

NEW DRUG EVALUATION

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EPLERENONE

Eplerenone is a selective aldosterone antagonist for the treatment of patients with symptomatic heart failure and left ventricular dysfunction after myocardial infarction (MI), to be used in addition to standard therapies including a beta-blocker. In one 16-month trial in patients meeting these criteria, eplerenone significantly reduced morbidity and mortality when initiated within 3 - 14 days of acute MI. It may cause serious hyperkalaemia, particularly in patients with impaired renal function. Serum potassium should be measured before and regularly during treatment. There are no data comparing eplerenone with spironolactone.

What is it?

Eplerenone (Inspra[®], Pfizer) is a selective aldosterone antagonist licensed for use, in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (left ventricular ejection fraction \leq 40%) and clinical evidence of heart failure after recent myocardial infarction (MI).¹

Compared with spironolactone, the only other aldosterone antagonist currently available, eplerenone has lower in vitro affinity for androgen and progesterone receptors and may therefore be associated with a lower risk of adverse effects such as gynaecomastia.² However; no comparative trials have been published.

How effective is it?

The licensed indication for eplerenone is based on the EPHEBUS study, a randomised, double-blind, placebo-controlled trial in 6634 patients with left ventricular dysfunction and symptomatic heart failure after acute MI.³ Ninety percent of patients had heart failure symptoms. Patients were randomised to eplerenone (25 mg/day for 4 weeks then increased to a maximum of 50 mg/day) or placebo within 3 - 14 days of acute MI in addition to optimal medical therapy (ACE inhibitor or angiotensin II receptor blocker in 87% of patients, beta-blocker (75%), diuretic (61%), aspirin (89%) and, in 47%, a statin).

After a mean follow-up of 16 months, the incidence of the first primary endpoint (death from any cause) was 14.4% with eplerenone and 16.7% with placebo (relative risk [RR] 0.85, CI_{95%} 0.75 - 0.96, p=0.008). The incidence of the second primary endpoint (cardiovascular death or admission due to a cardiovascular event) was 26.7% vs. 30.0% respectively (RR

0.87, CI_{95%} 0.79 - 0.95, p=0.002). Eplerenone was also associated with a reduction in cardiovascular deaths (absolute risk reduction 2.3%), due largely to a reduction in sudden cardiac death (absolute risk reduction 1.2%).

These findings suggest that, over 1 year, 50 patients would need to be treated to avoid one death and 33 would need to be treated to avoid one cardiovascular death or admission for a cardiovascular event.

How safe is it?

At one year, eplerenone was associated with a smaller mean increase in blood pressure than placebo (5/3 mmHg vs. 8/4 mmHg, p<0.01) but a greater mean increase in serum creatinine (5.3 micromol/l vs. 1.8 micromol/l, p<0.001). The incidence of serious hyperkalaemia (serum potassium \geq 6.0 mmol/l) was also greater with eplerenone (5.5% vs. 3.9%, p=0.002) and greater still in patients with a baseline creatinine clearance of less than 50 ml/minute. (10.1% vs. 5.9%, p=0.006).³ Serum potassium should be measured at baseline, within the first week and one month after the start of therapy or dose adjustment.¹ The incidence of gynaecomastia, impotence or, in women, breast pain was similar for eplerenone and placebo.³

The metabolism of eplerenone may be inhibited by hepatic CYP3A4 substrates; the starting dose should therefore be reduced in patients taking diltiazem, verapamil or amiodarone. Potassium-sparing diuretics and strong CYP3A4 inhibitors such as clarithromycin should be avoided.¹ Eplerenone is contraindicated in patients with hyperkalaemia, moderate or severe renal impairment or severe hepatic impairment.

What other options are there?

Spironolactone is currently licensed for the treatment of congestive heart failure. In a double-blind study in patients (n=1663) with heart failure and a left ventricular ejection fraction $\leq 35\%$, were randomly assigned to receive 25 mg spironolactone or placebo. The primary end-point was death from all causes. The trial was discontinued after 24 months as there were 386 deaths in the placebo group (46%) and 284 in the spironolactone group (35%).⁴ The National Institute of Clinical Excellence (NICE) recommends that

spironolactone may be indicated for patients with chronic heart failure who remain moderately to severely symptomatic despite optimal treatment with a diuretic, an ACE inhibitor and a beta-blocker.⁵

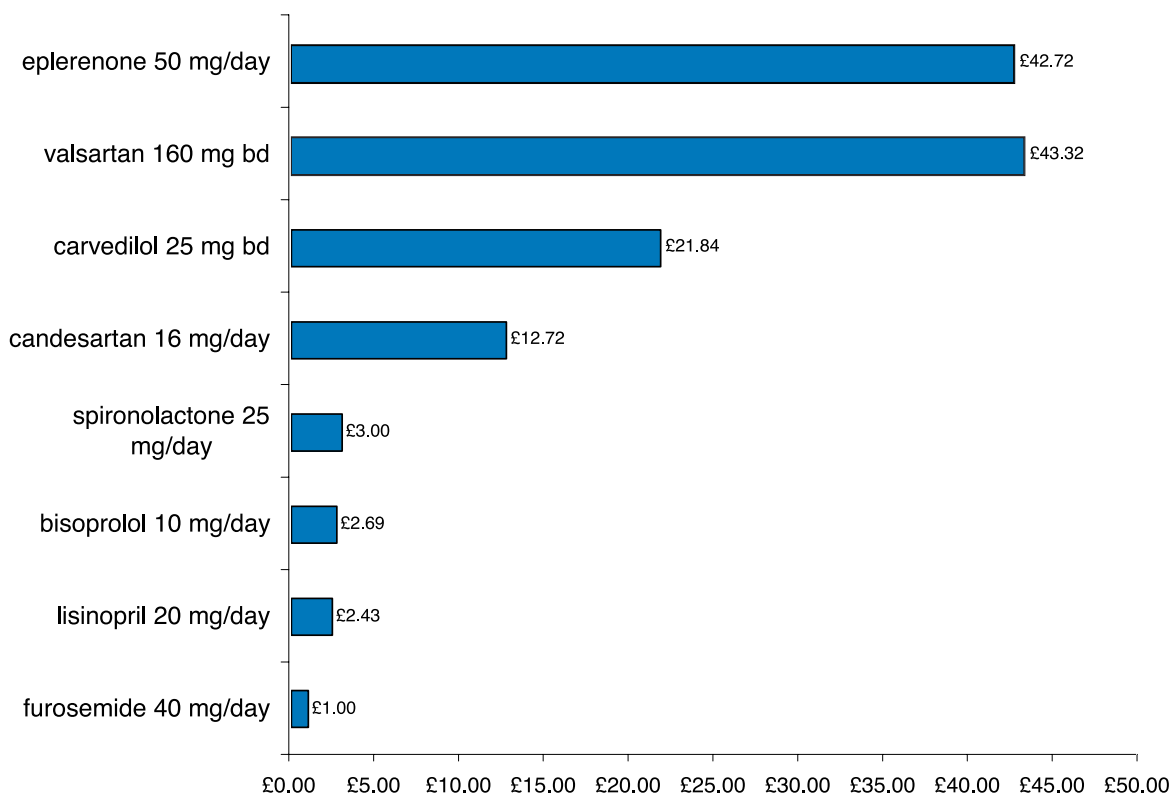
When should it be used?

No studies directly compare clinical and cost effectiveness of eplerenone and spironolactone.⁶

Eplerenone is currently licensed for the treatment of hypertension in the USA and the manufacturer expects to submit a license for this indication in 2006.⁷

How much does it cost?

Cost of 28 Days Treatment (prices from MIMS July 2005/Drug Tariff July 2005)



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

REFERENCES

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KEY RCT - randomised controlled trial, R - review, G - guideline

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