SHARED CARE GUIDELINE FOR FOR PRESCRIBING IVABRADINE (PROCORALAN®) AS TREATMENT FOR CHRONIC HEART FAILURE

INDICATION

Ivabradine (Procoralan ®) acts by selective and specific inhibition of the cardiac pacemaker if in the sinus node. It is licensed for the treatment of chronic heart failure (NHYA class II to IV) with systolic dysfunction, in patients in sinus rhythm and whose heart rate is 75bpm or more, in combination with standard therapy including beta blockers or when beta blockers are contraindicated or not tolerated.

NICE TA 267 states:
Ivabradine is recommended as an option for treating chronic heart failure for people:

- 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.
Ivabradine should be initiated by a heart failure specialist with access to a multidisciplinary heart failure team.

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 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 chronic heart failure should be consistent with NICE Clinical Guideline no. 108.

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 treatment (although this initiation may be via verbal recommendation or request direct to the GP or Community Heart Failure Teams) • obtain agreement from the patient's GP to continue the on-going prescribing • carry out ECG to monitor the patient for signs of atrial fibrillation if clinically indicated, • 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 arrangement.
3	Measure and record heart rate and notify specialist if resting ventricular rate falls below 50bpm
4	To titrate the dose as dictated by heart rate
5	To deal with general health issues of the patient.
6	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 are 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).

Chronic heart failure patients with intraventricular conduction defects and ventricular dyssynchrony should be monitored closely.

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 [Servier Laboratories 2012].

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.

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

Cautions

Hypotension
There is limited data available in patients with mild to moderate hypotension therefore caution should be used with these patients.

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-cardio version 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.

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.

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 extra systoles

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

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 BD (achieved by halving 5mg tablets)	£20.09
Procoralan® 5mg - 56 Tablets 5 mg BD	£40.17
Procoralan® 7.5mg - 56 Tablets 7.5 mg BD	£40.17

The Drug Tariff - http://www.drugtariff.nhsbsa.nhs.uk Pricing is correct as of November 2016.

References

Summary of Product Characteristics - Procoralan. Updated June 2016, accessed November 2016 https://www.medicines.org.uk/emc/medicine/17188/

NICE TA267 Ivabradine for treating chronic heart failure https://www.nice.org.uk/guidance/ta267 Published November 2012, accessed November 2016

NICE Clinical Guideline – Chronic heart failure in adults: management https://www.nice.org.uk/guidance/cg108

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

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