

## Pharmacotherapeutic report, summary

Ivabradine (Procoralan®) for the indication chronic heart failure

Recommendation by CVZ dated 25-03-2013, based on evaluation by the Scientific Advisory Committee (WAR).

**Medicine.** Ivabradine (Procoralan®), film-coated tablet

**Registered indication.** “Ivabradine is indicated in chronic heart failure NYHA II to IV class with systolic dysfunction, in patients in sinus rhythm and whose heart rate is  $\geq 75$  bpm, in combination with standard therapy including beta-blocker therapy or when beta-blocker therapy is contraindicated or not tolerated.”

**Posology.** 5 mg twice daily. After two weeks of treatment, the dose may be increased to 7.5 mg twice daily if the resting heart rate is persistently above 60 beats per minute or reduced to 2.5 mg twice daily if the resting heart rate is persistently below 50 beats per minute.

**Mechanism of action.** Ivabradine works via selective and specific inhibition of the cardiac pacemaker current  $I_f$  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.

**Specific details.** Ivabradine is also registered for the treatment of chronic stable angina pectoris. The current assessment relates to expanding the detailed conditions for ivabradine on List 2 of the Health Insurance Regulation for the above-mentioned indication.

### **Summary of the therapeutic value**

**Intended effects.** In a phase III study, the addition of ivabradine to the standard treatment of patients with chronic heart failure NYHA class II to IV in sinus rhythm with systolic dysfunction led to statistically significant reduction in mortality and (cardio-related) hospitalisation in a sub-group of patients with a confirmed resting heart rate of at least 75 beats per minute. However, no clinically relevant effect on quality of life was demonstrated in this sub-group.

**Unintended effects.** The unintended effects observed most frequently in the study due to the addition of ivabradine to the usual treatment are atrium fibrillation and symptomatic and asymptomatic bradycardia. There were only minor differences (<1%) in the incidence of other serious unintended effects of ivabradine and placebo (both added to the standard treatment). The profile of unintended effects of ivabradine is comparable with unintended effects mentioned in previous studies.

**Experience.** Sufficient experience has been obtained with ivabradine.

**Applicability.** Interactions and contraindications limit the applicability of ivabradine.

**Ease of use.** The addition of ivabradine reduces the treatment's ease of use.

**Final conclusion on therapeutic value.**

Ivabradine has an added therapeutic value in comparison with placebo in patients with chronic heart failure NYHA class II-IV in sinus rhythm with systolic dysfunction with a resting heart rate of  
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≥75 bpm if it is added to an individually determined and optimally dosed medicinal treatment drawn up in accordance with guidelines, and including, in principle, an ACE inhibitor, a diuretic, a beta-blocker and an anti-aldosterone agent, unless this is contraindicated or not tolerated by the patient.

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*Furthermore, CVZ points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.*