiotics). Diltiazem, verapamil and sotalol should all be avoided.
- Ivabradine exposure can be increased by grapefruit juice, intake of grapefruit juice should be restricted during the treatment with ivabradine.

### Cost

The cost of one year’s treatment with ivabradine 5mg or 7.5mg is £522.21.

### Shared Care Criteria

Ivabradine will be initiated by the consultant. Up titration of ivabradine will be undertaken by the consultant or by a specialist heart failure nurse. Patients’ care will only be transferred back to the GP when the dose of ivabradine and the heart rate is stable.

### Responsibilities

#### Consultant

1. To initiate ivabradine in line with the criteria recommended in NICE TA267, and only after the patient’s standard treatment of beta blockers, ACE inhibitors and aldosterone antagonists has been optimised for at least 4 weeks.
2. To up-titrate ivabradine to a stable dose where there is no specialist heart failure nurse support available, or to transfer care to specialist heart failure nurse for dose up-titration.
3. To provide the GP with appropriate prescribing information and any additional information requested.
4. To liaise with GP on any suggested changes in prescribed therapy.
5. To be available for advice if the patient’s condition changes.
6. To ensure the patient has given informed consent to their treatment.
7. To report adverse events to MHRA (Yellow card): [www.yellowcard.gov.uk](http://www.yellowcard.gov.uk)
Specialist heart failure nurse
1. To up–titrate ivabradine in accordance with the SPC to the optimum effective and tolerated dose.
2. To liaise with the GP for transfer of care of stabilised patients once the ivabradine dose has been optimised.

General practitioner
1. Where appropriate, to continue to prescribe ivabradine for stable patients as part of a shared care arrangement.
2. Monitor heart rate every three months and notify specialist if resting ventricular rate falls below 50bpm.
3. To deal with general health issues of the patient.
4. Monitor concordance with therapy.
5. Refer to the specialist if there are significant side-effects, if there is no benefit of treatment or if symptoms deteriorate.
6. To be responsive to urgent requests for review should patient circumstances change.
7. To ensure the patient continues to give informed consent to all treatments.
8. To report adverse events to MHRA (Yellow card): www.yellowcard.gov.uk
9. To ensure patient is compliant with heart failure therapies
10. To follow monitoring instructions from specialist care
11. To follow monitoring advice as specified in the NICE Quality Standard 9 relating to heart failure, i.e. 6 monthly clinical review or more frequently if indicated.

Commissioning and Commissioning Support Organisations
1. To support GPs in making the decision over whether or not to accept clinical responsibility for prescribing.
2. To support specialists and GPs in providing joint care
3. To support any relevant and involved provider Trust in resolving issues that may arise as a result of shared care.

Patient
1. Attend follow up appointments either at the GP surgery or hospital out-patient clinic, or heart failure specialist nurse clinic as requested, including 3 monthly attendance for pulse monitoring.
2. Share any concerns in relation to treatment with ivabradine.
3. Seek help if side effects are suspected, or if otherwise unwell.

Contact details of local cardiology specialist:
Telephone:

Contact details of Pharmacy Medicines Information:
Telephone:

References
- BNF http://www.bnf.org/bnf/index.htm accessed on 10th April 2013
- SPC Procoralan last updated: 31/8/10 http://www.medicines.org.uk/emc/medicine/17188/SPC/Procoralan/