

Prescribing IVABRADINE for the treatment of Postural Orthostatic Tachycardia Syndrome (POTS) or Inappropriate Sinus Tachycardia (IST)

At present there are no approved medicines for the treatment of POTS or IST and therefore, in this circumstance, ivabradine is prescribed for an unlicensed indication. Treatment must be tailored to each patient, taking into account the cause of their syndrome and their symptoms, since the same medicines can have very different effects on different individuals

Ivabradine (Procoralan®)▼ is the first specific heart rate-lowering agent. It is selective for the I_f current, lowering heart rate at concentrations that do not affect other cardiac ionic currents. Specific heart-rate lowering with ivabradine reduces myocardial oxygen demand, simultaneously improving oxygen supply. Ivabradine does not have negative inotropic effect, preserves ventricular contractility, and does not change any major electrophysiological parameters unrelated to heart rate.

In South London, ivabradine may be considered as an unlicensed option for the treatment of POTS or IST when causative factors have been corrected or ruled out and other forms of treatment have failed to control symptoms (fluid, exercise, and compression clothing).

Additional resources have been developed to support implementation including:

- [Notification of initiation of ivabradine for treating POTS or IST](#). This document **must be completed and sent to the General Practitioner (GP) on initiation.**
- [Transfer of prescribing responsibility to primary care for ivabradine](#). This document **must be completed and sent to the GP when transferring the prescribing responsibility** in accordance with South London guidelines.

Treatment must be initiated by a cardiology specialist, after careful evaluation of the overall balance of the patient's expected benefits and risks. The initiating clinician / organisation is responsible for ensuring the patient is provided with a structured support process (including availability of contact numbers for specialist nurses), follow-up and providing a supply of ivabradine for the first three months of treatment or until the dose is stable. During this time efforts should be made to reinforce adherence and address any adverse effects.

The MHRA issued advice for health professionals on the prescribing of ivabradine in chronic stable angina and many of the points apply equally in the setting of POTS / IST, in particular:

- Only start ivabradine if the resting heart rate is at least 70 beats per minute (bpm)
- Do not exceed the maximum maintenance total daily dose of 15mg
- Down-titrate the dose if resting heart rate decreases persistently below 50bpm or if the patient experiences symptoms of bradycardia. The dose can be down-titrated to 2.5mg twice daily if necessary
- Monitor patients regularly for atrial fibrillation (AF). If AF occurs, carefully reconsider whether the benefits of continuing ivabradine treatment outweigh the risks
- Do not prescribe ivabradine with other medicines that cause bradycardia, such as verapamil, diltiazem, or strong CYP3A4 inhibitors
- Consider stopping ivabradine if there is no or only limited symptom improvement after 3 months
- Stop ivabradine treatment if the resting heart rate remains below 50bpm or symptoms of bradycardia persist

Transfer of prescribing responsibility to patients own GP

Following the initial 3 month period and when the dose of ivabradine is stable, prescribing responsibility may be considered for transfer to the patient's own GP when the consultant and the GP are in agreement that the patient's condition is stable or predictable. Transfer of prescribing responsibility should be followed and appropriate documents completed and forwarded to GP to ensure seamless care.

This guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Contraindications (for full details see BNF or SPC)	Cautions (for full details see BNF or SPC)
<ul style="list-style-type: none"> • Hypersensitivity to the active substance or to any of the excipients • Resting heart rate < 70bpm at initiation • Severe hypotension (<90/50mmHg) • Cardiogenic shock • Sick sinus syndrome • Sino-atrial block & 3rd degree AV-block • Congenital QT syndrome • Pacemaker dependent* (i.e. heart rate imposed exclusively by the pacemaker) • Acute Myocardial infarction • Unstable angina • Unstable or acute heart failure • Severe hepatic impairment • Pregnancy and lactation • For contraindications for use with other medicines see overleaf 	<ul style="list-style-type: none"> • Pre-existing cardiac arrhythmia • Concurrent heart rate lowering agents • Severe heart failure (NYHA IV) • Post CVA (use not recommended immediately after stroke) • 2nd degree AV-block (use not recommended) • Retinitis pigmentosa • Moderate hepatic impairment • Established renal failure (CrCl <15ml/min) • For cautions for use with other medication – see overleaf

Note: BNF=British National Formulary; SPC=Summary of Product Characteristics. *Ivabradine is suitable for use in patients with specialist pacing devices under cardiology supervision.

Ivabradine is not recommended in patients with AF or other cardiac arrhythmias that interfere with the sinus node function as it is unlikely to be effective in this circumstance.

Dosing

The recommended dose is 2.5mg twice daily with or without food. The total daily dose can be increased up to a maximum daily dose of 15mg given in 2-4 divided and titrated according to response.

- No dose adjustment is necessary in patients with renal insufficiency and creatinine clearance >15mL/min. Ivabradine should be used with caution in patients with a creatinine clearance <15mL/min due to the lack of data.
- 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 those with severe hepatic impairment.

Monitoring

- Monitor heart rate every 3 months (resting ventricular rate must be more than 50bpm to continue treatment). If the heart rate falls persistently below 50 bpm (at rest) and / or the patient experiences symptoms related to bradycardia such as dizziness, fatigue or hypotension – This will require a dose reduction or cessation of therapy.
- Manual pulse rhythm check should be performed at every annual review to check for AF, including patients with a history of AF who are currently in sinus rhythm. If AF occurs during treatment ivabradine should be stopped.
- Renal and liver function should be monitored before starting treatment with ivabradine, then at least annually throughout treatment or more frequently if clinically indicated.
- Ensure potassium levels are maintained in range as hypokalaemia can increase the risk of arrhythmias and can potentiate bradycardia.

Side effects (for full details see the BNF or SPC)

Visual symptoms are the most common adverse effects reported. Luminous phenomena were reported in 14.5% of patients and therefore new patients should be warned about this potential side effect. Phosphenes generally begin to occur within the first two months of treatment after which they may occur repeatedly. Phosphenes were generally reported to be of mild to moderate intensity, all of which resolved during or after treatment. Blurred vision also occurs commonly. Cessation of treatment should be considered if any unexpected deterioration in visual function occurs.

Other common side effects (occurring in between 1 in 10 and 1 in 100 patients) include headache and dizziness, bradycardia, 1st degree AV block and ventricular extrasystoles and uncontrolled blood pressure (BP).

Ivabradine is a black triangle drug ▼ - any adverse effects must be reported to the MHRA using the [yellow card system](#) and via the local incident reporting system

Drug Interactions (for full details on drug interactions – see BNF or SPC)

Drug / Drug class	Recommendation
Strong inhibitors of CYP3A4 such as: <ul style="list-style-type: none"> • Azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole), • HIV protease inhibitors (e.g. ritonavir, nelfinavir), • Macrolide antibiotics (e.g. clarithromycin and erythromycin) 	Concomitant use not recommended - may increase ivabradine exposure.
Moderate inhibitors of CYP3A4 (e.g. diltiazem and verapamil)	Concomitant use not recommended - may increase ivabradine exposure.
CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's wort)	Use with caution as may decrease ivabradine exposure. May require closer monitoring and dose adjustment. Use of St John's wort is not recommended.
Drugs which prolong the QTc (e.g. amiodarone, sotalol, disopyramide and mefloquine)	Concomitant use not recommended - increased risk of ventricular arrhythmias.

Roles and responsibilities

Initiating clinician / organisation	Patient's own GP
<ul style="list-style-type: none"> • To initiate ivabradine in line with local guidance - notifying GP that ivabradine has been prescribed using the notification of initiation document. • To ensure patient has consented to treatment and is aware this specific use is unlicensed. • To provide counselling to improve adherence and address any adverse effects (including advice on dosage, frequency and the risks and benefits of treatment). • Perform baseline monitoring tests: BP, heart rate, ECG, baseline renal and liver function. • Patient is provided with contact information for specialist nurse advice during normal working hours. • To supply ivabradine for at least the first 3 months of treatment and until the dose is stable. • Following the initial three months of treatment and when the dose is stable, transfer care to the GP using the local transfer of prescribing responsibility document. • Provide the GP with relevant specialist contact information should further assistance be required during working hours. • To review the patient at the request of GP should any problems arise (side-effects / lack of efficacy). • To review the patient at least annually and communicate promptly with the GP if treatment is changed. • To report any suspected adverse effects to the MHRA: https://yellowcard.mhra.gov.uk/ 	<ul style="list-style-type: none"> • To ensure use of ivabradine is in line with local guidance. • To agree to take over prescribing responsibility when the patient is stable on therapy (at least 3 months after initiation and in line with the transfer of care guidance). • To provide on-going prescriptions for ivabradine after 3 months. • To monitor heart rate every 3 months and seek advice from the specialist if resting ventricular rate falls below 50bpm. • Manual pulse rhythm check should be performed at every annual review to check for AF. • Review renal and liver function at least annually and more frequently if clinically indicated. • To monitor patient for adverse effects and control of symptoms. • To report and seek advice regarding any concerns, for example: side-effects, co-morbidities, pregnancy, or lack of efficacy to the specialist team. • To advise the specialist if non-adherence is suspected. • To refer back to specialist if the patient's condition deteriorates or treatment failure. • To stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises. • To report any suspected adverse effects to the MHRA via the Yellow Card scheme: https://yellowcard.mhra.gov.uk/

Additional advice to patients

Patients should be advised not to consume grapefruit juice during treatment with ivabradine.

Note: A combination treatment with ivabradine and midodrine is prescribed in a few patients for treatment of POTS and/or IST

Ivabradine is also licensed for the management of on-going symptoms in patients with **chronic stable angina** and treatment of **chronic heart failure** due to left ventricular systolic dysfunction. Guidance for these indications can be found [here](#)

References

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ⁱ Estimate creatinine clearance (CrCl) using the Cockcroft-Gault equation