Ivabradine (Coralan) for chronic heart failure

KEY POINTS

Ivabradine may be added on to optimal medical therapy for CHF

Ivabradine is an option for patients with a heart rate $\geq 77$ bpm currently receiving optimal medical therapy for CHF, including maximum tolerated dose of beta blockers unless contraindicated or not tolerated.

Multiple PBS restrictions apply

Ivabradine is restricted to patients with symptomatic systolic CHF, a baseline heart rate $\geq 77$ bpm, left ventricular ejection fraction $< 35\%$ and New York Heart Association symptom class II or III.

Ivabradine reduces hospitalisation and mortality in patients with a heart rate $\geq 77$ bpm

The SHIFT trial showed a significant reduction in the number of hospital admissions due to CHF compared with placebo, but only reduced mortality in patients with a heart rate $\geq 77$ bpm.

Long-term safety and efficacy unknown

Trials in CHF patients were limited to a median of 23 months follow-up. Ivabradine may increase the risk of developing AF and is associated with bradycardia and temporary, mild visual disturbances.

PBS listing

Authority required

Ivabradine is PBS listed for patients with CHF who meet the following criteria:

- symptomatic systolic CHF with NYHA classes II or III
- in sinus rhythm
- documented left ventricular ejection fraction (LVEF) $\leq 35\%$
- resting heart rate $\geq 77$ bpm at the time ivabradine treatment is started
- receiving concomitant optimal standard CHF treatment, which must include the maximum tolerated dose of a beta blocker unless contraindicated or not tolerated.

Before treatment heart rate must be measured by an ECG after 5 minutes’ rest and the ECG result documented in the patient’s records.

May be prescribed by nurse practitioners (continuing therapy only)

Authorised nurse practitioners may prescribe continuing therapy of this medicine after it has been initiated by a medical practitioner. See the PBS website for more information on nurse practitioner PBS prescribing.

What is it?

Ivabradine is a heart rate lowering medicine. Heart rate is a predictor of adverse outcomes in patients with CHF. Increased heart rate is associated with increased mortality, while reducing heart rate is associated with a reduction in adverse outcomes.

Ivabradine acts by selectively inhibiting the current in the sino-atrial (SA) node responsible for pacemaking, known as the ‘funny current’ ($I_f$). Ivabradine is the first medicine to be available that specifically inhibits the $I_f$.
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**NPS RADA** | **DECEMBER 2013**

**EVIDENCE SNAPSHOT**

**WHAT IS KNOWN ABOUT THIS DRUG?**

Ivabradine specifically inhibits the sino-atrial ‘pacemaker’ current, leading to heart rate reduction with no additional cardiac effects.

The heart rate lowering effect of ivabradine has been shown to reduce hospitalisation due to CHF when added to optimal medical therapy for CHF, including ACE inhibitors and beta blockers.

Ivabradine is no better than placebo for reducing cardiovascular mortality in people with CHF, except in those with heart rate ≥ 77 bpm.

**AREAS OF UNCERTAINTY**

There are currently no long-term safety and efficacy data for ivabradine beyond 23 months (median time of follow-up in trials).

The long-term effects on CHF management and symptom control are unknown.

In addition there is evidence that ivabradine treatment is associated with an increase in symptomatic and asymptomatic bradycardia and some evidence that patients taking ivabradine may be at increased risk of developing AF.

There are limited data on the effect of ivabradine in patients over 75 years of age.

**WHAT DOES NPS SAY?**

Ivabradine may be an option for patients with CHF who have heart rate ≥ 77 bpm and are still symptomatic even with the maximum tolerated doses of standard therapy, which includes ACE inhibitors and beta blockers. Ivabradine may reduce the risk of hospitalisation and CV mortality in these patients.

Ivabradine is not recommended as a replacement for CHF medicines and should only be used as an add-on therapy, unless the maximum tolerated dose of beta blocker is contraindicated or not tolerated.

Take care to ensure that patients taking ivabradine are monitored for the development of rhythm disorders, including AF.

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The cardiac effects are specific to the SA node, with no effect on intra-atrial, atrioventricular (AV) or interventricular conduction times. There is also no effect on myocardial contractility or ventricular repolarisation at therapeutic doses.

**Who is it for?**

Ivabradine is an option for patients with symptomatic CHF (NYHA class II or III) who are in sinus rhythm, with LVEF ≤ 35% and a resting heart rate ≥ 77 bpm and who are currently receiving optimal standard treatment including maximum tolerated dose of beta blocker, unless contraindicated or not tolerated.

Ivabradine should not be used in patients with:

- sick sinus syndrome
- AV block
- SA block
- acute coronary syndromes
- severe hypotension and bradycardia or cardiogenic shock.

**New York Heart Association (NYHA) grading system for heart failure symptom severity**

<table>
<thead>
<tr>
<th>Class</th>
<th>Asymptomatic</th>
<th>No limitations in normal physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II</td>
<td>Mild</td>
<td>Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnoea or angina pectoris</td>
</tr>
<tr>
<td>Class III</td>
<td>Moderate</td>
<td>Marked limitation of physical activity. Less than ordinary activity results in symptoms</td>
</tr>
<tr>
<td>Class IV</td>
<td>Severe</td>
<td>Unable to carry out any physical activity without discomfort. Symptoms present at rest</td>
</tr>
</tbody>
</table>

Use with caution in patients who have altered rhythm or cardiac conduction.
Where does it fit?

Current pharmacological management of symptomatic CHF uses a combination of therapies aimed at alleviating symptoms and reducing mortality.

Current Australian guidelines recommend use of ACE inhibitors as first-line therapy for patients with symptomatic CHF. Beta blockers are usually added to therapy at a low starting dose and up-titrated. Diuretics as well as aldosterone inhibitors may also be added to therapy to improve symptoms.

Angiotensin-II receptor antagonists can be used as an alternative for patients intolerant of ACE inhibitors.

According to current Australian and European guidelines for the management of heart failure, ivabradine should be considered in addition to a patient’s current therapy if their heart rate remains ≥ 70 bpm despite efforts to maximise dosage of beta blocker (note: PBS listing and TGA indication state ≥ 77 bpm).

Ivabradine is only indicated as an additive therapy; there are no data on comparative efficacy of ivabradine with other CHF medicines.

Use ivabradine with caution in patients with other cardiac comorbidities related to conduction or rhythm. Ivabradine is not recommended for patients with cardiac arrhythmias, including AF, and there is some evidence that the chance of developing AF may be higher in patients with CHF taking ivabradine.

It is also not recommended for patients with conduction defects such as AV block, or with AV conduction defects such as left or right bundle-branch block. Ivabradine is contraindicated for patients with SA block.

Ivabradine is not indicated for patients with severe CHF (NYHA class IV), as only a very small number of patients have been investigated. In addition, only a limited number of patients over 75 have been studied, so use with caution in elderly patients. Ivabradine is not recommended for paediatric use.

Ivabradine in Australia: is the trial population representative?

Patients included in the main trial for ivabradine (SHIFT) were mainly white (89%) and male (76%) with an average age of 60.

The patient characteristics of the ivabradine trial population and the Australian heart failure population have been compared using data from The National Benchmarking and Evidence-Based National Clinical Guidelines for Heart Failure Management Programs (BENCH) study.

Comparing the baseline characteristics of the BENCH trial to the SHIFT trial population shows a similar composition of patients after at least one hospitalisation due to CHF. The BENCH population was older (69.8 years compared with 60 years in the SHIFT trial) with more patients who were at target beta-blocker dose (35% vs 26%).

The populations were well matched on sex and disease severity after recent hospitalisation, with the obvious exception of the numbers of patients with NYHA class I, as these were not included in the SHIFT trial.

Additionally there was a similar incidence of comorbidities such as diabetes and MI, although the SHIFT population had a much higher incidence of hypertension (66% vs 27% in the BENCH trial).

These data indicate that results from the SHIFT trial are applicable to the clinical setting for patients in Australia with heart failure.

How does it compare?

Ivabradine is a direct sinus node inhibitor that is already TGA approved for chronic stable angina. The rationale behind the investigation into ivabradine for CHF is the correlation between heart rate and cardiac mortality and morbidity in people with CHF.

The efficacy and safety of ivabradine has been assessed in comparison with placebo in patients with CHF stabilised on current standard therapies in the SHIFT trial. The relative efficacy and safety of ivabradine compared with that of current therapies such as ACE inhibitors and beta blockers has not been established.
Ivabradine may only be used in addition to optimal medical therapy, unless a beta blocker is contraindicated or not tolerated.

**The SHIFT trial**

The primary objective of the trial was to demonstrate superiority of ivabradine over placebo in reducing cardiovascular mortality or hospitalisation for worsening heart failure.2,10

The SHIFT trial was a randomised, double-blind, placebo-controlled parallel-group trial that included 6558 patients with symptomatic systolic CHF with an LVEF ≤ 35%, in sinus rhythm with a resting heart rate ≥ 70 bpm.2,8

The primary endpoint of the study was the composite of cardiovascular death or hospital admission for worsening heart failure. Secondary endpoints for the trial were all-cause mortality, death from CHF, hospitalisation (any cause) and hospitalisation (CV reason).2,8

To be included in the trial, patients were required to be in stable clinical condition, NYHA class II, III or IV, with optimised pharmaceutical management and a hospital admission for CHF within the previous 12 months. They also had to be in sinus rhythm with a resting heart rate ≥ 70 bpm and an LVEF ≤ 35%.8

Patients were excluded if they had experienced:8
- recent MI (< 2 months)
- ventricular or atrioventricular pacing operative for 40% or more of the day
- atrial fibrillation/flutter
- symptomatic hypotension.

Additional exclusion criteria included:2
- sick sinus syndrome
- congenital long-QT syndrome and other congenital heart diseases
- stroke within the previous 4 weeks.

Patients included in the trial received other CHF therapies, including ACE inhibitors (79%), beta blockers (89%), diuretic agents (84%) and anti-aldosterone agents (61%).8

Of the patients taking beta blockers, 26% were at maximum recommended dose, 56% were at ≥ 50% of target dose. The reasons for not meeting target dose included hypotension and fatigue.8

**Ivabradine efficacy: SHIFT results**

During the trial the overall mean heart rate reduction in patients treated with ivabradine was 15 bpm.8

Over the 22.9-month period of the trial the incidence of the primary efficacy endpoint (composite of CV death or hospitalisation for worsening heart failure) was 24% in the ivabradine group compared with 29% in the placebo group (hazard ratio 0.82, 95% CI 0.75 to 0.90, p < 0.0001).8

This result was statistically significant and the number needed to treat was calculated as 26 patients for 1 year to prevent one CV death or one hospitalisation from CHF.

The treatment effect on the composite endpoint was driven by hospital admissions for heart failure — 21% of patients taking placebo compared with 16% of patients taking ivabradine were hospitalised for worsening CHF.8

In patients with heart rate ≥ 70 bpm, the difference between placebo and ivabradine for CV mortality was non-significant (p = 0.128). The secondary endpoints of deaths due to heart failure and all-cause hospital admissions were reduced significantly. There was no difference in the other secondary endpoints.8

There were also small but significant improvements in NYHA class in patients taking ivabradine — 28% of patients taking ivabradine improved compared with 24% of patients on placebo (p = 0.001).8

**Efficacy in patients with heart rate ≥ 77 bpm**

Additional analyses were performed on a pre-specified subgroup of patients with resting heart rate ≥ 77 bpm.8 Compared with patients with resting heart rate ≤ 77 bpm, ivabradine treatment was associated with a larger reduction in hospitalisations and reduced CV mortality (Table I).
The effect on CV mortality is small but statistically significant in this group; 15% in the treated group vs 18% for placebo (p = 0.0137).

The effect of ivabradine in reducing hospitalisations in CHF patients has only been established as an additive therapy to current standard treatment. However, ivabradine has also been PBS listed as an option for patients for whom beta blockers are contraindicated or not tolerated.

A sub-analysis of the SHIFT trial in patients unable to tolerate, or with contraindications to, beta blockers showed that ivabradine was still effective in reducing hospitalisations due to CHF. However, ivabradine should not be considered as replacement therapy for any of the standard therapies available to treat CHF. It should only be used as a means of reducing mortality and hospitalisation in patients with a heart rate ≥ 77 bpm who are still symptomatic despite optimal therapy.

Overall the SHIFT trial data support the hypothesis that targeted heart rate reduction reduces the composite of CV mortality and hospitalisation due to heart failure in patients with stable CHF already treated with optimal medical therapy who have a heart rate ≥ 70 bpm, with a larger effect seen in patients with a heart rate ≥ 77 bpm.

The SHIFT trial did not show any effect of ivabradine in reducing CV mortality in the main trial population with heart rate ≥ 70 bpm. There was a small but statistically significant reduction in CV mortality in patients with heart rate ≥ 77 bpm. The relative efficacy of ivabradine compared with other CHF medicines has not been established.

### Safety issues

The safety and efficacy of ivabradine for CHF were assessed in 3241 patients for a median of 22.9 months; the long-term safety of ivabradine in CHF patients has not been established. The SHIFT trial did not have a primary safety endpoint and may not be adequately powered to detect potential rare side effects of ivabradine therapy.

The adverse events seen in the SHIFT trial were consistent with previously known effects of ivabradine. Patients in the treatment arm of the SHIFT trial were more likely to experience symptomatic and asymptomatic bradycardia compared with patients taking placebo (p < 0.0001, Table 2). They were also more likely to develop AF and experience visual disturbances (phosphenes*).

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Table 1. Effect of treatment with ivabradine on the primary and secondary endpoints in patients with heart rate ≥ 77 bpm

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ivabradine (n = 1657) n (%)</th>
<th>Placebo (n = 1700) n (%)</th>
<th>Hazard ratio [95% CI]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>255 (15)</td>
<td>312 (18)</td>
<td>0.81 [0.69 to 0.96]</td>
<td>0.0137</td>
</tr>
<tr>
<td>Hospitalisation for worsening HF</td>
<td>298 (18)</td>
<td>418 (25)</td>
<td>0.69 [0.59 to 0.80]</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>285 (17)</td>
<td>350 (21)</td>
<td>0.81 [0.69 to 0.94]</td>
<td>0.0074</td>
</tr>
<tr>
<td>Death from heart failure</td>
<td>67 (4)</td>
<td>107 (6)</td>
<td>0.61 [0.45 to 0.83]</td>
<td>0.0017</td>
</tr>
<tr>
<td>All-cause hospitalisation</td>
<td>667 (40)</td>
<td>778 (46)</td>
<td>0.82 [0.74 to 0.91]</td>
<td>0.0002</td>
</tr>
<tr>
<td>CV hospitalisation</td>
<td>534 (32)</td>
<td>647 (38)</td>
<td>0.79 [0.71 to 0.89]</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

*Visual disturbances are described as ‘transient enhanced brightness in a limited area of the visual field’.*

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*CI: confidence interval*
Cardiac conduction and rhythm disorders

Ivabradine is contraindicated for patients with third-degree AV block and SA block.\textsuperscript{10}
Closely monitor patients with intraventricular conduction defects.\textsuperscript{10}
In addition, there is evidence that patients taking ivabradine may be at a higher risk of developing AF.\textsuperscript{10}
In the SHIFT trial there was a small but statistically significant difference (p = 0.012, Table\textsuperscript{2}) between the ivabradine and placebo treatment groups.\textsuperscript{8}
As ivabradine is not recommended in patients with AF, these patients should be checked regularly for rhythm disorders.\textsuperscript{3}
This should include ECG monitoring if clinically indicated, for example, if a patient has palpitations or irregular pulse.\textsuperscript{3}
As ivabradine is a selective sinus node inhibitor it will be ineffective in patients with AF. Therefore consider stopping therapy if a patient develops AF while on ivabradine.

**Ivabradine may cause visual disturbances (phosphenes)**
Ivabradine may influence retinal function in humans through interaction with hyperpolarisation-activated currents (I\textsubscript{h}) in the retina.\textsuperscript{3,11}
These visual disturbances\textsuperscript{8} usually resolve spontaneously.\textsuperscript{3}
No retinal toxicity has been found, but effects on the retina in patients being treated with ivabradine long term have not been established.\textsuperscript{3}
In the SHIFT trial 3% of patients taking ivabradine experienced phosphenes compared with 1% of patients taking placebo (p < 0.0001).\textsuperscript{8}
In the ivabradine group seven patients (< 1%) withdrew because of this adverse event.\textsuperscript{8}
Caution is recommended in patients with retinitis pigmentosa, and consider stopping therapy in patients experiencing any unexpected deterioration in vision.\textsuperscript{3}

**Bradycardia**
In the SHIFT trial patients taking ivabradine had an increased incidence of symptomatic and asymptomatic bradycardia compared with placebo.\textsuperscript{8}
Dosing advice in the Product Information suggests that if a patient’s heart rate decreases persistently below 50 bpm or if a patient experiences symptoms such as dizziness, fatigue or hypotension, that the dose of ivabradine be titrated down.\textsuperscript{3}
Discontinue treatment if heart rate remains < 50 bpm or symptoms persist after dose adjustment.\textsuperscript{3}

**QT-interval effects**
Ivabradine treatment leads to QT-interval prolongation through reduced heart rate, but this is in the absence of any significant effect on ventricular repolarisation.\textsuperscript{13}
Ivabradine therefore does not have any direct potential to cause torsades de pointes.\textsuperscript{5}
However, avoid prescribing other medicines known to affect the QT interval in people taking ivabradine. In addition, do not use ivabradine in people with familial long-QT syndrome.\textsuperscript{3}

**Pregnant women, children and adolescents, and people over 75**
Ivabradine should not be used by pregnant or breastfeeding women.\textsuperscript{3}
Efficacy and safety has not been assessed in children and adolescents.\textsuperscript{3}
The SHIFT trial included only a small sample of patients aged over 75 (722, 11%).\textsuperscript{8} This sample size may be inadequate to assess the safety and efficacy of ivabradine in this population.\textsuperscript{8} The approved Product Information suggests a lower starting dose with up-titration if necessary.\textsuperscript{3}

### Table 2.
Selected adverse events and withdrawal rates in the SHIFT trial\textsuperscript{8}

<table>
<thead>
<tr>
<th>Event</th>
<th>Patients with an adverse event</th>
<th>Patients with an adverse event leading to drug withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ivabradine</td>
<td>Placebo</td>
</tr>
<tr>
<td>Symptomatic bradycardia</td>
<td>150 (5%)</td>
<td>32 (1%)</td>
</tr>
<tr>
<td>Asymptomatic bradycardia</td>
<td>184 (6%)</td>
<td>48 (1%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>306 (9%)</td>
<td>251 (8%)</td>
</tr>
<tr>
<td>Phosphenes</td>
<td>89 (3%)</td>
<td>17 (1%)</td>
</tr>
</tbody>
</table>
**Hepatic insufficiencies**

Ivabradine may be used in patients with mild or moderate hepatic insufficiency; however, use with caution in people with moderate insufficiency. 3

Ivabradine is contraindicated in patients with severe hepatic insufficiency. 3

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website (www.tga.gov.au/safety/problem.htm#medicine) or use the ‘Blue Card’ distributed with the October issue of Australian Prescriber.

**Reason for PBS listing**

The PBAC recommended listing of ivabradine (5 mg and 7.5 mg) tablets on the PBS for patients who meet criteria on a cost-effectiveness basis over placebo. The PBAC considered it important to restrict the listing of ivabradine to the TGA-approved indication of patients who are already receiving optimal standard therapy for CHF, which must include maximum tolerated dose of beta blocker unless contraindicated or not tolerated.

The PBS restriction for patients who have a resting heart rate \( \geq 77 \) bpm is based on the sub-study analysis that showed that ivabradine was associated with a greater reduction in hospitalisation and CV mortality compared with patients with a resting heart rate \( \leq 77 \) bpm.

**Dosing issues**

- The recommended starting dose for ivabradine is 5 mg twice daily. After 2 weeks of treatment the patient’s heart rate should be determined and dose adjusted according to heart rate:
  - persistently > 60 bpm: increase dose to 7.5 mg twice daily
  - persistently 50–60 bpm: maintain dose at 5 mg twice daily
  - persistently < 50 bpm or with symptoms of bradycardia: decrease dose to a minimum of 2.5 mg twice daily (half a tablet).

- Ivabradine should be taken once in the morning and once in the evening with food.

- Start elderly patients (> 75 years) on a lower dose (2.5 mg twice daily, this would require half a tablet) and up-titrate if necessary.

- No dose adjustment is required in patients with creatinine clearance > 15 mL/min.

- No dose adjustment is required in patients with mild hepatic impairment. Use with caution in patients with moderate impairment; ivabradine is contraindicated in patients with severe impairment.

- Ivabradine is metabolised by CYP3A4; refer to the Product Information for advice about concomitant use with CYP3A4 inhibitors or inducers.

**Information for patients**

Advise patients that ivabradine is intended to slow the heart rate, and discuss the symptoms they may experience because of this (such as dizziness or fatigue). Tell your patients to inform you if they experience any prolonged symptoms of low heart rate.

Discuss with patients the importance of continued heart rate monitoring during the initial phase of treatment and explain that the dose may need to be adjusted. This may require multiple visits to their GP.

Inform patients of the risk of developing visual disturbances (phosphenes) and that these are not associated with retinal damage. Advise the patient that any deterioration of vision should be investigated immediately.

Discuss with patients the importance of continuing with their other therapies.

Patients should also be informed of important drug interactions. St Johns wort and grapefruit juice may interact with ivabradine and should be avoided.

Discuss the Coralan consumer medicine information (CMI) leaflet with the patient. Search for CMI at http://www.nps.org.au/search_by_medicine_name.
REFERENCES


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