New Indication Assessment

Ivabradine for treatment of POTS

Recommendation: Amber 0 for the following indications:

Treatment of POTS (postural orthostatic tachycardia syndrome).

It is recommended that the existing LSCMMG ivabradine Prescribing Information Sheet be updated to reflect any recommendations agreed on.

The sheet should also be updated to highlight the risk of teratogenic affects in pregnancy.

Summary of supporting evidence:

- Ivabradine is an established drug with existing LSCMMG RAG rating Amber 0 for licensed indications and a prescribing information sheet. Unlicensed for POTS.
- Monitoring and dose titration required for all indications.
- Unique mode of action vs other treatment options for POTS.
- Treatment options for POTS are limited, often have problematic side effects, and require a trial-and-error approach to find a suitable regimen for the individual patient. Lifestyle adaptations are first line treatment for POTS.
- There is no national guidance for POTS; internationally ivabradine is recommended, but it is acknowledged that the evidence base is weak.
- There are no large-scale randomized placebo-controlled trials for the treatment of POTS. Due to the rare nature of the condition, current methods are based on small scale trials or case based outcomes; ivabradine has shown positive outcomes in some patients.
- The side effect profile of ivabradine is well documented.
- Ivabradine may be teratogenic. Adequate contraception is required when using ivabradine in women with child-bearing potential. This is of particular note as POTS is more prevalent in women.
- Potentially growing patient cohort due to emerging association with long-COVID.
- The cost of ivabradine treatment is comparable to other treatment options and the patient cohort is expected to be low in number.

Details of Review

Name of medicine (generic & brand name)**:**

Ivabradine

Strength(s) and form(s):

2.5mg, 5mg and 7.5mg film-coated tablets

Dose and administration:[1]

Tablets must be taken orally twice daily; once in the morning and once in the evening during meals.

Symptomatic treatment of chronic stable angina pectoris

It is recommended that the decision to initiate or titrate treatment takes place with the availability of serial heart rate measurements, ECG or ambulatory 24-hour monitoring. The starting dose of ivabradine should not exceed

5 mg twice daily in patients aged below 75 years. After three to four weeks of treatment, if the patient is still symptomatic, if the initial dose is well tolerated and if resting heart rate remains above 60 bpm, the dose may be increased to the next higher dose in patients receiving 2.5 mg twice daily or 5 mg twice daily. The maintenance dose should not exceed 7.5 mg twice daily.

Treatment of chronic heart failure

The usual recommended starting dose of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily if resting heart rate is persistently below 50 bpm or in case of symptoms related to bradycardia such as dizziness, fatigue or hypotension.

In patients aged 75 years or more, a lower starting dose should be considered (2.5 mg twice daily).

BNF therapeutic class / mode of action:

Ivabradine is a pure heart rate lowering agent, acting by selective and specific inhibition of the cardiac pacemaker current that controls the spontaneous diastolic depolarisation in the sinus node and regulates heart rate. The cardiac effects are specific to the sinus node with no effect on intra-atrial, atrioventricular or intraventricular conduction times, nor on myocardial contractility or ventricular repolarisation.[1]

Licensed indication(s):[1]

Symptomatic treatment of chronic stable angina pectoris in coronary artery disease adults with normal sinus rhythm and heart rate ≥ 70 bpm. Ivabradine is indicated:

- in adults unable to tolerate or with a contra-indication to the use of beta-blockers

- or in combination with beta-blockers in patients inadequately controlled with an optimal beta-blocker dose.

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

Proposed use (if different from, or in addition to, licensed indication above):

Treatment of POTS (postural orthostatic tachycardia syndrome).

Course and cost:

56 x 2.5mg tabs £39.99

56 x 5mg tabs £8.61

56 x 7.5mg tabs £4.46

Price as per drug tariff May 2024

Current standard of care/comparator therapies:

- Lifestyle adaptations, such as[2,3]:
  - Eating and drinking at regular times
  - Trying to manage stress
  - Sit or stand up slowly when you've been lying down
  - Raise the head of your bed so you're not fully horizontal at night
  - Avoid lots of caffeine or alcohol
  - Avoid long periods of standing.
- Pharmacological: Beta blockers, midodrine, SSRIs, fludrocortisone.

Relevant NICE guidance:

None

Background and context

Postural tachycardia syndrome, also known as postural orthostatic tachycardia syndrome (POTS), is a condition that causes an abnormal increase in heart rate (HR) after sitting up or standing up.[3] It is defined as a condition where the HR increases ≥30 bpm or is sustained ≥120 bpm within 10 min of sustained orthostasis.[10] The most common symptoms are feeling lightheaded or dizzy, palpitations and fatigue.

In POTS, usual autonomic changes don't happen so that when sufferers move to an upright position the supply of blood to the heart and brain drops and the HR increases to compensate and to try and increase the blood flow.[3]

POTS is common in people suffering from long-COVID[4]. There is emerging evidence that a proportion of patients who develop long-COVID have abnormalities in the regulation of their autonomic nervous system manifesting as POTS.[5]

A wide range of pharmacological treatments have been used in POTS with approaches including increasing intravascular volume with fludrocortisone, increasing peripheral vasoconstriction with agents such as midodrine, and suppressing HR with beta-blockers or calcium channel blockers. Conventional therapies, however, are often poorly tolerated due to side-effects, such as supine hypertension or orthostatic hypotension. Clinicians frequently find that a treatment that is effective in one patient may have no effect in others and there is limited evidence to predict response. Cross-sectional studies fail to demonstrate a clear superiority of one agent over the others. Beta-blockers, fludrocortisone, midodrine, and selective serotonin reuptake inhibitors are partially effective in 40–60% of patients. Effective treatment is, therefore, often only found through trial and error, a lengthy and frustrating process for patients.[10]

Ivabradine is an emerging treatment option as it reduces sinus node firing rate without affecting blood pressure.[10] Ivabradine has an existing LSCMMG RAG position of Amber 0 for chronic angina and for heart failure. LSCMMG also have an ivabradine prescriber information sheet for these indications.

Summary of evidence

Summary of efficacy data in proposed use:

Abdelnabi et al. Single centre prospective study (2023)[6]

A total of 55 COVID-19-associated POTS patients (after the exclusion of other causes of tachycardia) were commenced on Ivabradine 5 mg twice daily. Re-assessment of patients' symptoms, heart rate, and heart rate variability (HRV) parameters' changes after 3 days of ivabradine therapy was done.

The mean age of the included patients was 30.5±6.9 years with 32 patients being males (58.2%). 43 of 55 (78%) of the included patients reported significant improvement of the symptoms within 7 days of ivabradine therapy. 24-hour heart rate (minimum, average, and maximum) was significantly lower (p-value < 0.0001, = 0.001, < 0.0001 consecutively) with a significant difference in HRV time-domain parameters

(SDNN, rMSSD) (p-value < 0.0001*) after ivabradine therapy.

Taub PR et al. Randomised trial (2021)[7]

This study investigated the effect of ivabradine on heart rate, quality of life (QOL), and plasma norepinephrine (NE) levels in patients with hyperadrenergic POTS defined by plasma NE >600 pg/ml and abnormal tilt table test. In total, 22 patients with hyperadrenergic POTS as the predominant subtype completed a randomised, double-blinded, placebo-controlled, crossover trial with ivabradine. Patients were randomized to start either ivabradine or placebo for 1 month, and then were crossed over to the other treatment for 1 month. Patients on medications for their POTS symptoms were required to undergo a 1-week washout before their screening visit.

Heart rate, QOL, and plasma NE levels were measured at baseline and at the end of each treatment month. In healthy patients, supine plasma NE has been reported to be approximately 200 pg/ml and doubles to 400 to 500 pg/ml upon standing (9–11). In patients with POTS, however, NE levels can triple or quadruple upon standing (405 to 1,207 pg/ml).

Of the 26 randomized patients, 22 patients completed the study and were included in the final data analysis. The average age was 33.9 +/- 11.7 years, 95.5% were women (n = 21), and 86.4% were White (n = 23). There was a significant reduction in heart rate between placebo and ivabradine (p < 0.001). Patients reported significant improvements in QOL with RAND 36-Item Health Survey 1.0 for physical functioning (p = 0.008) and social functioning (p = 0.021). There was a strong trend in reduction of NE levels upon standing with ivabradine (p = 0.056). Patients did not experience any significant side-effects, such as bradycardia or hypotension, with ivabradine.

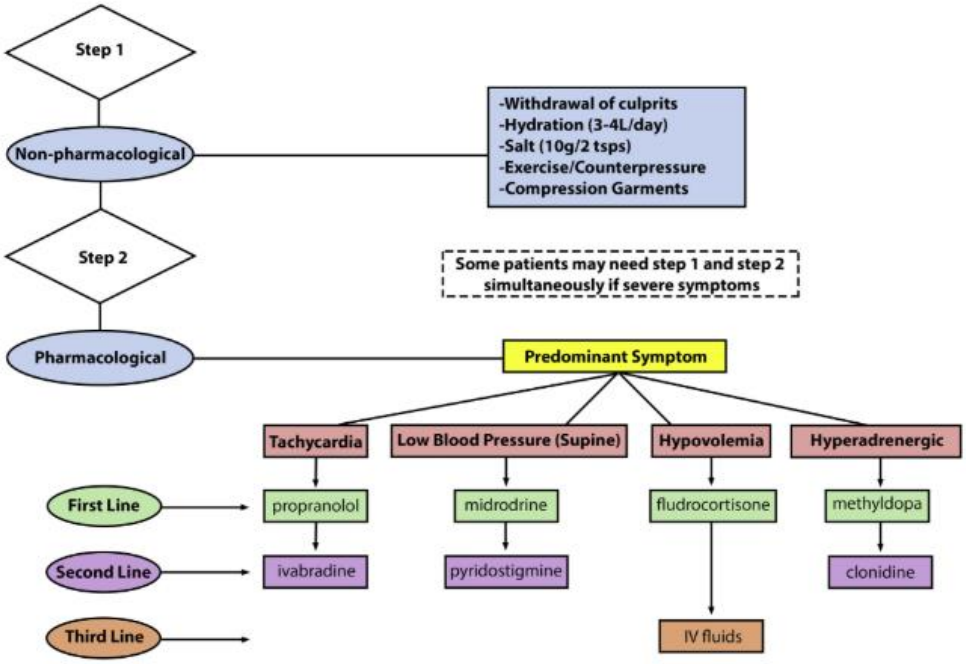
Raj et al. Canadian Cardiovascular Society Position Statement (2020)[8]

For patients with POTS, the Canadian Cardiovascular society recommend:

- Midodrine (2.5-15 mg every 4 hours up to 3 times per day) to improve symptom control (Strong Recommendation, Moderate-Quality Evidence).
- Low-dose propranolol (10-20 mg 4 times per day), a nonselective b-blocker to reduce standing heart rate, improve exercise capacity, and improve symptom control (Strong Recommendation, Moderate-Quality Evidence).
- Pyridostigmine (30-60 mg 3 times per day) be considered for symptom relief (Weak Recommendation, Low Quality Evidence).
- Fludrocortisone (dose 0.1-0.3 mg daily) be considered to improve symptoms (Weak Recommendation, Low-Quality Evidence).
- Ivabradine (2.5- 7.5 mg twice per day) be considered as a treatment option (Weak Recommendation, Low-Quality Evidence).

  Ivabradine might be an alternative to nonselective b-blocker therapy particularly when the patient has prominent symptomatic orthostatic tachycardia and is a non-responder and/or has intolerance because of exacerbation of symptoms of fatigue, comorbid asthma, or a tendency to hypotension. Ivabradine may be teratogenic. Adequate contraception is required when using ivabradine in women with child-bearing potential.

- Patients with prominent hyperadrenergic symptoms may be treated with central sympatholytic agents (eg, clonidine 0.1-0.2 mg to a maximum of 3 times per day; methyldopa starting at 125 mg once at bedtime, which can be titrated up to 250 mg twice per day) (Weak Recommendation, Low-Quality Evidence).



Sheldon RS et al. Expert Consensus Statement (2015)[9]

International consensus statement written by experts in the field who were chosen by the Heart Rhythm Society, in collaboration with representatives from a range of international cardiology societies.

The treatment of POTS is difficult; there are no therapies that are uniformly successful, and combinations of approaches are often needed. Few treatments have been tested with the usual rigor of randomised clinical trials, and there is no consensus as to whether specific treatments should be targeted to subsets of POTS or whether a uniform approach should be used. Non-pharmacologic treatments should be attempted first with all patients. These include withdrawing medications that might worsen POTS, such as norepinephrine transport inhibitors, increasing blood volume with enhanced salt and fluid intake, reducing venous pooling with compression garments, and limiting deconditioning.

Fludrocortisone might be useful for boosting sodium retention and expanding the plasma volume, although these pharmacodynamic effects might last only 1–2 days, and its effectiveness has not been tested in randomised clinical trials. Midodrine is metabolised to a peripheral alpha-1 agonist that constricts veins and arteries and might be useful for increasing venous return. Midodrine significantly reduces orthostatic tachycardia but to a lesser degree than intravenous saline. Midodrine has a rapid onset with only brief effects and should be administered 3 times daily.

To reduce unpleasant sinus tachycardia and palpitations, low-dose propranolol (10–20 mg PO) acutely lowers standing heart rate and improves symptoms in patients with POTS, while higher doses of propranolol are less well tolerated. Long-acting propranolol does not improve the quality of life of patients with POTS, and other beta-blockers have not been studied. Ivabradine slows sinus rates without impacting blood pressure. Approximately 60% of patients with POTS treated with ivabradine in an open-label study had symptom improvement.

Central sympatholytic agents can be useful in patients with the central hyperadrenergic form of POTS but might not be as well tolerated in neuropathic POTS. Clonidine is an alpha-2 agonist that can stabilize hemodynamics in patients with high sympathetic nervous system involvement. Methyldopa is sometimes better tolerated. Unfortunately, both drugs can cause drowsiness and fatigue and can worsen mental clouding, a condition that troubles many patients. Modafinil may be considered for the fatigue and cognitive dysfunction (“brain fog”) seen in patients with POTS. Modafinil, however, can worsen the symptoms of tachycardia.

McDonald C et al. Retrospective case-series (2011)[10]

Postural orthostatic tachycardia syndrome patients prescribed ivabradine were identified, case notes were reviewed and participants completed a symptom assessment tool. Twenty-two patients were identified. All patients had tried at least one other treatment for POTS prior to taking ivabradine, most commonly a beta-blocker. Three patients took fludrocortisone and one took midodrine in conjunction with ivabradine. Data was available from 20. Eight patients reported reduced tachycardia and fatigue and four reported only reduced tachycardia. The most common reason for discontinuing ivabradine was lack of efficacy (n = 6). Five patients reported side-effects resulting in two discontinuing treatment. This retrospective case series indicates that 60% of patients treated with ivabradine report a symptomatic improvement.

Summary of safety data:

Taub PR et al. Randomised trial (2021)[7]

Of the 4 patients who withdrew after randomization, 1 dropped out on placebo due to other health concerns, and 3 dropped out while on ivabradine due to nausea and drowsiness after 3 days, fatigue after 21 days, and phosphenes after 4 days. These side-effects were among the typical side-effects associated with ivabradine, such as phosphenes, tiredness, and palpitations.

McDonald C et al. Retrospective case-series (2011)[10]

Five patients reported side-effects, resulting in two patients discontinuing treatment, one of whom reported a reduction in HR but increased fatigue. Two patients reported visual abnormalities; phosphenes.

Adverse effect	Number of patients reporting adverse effect	Number of patients discontinuing ivabradine due to adverse effect
Light sensitivity	2	0
Headache	1	0
Dizziness	2	1
Nauseas	1	0
Increased fatigue	1	1

Summary of product characteristics[1]

Ivabradine has been studied in clinical trials involving nearly 45,000 participants.

The most common adverse reactions with ivabradine, luminous phenomena (phosphenes) and bradycardia, are dose dependent and related to the pharmacological effect of the medicinal product.

For a full list of undesirable effects reported for ivabradine, please see product SPC.

Strengths and limitations of the evidence:

Strengths

- There is growing discussion around the treatment of POTS due to its apparent association with long-COVID.
- Several large, international cardiology societies have issued advice on the treatment of POTS.

Limitations

- There are no large-scale randomized placebo-controlled trials for the treatment of POTS. Due to the rare nature of the condition, current methods are based on small scale trials or case based outcomes.
- Treatment is often based on a trial and error pattern; there is no one-size fits all approach.

Summary of evidence on cost effectiveness:

Approx. cost/month of treatments based on a stated regimen:

Ivabradine 5mg bd = £9

Fludrocortisone 200mcg od = £12

Propranolol 10mg qds = £3

Midodrine 5mg tds = £25

NB. Patients may be on a combination of the above medications and dosage regimens will vary widely from patient to patient. The patient cohort is small and prescribing decisions will be based on improvement in symptoms and tolerance of medication.

Price as per drug tariff May 2024

Prescribing and risk management issues:

POTS is a rare condition which clinicians may have limited experience in managing.

The use of ivabradine for the treatment of POTS is unlicensed.

Ivabradine is teratogenic.

Ivabradine must not be initiated in patients with a pre-treatment resting heart rate below 70 beats per minute.

Dose titration is required based upon the patients heart rate.

Serial heart rate measurements, ECG or ambulatory 24-hour monitoring should be considered when determining resting heart rate before initiation of ivabradine treatment and in patients on treatment with ivabradine when titration is considered.

In patients treated with ivabradine the risk of developing atrial fibrillation is increased

Cessation of treatment should be considered if any unexpected deterioration in visual function occurs.

Ivabradine is teratogenic; women of child-bearing potential should use appropriate contraceptive measures during treatment. Ivabradine is contra-indicated during pregnancy. This is of particular note as POTS is more prevalent in women.

Commissioning considerations:

Innovation, need and equity implications of the intervention:

There are currently no licensed medicines for the treatment of POTS.

Prevalence of POTS related symptoms has increased since its link to long-covid.

Financial implications of the intervention:

Ivabradine is comparable in cost to other pharmacological treatments in POTS. It is unlikely to cause any cost pressure to the health economy and may reduce cost pressures if used in place of midodrine.

Service Impact Issues Identified:

Increased prescribing in primary care if an Amber RAG is agreed.

Equality and Inclusion Issues Identified:

There are limited treatment options for this patient cohort and no licensed pharmacological options.

Cross Border Issues Identified:
Pan Mersey have ivabradine as RAG Green for angina and Amber Initiated for heart failure. They do not have a RAG position or any published guidance relating to POTS. **GMMMG** have ivabradine as RAG Green (specialist initiation) for heart failure. They do not have a RAG position or any published guidance relating to POTS.
Legal Issues Identified:
None identified
Media/ Public Interest:
None identified

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

References

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[4] NHS Inform, "Postural orthostatic tachycardia syndrome (PoTS)", October 2023 [Online]. Available: https://www.nhsinform.scot/long-covid/postural-orthostatic-tachycardia-syndrome-pots/ [Accessed: 02 May 2024]

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[9] Sheldon RS et al, "2015 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of Postural Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope", *Heart Rhythm*, vol. 12(6), pp 41– 63, 2015

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