Shared Care Guideline for prescribing Ivabradine (Procoralan®) as a monotherapy rate-limiting agent in angina.

INDICATION

Ivabradine (Procoralan®) acts by selective and specific inhibition of the cardiac pacemaker if in the sinus node. It is licensed for the symptomatic treatment of chronic stable angina in patients with normal sinus rhythm **who have a contra-indication to or intolerance of beta blockers**.

Ivabradine should only be initiated as a third-line, rate-limiting anti-anginal agent for patients unable to take beta blockers or rate limiting calcium antagonists. Use outside these criteria would not be covered under this shared care guideline and its use would be considered as a red drug to be maintained by secondary care (i.e. if used in combination with other rate limiting anti-anginal agents).

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of ivabradine can be shared between the specialist setting and the patient's GP (if different). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about their treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Shared Care is only appropriate if it provides the optimum solution for the patient.

- Patients will only be referred to the GP once the GP has agreed in each individual case
- Management of hypertension should be consistent with NICE Clinical Guideline no. 34.

Specialist Responsibilities	
1	To assess the patient and establish the diagnosis, determine a management strategy and ensure appropriate follow-up in conjunction with the GP.
2	Where appropriate: • To initiate and stabilise treatment; • To obtain consent from the patient's GP to continue prescribing once treatment has been stabilised (usually after 4 weeks); • To carry out ECG to monitor the patient for signs of atrial fibrillation if clinically indicated, • To monitor the patient and their therapy at six monthly intervals.
3	To provide the GP with appropriate prescribing information and any additional information requested.
4	To be available for advice if the patient's condition changes.
5	To ensure that procedures are in place for the rapid re-referral of the patient by the GP.
6	To ensure the patient has given informed consent to their treatment.
7	To liaise with the GP on any suggested changes in prescribed therapy.

General Practitioner Responsibilities	
1	Initially, to refer the patient for specialist advice.
2	Where appropriate, to continue to prescribe Ivabradine as part of a shared care agreement (usually after 4 weeks).
3	Measure and record heart rate and notify specialist if resting ventricular rate falls below 50bpm
4	To deal with general health issues of the patient.
5	Monitor concordance with therapy.

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Attend appropriate GP and other follow up appointments.
3	Share any concerns in relation to treatment with Ivabradine.
4	Use written and other information on the medication.
5	Seek help urgently if side effects are suspected, or is otherwise unwell.

SUPPORTING INFORMATION

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).

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.

For angina, the usual recommended starting dose of ivabradine is 5 mg twice daily. After three to four weeks of treatment, the dose may be increased to 7.5 mg twice daily depending on the therapeutic response.

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 5 mg tablet twice daily) before up-titration if necessary.

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. Treatment must be discontinued if heart rate is below 50 bpm or symptoms of bradycardia persist.

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 insufficiency.
- Sick sinus syndrome.
- Sino-atrial block.
- Heart failure patients with NYHA functional classification III-IV.
- 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

Side effects

Very common: visual disturbances as luminous phenomena (phosphenes) 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.

Special Warnings

No dose adjustment is required in patients with renal insufficiency and creatinine clearance above 15 ml/min.

No dose adjustment is required in patients with mild hepatic impairment. Caution should be exercised when using Ivabradine in patients with moderate hepatic impairment. Ivabradine is contra-indicated for use in patients with severe hepatic insufficiency, since it has not been studied in this population and a large increase in systemic exposure is anticipated.

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.

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.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug costs:

Drug	28 day cost
Procoralan® 2.5mg tablets (5mg tablets halved)	£20.09
Procoralan® 5mg Tablets	£40.17
Procoralan® 7.5mg Tablets	£40.17

Prices referenced from Drug Tariff accessed November 2016

References

Summary of Product Characteristics Ivabradine (Procoralan) https://www.medicines.org.uk/emc/medicine/17188/ updated June 2016, accessed November 2016

NICE clinical pathway: stable angina - https://pathways.nice.org.uk/pathways/stable-angina accessed November 2016.

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