

# RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

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## Ivabradine

Angina occurs when there is insufficient perfusion of the myocardium to meet metabolic demand. An increase in heart rate results in increased myocardial oxygen demand which can lead to an exacerbation of myocardial ischaemia and subsequent angina. When the heart rate rises from 60 to 80 beats per minute, the incidence of ischemic episodes is doubled. In stable angina, the benefits of heart rate reduction are well accepted explaining the common use of beta-blockers, verapamil and diltiazem in this condition.

Ivabradine is a new and specific heart rate lowering drug which acts on the sinoatrial (SA) node by selectively inhibiting the pacemaker current  $I_f$ . It slows the diastolic depolarisation period of the action potential of SA node cells and decreases heart rate without affecting myocardial contractility, relaxation and peripheral vascular resistance. The heart rate reduction associated with ivabradine has been shown to be dose-related in clinical trials. Ivabradine does not block atrioventricular node and is ineffective at reducing heart rate in patients with atrial fibrillation. Naturally, Ivabradine should not be used in conditions where the SA node is not the cardiac pace maker: these circumstances include those where the patient has an artificial pacemaker, or has sick sinus syndrome or third degree heart block (as ivabradine will not be effective).

Animal studies suggest that Ivabradine may also have benefits in patient with heart failure. Two large randomised controlled trials are underway to evaluate the effect of ivabradine in patients with left ventricular dysfunction. The BEAUTIFUL study is designed to investigate whether ivabradine may delay death and cardiovascular outcomes in more than 10,000 patients with ejection fraction less than 40%. It is expected that this trial will be completed in late 2008. The SHIFT trial will recruit about 5500 patients with moderate to severe heart failure and an ejection fraction less than 35%.

In terms of adverse effects, ivabradine appears to be well tolerated with the most common side effects being visual symptoms (phosphenes) and bradycardia. Ivabradine should not be commenced when the baseline resting heart rate is less than 60 beats per minute. Ivabradine is metabolised by the hepatic enzyme CYP3A4. The concurrent use of potent CYP3A4 enzyme inhibitors such as ketoconazole, itraconazole, clarithromycin, and erythromycin is contraindicated as these drugs may increase plasma concentration of ivabradine and potentiate bradycardia.

Ivabradine can be used as an alternative agent in patients with chronic stable angina who can not tolerate or have contraindications to beta-blockers. It can also be added to previous treatment of angina when symptoms are not controlled.

Ivabradine (Coralan®) is marketed in Australia for treatment of stable angina as 5 mg and 7.5 mg tablets. Its supply to patients is not, however, currently subsidised through the PBS scheme.

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**FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: [chris.alderman@rgh.sa.gov.au](mailto:chris.alderman@rgh.sa.gov.au)**  
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