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Information sheet
Ivabradine

Treatment in selected patients with chronic, stable heart failure (NYHA II – IV)

The Prescribing Clinical Network recommends Ivabradine in line with NICE guidance (TA267 November 2012). Ivabradine should be initiated under the supervision of a cardiologist.

Prescribing Clinical Network classification: **Amber***

Amber*: Drugs that require initiation by a specialist in secondary / tertiary care but due to more widespread experience in primary care GPs are generally happy to prescribe on specialist advice without the need for a formal shared care protocol. This information sheet is available on the internet (**www.surreyhealth.nhs.uk**) forming part of Prescribing Advisory Database (PAD) giving GPs appropriate advice / guidance and is not required to be sent to the GP with the clinic letter. A minimum of one month supply of medication will be provided by the initiating consultant.

RESPONSIBILITIES and ROLES

Specialist responsibilities
1. Assess the patient to determine suitability for prescribing of ivabradine; ensuring other treatment options have been fully explored. 2. The treatment to be initiated in patients with stable heart failure. Initiate treatment with Ivabradine (initial 1 month supply from Acute Trust Pharmacy). 3. Carry out ECG to monitor the patient for signs of atrial fibrillation if clinically indicated, 4. Provision of advice to patient and GP on further management of treatment for optimum control of symptoms and related issues such as drug interactions. 5. The patient, once stable after 6 months, will be discharged back to the GP with a management plan. (Patients would be referred back to the specialist if there were any safety concerns). Advise GP of any changes and additions to prescribed therapy if necessary. 6. Ensure that the patient has a hospital contact number if they experience adverse events or an exacerbation of their condition. 7. To ensure that procedures are in place for the rapid re-referral of the patient by the GP. 8. Explain to patient / carer their role(s). 9. Provide a copy of the information sheet to the patient / carer. Highlight to patient the very common side effect of visual disturbances such as luminous phenomena (phosphenes) and inform patient that "cessation of treatment should be considered if any unexpected deterioration in visual function occurs," as recommended in the SPC. **Patient Information Leaflets** This can be obtained from the Electronic Medicines Compendium. http://www.medicines.org.uk/EMC/medicine/17234/XPIL/Procoralan/.

General Practitioner responsibilities
1. Subsequent prescribing of ivabradine at the dose recommended. 2. Monitoring the patient's overall health and well being. 3. Observing patient for evidence of ADRs/abnormalities induced by ivabradine and raising with secondary care clinician if necessary. 4. Reviewing the patient on a regular basis to monitor heart rate and general condition in line with their usual appointments as deemed appropriate by the CHD register. If the resting heart rate falls below 50 beats per minute then consider reducing dose and seek opinion of referring consultant if necessary. If there is evidence of atrial fibrillation seek advice from referring consultant. 5. Ensuring advice is sought from the secondary care clinician if there is any significant change in the patient's physical health status.

6. Report any serious adverse events to the Consultant.

Patient's / Carer's roles
1. Ask the specialist for information, if he or she does not have a clear understanding of the treatment. 2. Share any concerns in relation to treatment with Ivabradine 3. Tell the specialist or GP of any other medication being taken, including over-the-counter products. 4. Read the patient information leaflet included with your medication and report any side effects or concerns you have to the specialist or GP.

BACK-UP ADVICE AND SUPPORT

Contact details	Specialist	Telephone No.	Email address:
Specialist:	Dr I. Beeton, Consultant cardiologist Tracey Bradshaw, Heart Failure Specialist Nurse	01932 723933 01932 723600	ian.beeton@asph.nhs.uk tracey.bradshaw@asph.nhs.uk
Hospital Pharmacy:	Carolyn Adamson, Lead Pharmacist - Medicine	01932 723422	carolyn.adamson@asph.nhs.uk

Supporting Information

This information sheet does not replace the SPC, which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF.

The GP has the right to refuse to agree to shared care, in such an event the total clinical responsibility will remain with the consultant.

Dosage and Administration

Ivabradine (Procoralan ®) is available as a 5mg and 7.5mg scored tablet. Tablets must be taken orally twice daily, once in the morning and once in the evening during meals. The usual recommended starting dose of ivabradine for heart failure is 5 mg twice daily. After 2 weeks of treatment, the patient should be reviewed. If the resting heart rate is persistently above 60bpm, the dose should be increased to 7.5mg twice daily. If the resting heart rate is persistently below 50bpm or the patient experiences symptoms of bradycardia (e.g. dizziness, fatigue or hypotension), the dose should be reduced to 2.5mg twice daily. If the resting heart rate is between 50-60bpm, the dose should remain at 5mg twice daily. If, during treatment, the heart rate falls persistently below 50bpm at rest or the patient has symptoms of bradycardia, the dose should be reduced to the next lower dose for those patients receiving 7.5mg or 5mg doses. If the heart rate is persistently above 60bpm, the dose should be increased to the next higher dose for those patients taking 2.5mg or 5mg doses.

Treatment must be discontinued if the heart rate remains persistently below 50bpm or symptoms of bradycardia persist. Whilst taking this medication the manufacturers recommend the ventricular rate at rest should not be allowed to fall below 50 beats per minute. If this occurs the dose must be titrated downward including the possible dose of 2.5 mg twice daily.

Elderly patients:

Since ivabradine has been studied in a limited number of elderly patients, a lower starting dose should be considered for patients aged 75 years or more (2.5 mg twice daily i.e. one half of a 5 mg tablet twice daily) before up-titrating if necessary.

Renal impairment:

No dose adjustment is necessary in patients with renal insufficiency and creatinine clearance above 15mL/minute. Ivabradine should be used with caution in patients with a creatinine clearance of less than 15mL/min due to the lack of data in these patients.

Hepatic impairment:
No dose adjustment is necessary for patients with mild hepatic impairment. Caution should be exercised when using ivabradine in patients with moderate hepatic impairment. Ivabradine is contraindicated in patients with severe hepatic impairment.

Monitoring
It is recommended to regularly clinically monitor ivabradine treated patients for the occurrence of atrial fibrillation (sustained or paroxysmal), which should also include ECG monitoring if clinically indicated (e.g. in case of exacerbated angina, palpitations, irregular pulse).
Chronic heart failure patients with intraventricular conduction defects and ventricular dyssynchrony should be monitored closely.

Contraindications

- Pregnancy or lactation
- Hypersensitivity to ivabradine or to any of the excipients, which include lactose
- Resting heart rate below 60 beats per minute prior to treatment
- Cardiogenic shock
- Acute myocardial infarction
- Severe hypotension (< 90/50 mmHg)
- Severe hepatic impairment
- Sick sinus syndrome
- Sino-atrial block
- Acute heart failure
- Pacemaker dependent patients
- 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 and lactation

Special Warnings

- Ivabradine is not recommended in patients with atrial fibrillation or other cardiac arrhythmias that interfere with sinus node function.
- Ivabradine is not recommended in patients with AV-block of 2nd degree.
- The use of ivabradine is not recommended immediately after a stroke since no data is available in these situations.
- Cessation of treatment should be considered if any unexpected deterioration in visual function occurs. Caution should be exercised in patients with retinitis pigmentosa.
- The use of ivabradine in patients with congenital QT syndrome or treated with QT prolonging medicinal products should be avoided. If the combination appears necessary, close cardiac monitoring is needed.
- Heart failure must be stable before considering treatment with ivabradine. Caution should be exercised in heart failure patients with NYHA class IV due to limited amount of data in this population.

Cautions

Hypotension

There is limited data available in patients with mild to moderate hypotension therefore caution should be used with these patients. Ivabradine is contra-indicated in patients with severe hypotension (blood pressure < 90/50 mmHg)

Atrial fibrillation – cardiac arrhythmias
There is no evidence of risk of excessive bradycardia or return to sinus rhythm when pharmacological cardioversion is initiated in patients treated with ivabradine. Due to the lack of data, non urgent DC-cardioversion should be considered 24 hours after the last dose of ivabradine.

Congenital QT syndrome or patients taking medications that prolong the QT interval
The use of ivabradine in patients with congenital QT syndrome or those treated with QT prolonging medications should be avoided. If this combination is necessary, close cardiac monitoring should be performed.

Hypertension requiring treatment modifications
In the SHIFT trial more patients experienced episodes of increased blood pressure whilst treated with ivabradine than placebo. These episodes occurred more frequently after blood pressure treatment was modified, were transient and did not affect treatment with ivabradine. When treatment modifications are made in chronic heart failure patients, blood pressure should be monitored.

Side Effects

Very common: visual disturbances such as luminous phenomena (phosphenes) were reported by 14.5% of patients.

Common: 3.3% of patients report bradycardia particularly within the first 2 to 3 months of treatment. 0.5% of patients experienced a severe bradycardia below or equal to 40 bpm. Also, AV 1st degree block (ECG prolonged PQ interval) and ventricular extrasystoles

Other common side effects: blurred vision, headache (generally during the first month of treatment) and dizziness, possibly related to bradycardia.

Drug Interactions

Concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is not recommended. No safety issue has been raised on the combination of ivabradine with nitrates and dihydropyridine calcium channel blockers such as amlodipine.

Ivabradine is metabolised by CYP3A4 and both inhibitors (e.g. ketoconazole, clarithromycin, grapefruit juice) or inducers (e.g. rifampicin, St. Johns Wort) have been shown to interfere with plasma levels.

Ivabradine is contraindicated in patients taking strong cytochrome P450 3A4 inhibitors, macrolide antibiotics, and HIV protease inhibitors.

References

1. British National Formulary no. 63 2012.
2. Servier Laboratories 2012. Summary of Product Characteristics, Procorolan. Accessed via http://www.medicines.org.uk/EMC/medicine/17188/SPC/Procoralan/ on 28/2/13
3. Swedburg K., Komajda M., Bohm M., Borer J., Ford I., Dubost-Brama A., Lerebours G. and Tavazzi L. on behalf of the SHOFT investigators 2010. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomized placebo-controlled study. The Lancet, vol. 376, pp. 875-885