



Coralan® (ivabradine) – The first selective and specific I_f inhibitor

Mode of action

Ivabradine is a heart rate lowering agent. It acts by selective and specific inhibition of the cardiac pacemaker I_f current, an important ionic current that usually controls spontaneous diastolic depolarisation in the sinus node and thereby regulates heart rate.

The cardiac effects of ivabradine are specific to the sinus node and ivabradine has no effect on intra-atrial, atrioventricular or intraventricular conduction times, myocardial contractility or ventricular repolarisation.

An elevated heart rate increases myocardial oxygen demand and limits tissue perfusion, the latter by reducing the duration of diastole, during which most myocardial perfusion occurs. Therefore, a pure reduction in heart rate can reduce myocardial ischaemia and prevent angina pectoris.

Approved indication

Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who are intolerant to beta-blockers or in whom these agents are contraindicated.

Dosage

The usual recommended dose is 5 mg twice daily. The dose may be increased after 2 to 4 weeks to 7.5 mg twice daily, if necessary.

If the heart rate decreases below 50 bpm at rest or if the patient experiences symptoms related to bradycardia, the dose should be reduced to 2.5 mg twice daily. Treatment should be stopped if the heart rate remains below 50 bpm or if symptoms of bradycardia persist.

Adults over the age of 75 years should start treatment with a lower dose i.e. 2.5 mg twice daily.

Evidence of efficacy

Treatment with ivabradine provides the opportunity to assess the effects of lowering heart rate without directly altering other aspects of cardiac function because the drug is a pure heart-rate lowering agent.

- Ivabradine, when given as monotherapy (with short-acting nitrates allowed as required), has demonstrated anti-ischaemic and anti-anginal efficacy in randomised clinical trials conducted in patients with chronic stable angina pectoris. Ivabradine has been shown to be non-inferior to atenolol and to amlodipine.
- The combination of ivabradine plus atenolol in patients with chronic stable angina pectoris produces additional efficacy with no adverse effects on safety and tolerability.
- Although ivabradine may not improve cardiac outcomes in all patients with stable coronary artery disease, it does reduce the incidence of coronary artery disease outcomes in patients who have heart rates of 70 bpm or more.

Precautions

o General

Ivabradine is contraindicated in patients with cardiac dysrhythmias, unstable angina pectoris, acute coronary syndrome, class III to IV heart failure, 3rd degree AV block, cardiogenic shock, those with a

pacemaker, a resting heart rate below 60 bpm or severe hypotension (< 90/50 mm Hg).

Ivabradine is not recommended for use in patients with liver dysfunction and is contraindicated in patients with severe liver dysfunction.

o Pregnancy and lactation

Ivabradine is contraindicated for use during pregnancy and lactation.

Major adverse effects

Luminous phenomena (phosphenes) i.e. enhanced brightness in the visual field, have been reported in 14.5% of patients. These effects usually resolve spontaneously during treatment.

Other common side effects include bradycardia, AV 1st degree heart block, ventricular extrasystoles, headache and dizziness.

Drug interactions

The concurrent use of ivabradine with St John's Wort, strong cytochrome P450 inhibitors (such as the azole antifungals, macrolides, HIV protease inhibitors and nefazodone) is contraindicated.

The concomitant use of medicines that prolong the QT intervals should be avoided since QT prolongation may be exacerbated by heart rate reduction.

The concomitant use of ivabradine with heart rate reducing calcium channel blockers such as verapamil or diltiazem is not recommended.

Cost: SEP (Excl VAT)

Coralan® 5 mg tablets: R357.00/56 tablets

Coralan® 7.5 mg tablets: R357.00/56 tablets

Patient information

Ivabradine should be taken twice daily – in the morning and in the evening.

The tablets should be swallowed with a little water and taken with some food.

Changes in vision may occur, but usually resolve with continued treatment.

Conclusion

Ivabradine is the first agent in a new therapeutic class, the selective and specific I_f inhibitors. It has demonstrated efficacy in the treatment of chronic stable angina pectoris and may be recommended for symptomatic patients in whom beta-blockers are contraindicated or not tolerated. Ivabradine may also be used in combination with a beta-blocker in patients who remain symptomatic despite beta-blocker therapy. □

References:

1. Coralan® package insert.
2. Tardif JC, Ponikowski P, Kahan T for the Associate study investigators. Efficacy of the I_f current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month randomized, placebo-controlled trial. *Eur Heart J*. Advanced access published Jan 9, 2009.
3. Fox K, Ford I, Steg PG, *et al*. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *The Lancet*. Published online Aug 31, 2008.