

**6.10 IVABRADINE  
tablets, 5 mg and 7.5 mg (as hydrochloride);  
Coralan®; Servier Laboratories Pty Ltd**

**1 Purpose of Application**

- 1.1 The minor submission requested the following changes to the ivabradine restriction for the treatment of heart failure:
- (i) Change the listing from Authority Required to Authority Required (Streamlined); and
  - (ii) Change the wording of the restriction to include echocardiography as an appropriate test for measuring resting heart rate.

**2 Requested listing**

- 2.1 The submission requested a change to the existing restriction from July 2013 PBAC meeting to include echocardiography reports to the existing prescriber instructions. It also requested to change the restriction level to Authority required (Streamlined). The current restriction wording reads as shown below, with the requested deletions are in strikethrough and additions in italics.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
IVABRADINE				
TABLET 5 MG	56	5	\$ [REDACTED]	Coralan SE
TABLET 7.5 MG	56	5	\$ [REDACTED]	Coralan SE

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity	Chronic
Condition:	heart failure
PBS Indication:	Chronic heart failure
Restriction Level / Method:	<del>Authority Required – In Writing</del> <del>Authority Required – Telephone</del> <del>Authority Required – Emergency</del> <del>Authority Required – Electronic</del> <i>Streamlined</i>

<p><b>Clinical criteria:</b></p>	<p>Patient must be symptomatic with NYHA classes II or III, AND Patient must be in sinus rhythm; AND Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 35%, AND Patient must have a resting heart rate at or above 77 bpm at the time ivabradine treatment is initiated; AND Patient must receive concomitant optimal standard chronic heart failure treatment, which must include the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated.</p>
<p><b>Prescriber Instructions</b></p>	<p>Resting heart rate should be measured by ECG <i>or echocardiography</i>, after 5 minutes rest.</p> <p>The ECG <i>or echocardiography</i>, result must be documented in the patient's medical records when treatment is initiated.</p>
<p><b>Administrative Advice</b></p>	<p>Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.</p>

### 3 Background

- 3.1 At the March 2013 meeting, the PBAC recommended listing for ivabradine as an Authority Required benefit for treatment of chronic heart failure in patients who meet certain criteria on a cost-effectiveness basis over placebo.

### 4 Current status

- 4.1 The PBAC noted that the TGA is currently reviewing new information regarding ivabradine identified in the preliminary results of a study into the drug. The SIGNIFY study is evaluating the efficacy of ivabradine in patients who have cardiovascular disease affecting the blood vessels but no heart failure. Preliminary results from the study have indicated that some patients with angina have a small but statistically significant increase in the combined risk of death and non-fatal heart attack compared to placebo.
- 4.2 The PBAC requested that the sponsor provide further information relating to the SIGNIFY study and the status of the TGA review as a late paper.
- 4.3 In its pre-PBAC response, the sponsor provided an update on the TGA review. The sponsor stated that the European Medicines Agency (EMA) "...concluded in November 2014 that the benefit-risk profile of ivabradine remains positive for its authorised indications." The sponsor also stated that the SIGNIFY study evaluated "...the efficacy of ivabradine in preventing CV events... in patients with coronary artery disease without heart failure..." The sponsor also quoted the EMA's Scientific Advisory Group, which "...was of the opinion that the results of the SIGNIFY trial do not impact on ivabradine in the treatment of chronic heart failure." The sponsor also noted that the PBS population of patients with heart failure was based on the SHIfT study. The sponsor also advised that the TGA is currently considering amendments to the Australian Product Information (PI), and that once approved the changes would be communicated by the sponsor to prescribers.

## **5 Clinical trials**

- 5.1 As a minor submission, no new clinical trials were presented in the submission.
- 5.2 The basis of the minor submission's request, to amend the wording of the restriction to include echocardiography, is that it provides a verifiable measurement of heart rate and is routinely used by some cardiologists. The submission provided no supporting evidence on the clinical benefit or appropriateness of this diagnostic test compared with ECG.

## **Economic analysis**

- 5.3 As a minor submission, no economic comparison was presented.

## **Estimated PBS usage & financial implications**

- 5.4 The minor submission noted that a risk share agreement (RSA) is in place for ivabradine. The submission estimated that expenditure on ivabradine is 39% below the first year RSA threshold.
- 5.5 The submission notes that the October 2014 monthly PBS usage statistics indicate that 3,293 patients are currently taking ivabradine.

## **6 PBAC Outcome**

- 6.1 The PBAC recommended amending the listing of ivabradine from Authority Required to Authority Required (Streamlined).
- 6.2 The PBAC also recommended a change to the restriction wording to include echocardiography as an alternative diagnostic test to electrocardiogram (ECG). The PBAC considered that echocardiography is regularly used in clinical practice, and that the change was therefore appropriate.
- 6.3 The PBAC noted that the minor submission's estimates of ivabradine utilisation were lower than the Committee had considered in its initial recommendation. The PBAC considered that the recommended changes would not change utilisation patterns for ivabradine.
- 6.4 The PBAC noted the sponsor's update in its pre-PBAC response regarding the EMA review of ivabradine and the TGA status on PI amendments. The PBAC considered that the information provided was satisfactory and that at this time there was no cause for concern regarding the safety of ivabradine.
- 6.5 The PBAC noted that this submission is not eligible for an Independent Review.

### **Outcome:**

Recommended

## **7 Recommended listing**

- 7.1 Amend existing listing as follows:

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Condition:	heart failure
PBS Indication:	Chronic heart failure
Restriction Level / Method:	Streamlined
Clinical criteria:	Patient must be symptomatic with NYHA classes II or III, AND Patient must be in sinus rhythm; AND Patient must have a documented left ventricular ejection fraction (LVEF) of less than or equal to 35%, AND Patient must have a resting heart rate at or above 77 bpm at the time ivabradine treatment is initiated; AND Patient must receive concomitant optimal standard chronic heart failure treatment, which must include the maximum tolerated dose of a beta-blocker, unless contraindicated or not tolerated.
Prescriber Instructions	Resting heart rate should be measured by ECG or echocardiography, after 5 minutes rest.  The ECG or echocardiography, result must be documented in the patient's medical records when treatment is initiated.
Administrative Advice	Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.

**8 Context for Decision**

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

**9 Sponsor's Comment**

The sponsor had no comment.