

NEW DRUG EVALUATION

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IVABRADINE

Ivabradine (Procoralan[®]) is an I_f inhibitor licensed for the treatment of chronic stable angina in patients in normal sinus rhythm in whom beta-blockers are either not tolerated or contra-indicated. Although effective for angina symptoms there is currently no efficacy data on mortality, long term survival or hospital admissions. Visual disturbances are commonly reported but are not thought to affect driving ability. Ivabradine has not been compared with rate limiting calcium channel blockers such as verapamil and diltiazem which should remain first choice alternative in patients who cannot tolerate first-line beta blockade.

What is it?

Ivabradine (Procoralan[®], Servier Laboratories) is the first I_f inhibitor licensed at a dose of 5 and 7.5 mg twice daily for the treatment of chronic stable angina in patients with normal sinus rhythm in whom beta-blockers are either not tolerated or contra-indicated.⁽¹⁾ In patients over 75 years old, a lower starting dose of 2.5 mg twice daily should be considered. It blocks a specific ion channel (funny channel) which results in a lowering of heart rate.⁽¹⁾

How effective is it?

Only one phase III trial has been fully published. The INITIATIVE study was a 16 week RCT non-inferiority study of 939 patients with stable angina.⁽²⁾ Patients were randomised initially to either atenolol 50 mg daily or ivabradine 5 mg twice a day for 4 weeks. The ivabradine group was then randomised to either 7.5 or 10mg and all patients in the atenolol group were increased to 100mg daily for a further 12 weeks. The primary endpoint was the change in total exercise duration during exercise tolerance (ETT) testing from baseline to the end of the treatment period. Non inferiority to atenolol was demonstrated for both the 7.5mg and the unlicensed 10mg dose of ivabradine for the primary endpoint.⁽²⁾

A further double blind non-inferiority study, only reported in abstract form concluded that ivabradine was as effective as amlodipine in patients with stable angina.⁽³⁾

A further unpublished study demonstrated no additional anti-anginal effects with 5 or 7.5 mg of ivabradine compared with placebo in patients already taking amlodipine 10mg daily, but appeared to show an additional benefit in total exercise duration and time to angina onset at peak of drug effect.⁽⁴⁾ This suggests additional clinical benefit in patients already taking calcium channel blockers is unlikely. As yet there is no long term outcome data on morbidity and mortality for ivabradine.

How safe is it?

No evidence of the rebound angina phenomenon often encountered with beta blockers has been shown. Due to its pharmacological effect, interaction can occur with the structurally similar retinal I_h channels in the eye, involved in the response to light stimuli. Visual disturbances (phosphenes or luminous phenomena) were commonly reported within the phase 3 studies (17% vs. 3-7%). The impact of these events on patients' daily life was low and most events (76%) resolved during treatment. Such visual disturbances do not appear to affect driving ability.⁽⁴⁾

Cardiac arrhythmias were more common in the ivabradine treated patients compared with other groups (1.1% vs. 0.2-0.7%). The incidence of deaths per 100 patient years appeared higher for patients receiving ivabradine (2.4) than in those receiving atenolol (0.50), but were similar to those receiving placebo (3.1) and amlodipine (2.1). However, the number of events was low and these differences did not reach statistical significance.⁽⁵⁾

Ivabradine is contraindicated in patients with NYHA grade III or IV heart failure. The use of ivabradine with heart rate reducing calcium channel blockers e.g. verapamil or diltiazem, is not recommended.⁽¹⁾ Ivabradine should also not be used in combination with QT prolonging agents. It is metabolized extensively by the CYP3A4 enzyme and is a weak inhibitor of this enzyme; it is thought not to influence the metabolism of other drugs metabolized by this enzyme such as statins. Inhibitors of CYP3A4 such as anti-fungals, macrolide antibiotics and anti-retro virus drugs may increase ivabradine plasma concentrations and are contra-indicated. CYP3A4 inducers such as rifampicin, phenytoin and St John's Wort may decrease ivabradine levels and adjustment of the dose may be necessary.⁽¹⁾

What other options are there?

Calcium channel blockers, particularly rate limiting agents such as verapamil and diltiazem have an established role as alternatives to beta blockade and have been demonstrated to reduce mortality following non-Q wave myocardial infarction, in patients with no pulmonary congestion.⁽⁶⁾

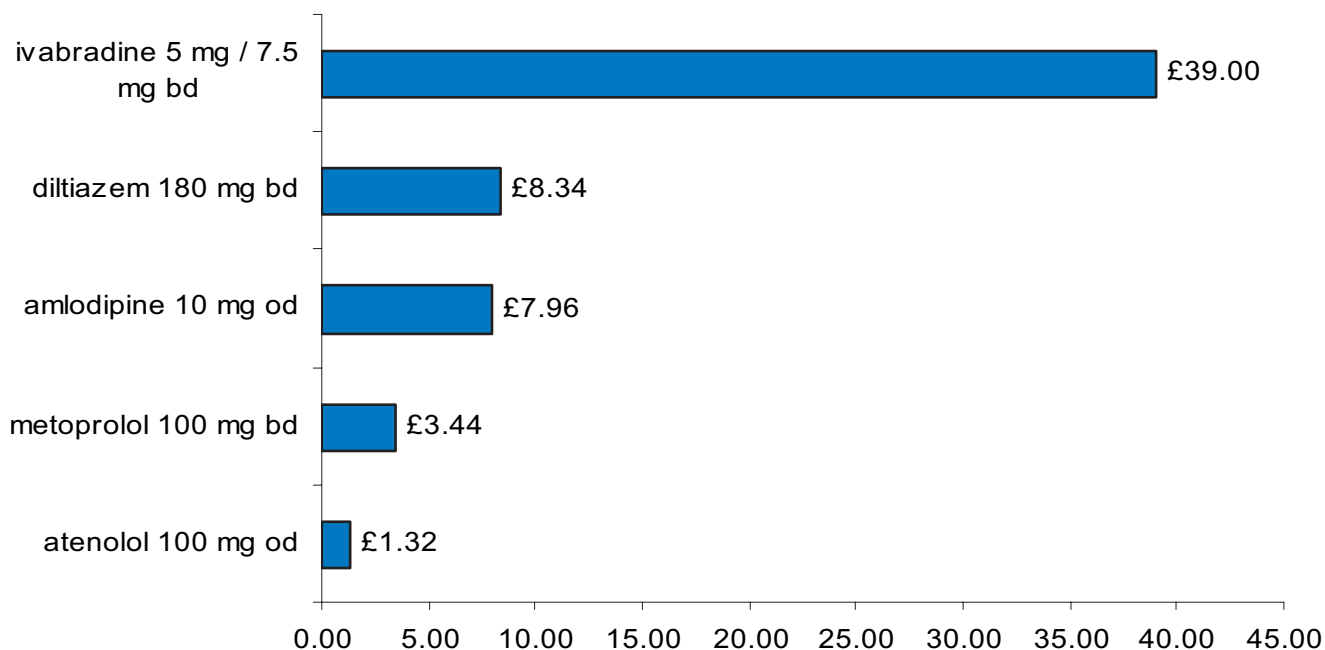
When should it be used?

Beta blockers remain the treatment of choice for the management of patients with stable angina and have been demonstrated to reduce the risk of subsequent events in patients with previous MI.⁽⁷⁾ Ivabradine is only licensed for use in patients for whom beta blockers are either

contraindicated (e.g. asthmatics) or where they may not be tolerated (e.g. due to side effects of cold peripheries, impotence etc). Based on currently available evidence, a rate limiting calcium channel blocker such as verapamil or diltiazem may be a more appropriate initial alternative choice.

How much does it cost?

Cost for 28 days treatment (Drug Tariff/eMIMS May 2006)



N.B. Doses shown are for general comparison only and do not imply therapeutic equivalence

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KEY RCT - randomised controlled trial, CT-controlled trial, G-guideline, R-review, Abs- abstract

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