

Resubmission

epplerenone 25mg and 50mg tablets (Inspra[®]) No. (136/04)
Pfizer Ltd

4 March 2005

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a resubmission

Eplerenone (Inspra[®]) is accepted for use within NHS Scotland in addition to standard therapy including beta blockers, to reduce the risk of cardiovascular mortality and morbidity between 3-14 days after myocardial infarction (MI) in stable patients with left ventricular dysfunction (left ventricular ejection fraction $\leq 40\%$) and clinical evidence of heart failure.

Eplerenone is the second aldosterone antagonist marketed in the UK. It reduces all-cause mortality and cardiovascular-related mortality and hospitalisation in patients with left ventricular dysfunction and clinical evidence of heart failure after an MI. There are no data on its clinical and cost effectiveness in patients with chronic heart failure compared to the other aldosterone antagonist marketed in the UK, which reduces mortality and morbidity in patients with chronic heart failure and is considerably cheaper.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Eplerenone 25mg and 50mg tablets (Inspra®)

Licensed indication under review 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.

Dosing information under review 25mg daily initially, titrated to recommended maintenance dose of 50mg daily preferably within four weeks.

UK launch date October 2004

Comparator medications

The other aldosterone antagonist marketed in the UK, spironolactone, is licensed for the treatment of congestive heart failure. The Scottish Intercollegiate Guidelines Network (SIGN) recommend that spironolactone 25mg daily should be considered for patients with New York Heart Association (NYHA) classes III or IV heart failure who are already receiving diuretics, an angiotensin-converting enzyme (ACE)-inhibitor and/or digoxin. The National Institute of Clinical Excellence (NICE) recommends that patients who have had a myocardial infarction (MI) and have heart failure, NYHA grade III or IV, should be given spironolactone.

Cost per treatment period and relevant comparators

Aldosterone antagonist	Dose for heart failure	Annual Cost (£)
Eplerenone	50mg daily	558
Spironolactone	25mg daily	26

Summary of evidence on comparative efficacy

A double-blind trial recruited 6632 adults who had an acute MI and had left ventricular dysfunction, defined as a left ventricular ejection fraction $\leq 40\%$, and symptoms of heart failure (pulmonary rales, pulmonary venous congestion on x-ray or the presence of a third heart sound). If the patient was diabetic, the later inclusion criterion was not required. On a background of optimal therapy, which could include an ACE-inhibitor, angiotensin receptor blocker, diuretic and beta-blocker, patients were randomised 3 to 14 days post-MI to placebo or eplerenone 25mg daily for four weeks, then 50mg daily thereafter, if tolerated. The co-primary endpoints, (1) all cause mortality and (2) death from cardiovascular mortality or hospitalisation for a cardiovascular event (heart failure, recurrent acute MI, stroke or ventricular arrhythmia) were assessed in the intention-to-treat population via a Cox proportional-hazards regression model, which was used to estimate relative risks.

Eplerenone was associated with significantly reduced relative and absolute risks of all cause mortality of 15% and 2.3%, respectively. Corresponding figures for the significant reductions in death or hospitalisation due to cardiovascular causes with eplerenone were 13% and 3.3%, respectively. The significant reduction in death due to cardiovascular causes was influenced

by a significant reduction in sudden deaths. The significant reduction in episodes of hospitalisation due to cardiovascular events was influenced by a significant reduction in episodes of hospitalised for heart failure. The numbers of patients hospitalised for these events were also reduced, but these were not significant. Results are detailed below.

Results of the EPHESUS trial comparing eplerenone with placebo in patients with left ventricular dysfunction and symptoms of heart failure post-MI.

Outcome	Incidence n (%)		Absolute risk reduction	Relative risk reduction (95% confidence intervals)
	Eplerenone N=3319	Placebo N=3313		
Death (any cause)*	478 (14)	554 (17)	2.3%	15% (4%, 25%)
Death from cardiovascular cause or hospitalisation for cardiovascular event*	885 (27)	993 (30)	3.3%	13% (5%, 21%)
Death due to cardiovascular cause	407 (12)	483 (15)	2.3%	17% (6%, 28%)
Sudden death from cardiovascular cause	162 (4.9))	201 (6.1)	1.2%	21% (3%, 36%)
Patients hospitalised for cardiovascular events	606 (18)	649 (20)	1.3%	9% (-1%, 19%)
Patients hospitalised for heart failure	345 (10)	391 (12)	1.4%	15% (1%, 26%)
Episodes of hospitalisation for cardiovascular events ⁺	876 (31)	1004 (34)	2.5%	13%
Episodes of hospitalisation for heart failure ⁺	477 (17)	618 (21)	3.8%	23%

* primary endpoint; + denominators (number of episodes of hospitalisation) for the eplerenone and placebo groups were 2815 and 2984, respectively.

Summary of evidence on comparative safety

Eplerenone appears to have a similar adverse effect profile to spironolactone. Incidences of hyperkalaemia reported as an adverse effect in a 12-week dose-finding study were similar in the eplerenone 50mg groups, 5.8%-7.3%, and the spironolactone 25mg group, 8.7%.

There are no trials directly comparing these drugs over a sufficient period of time to reliably quantify differences in sex-hormone mediated adverse effects, which can occur with both drugs. These adverse effects have been observed with eplerenone at doses used for hypertension, 25mg-400mg. However, in treatment of patients with heart failure post-MI in the pivotal trial described previously the incidence of these adverse effects with eplerenone (mean dose 43mg/day and mean duration of follow-up of 16 months) were similar to the placebo group. In the trial described below, spironolactone at a dose used in the treatment of heart failure, 25mg (mean duration of follow-up 24 months), compared with placebo, was associated with significantly greater incidences of gynaecomastia (9% vs. 1%) and breast pain (2% vs. 0.1%) in men, with 1.7% of men discontinuing spironolactone due to these adverse effects.

Summary of clinical effectiveness issues

In practice, patients with chronic heart failure post-MI could be treated with spironolactone, the other aldosterone antagonist marketed in the UK, in accordance with its licence and guidance from the Scottish Intercollegiate Guidelines Network (SIGN) and the National Institute of Clinical Excellence (NICE).

Spironolactone reduced morbidity and mortality in patients with NYHA class III or IV heart failure and a history of class IV NYHA heart failure plus left ventricular ejection fraction $\leq 35\%$ in the preceding six months. Relative reduction (95% confidence intervals) in all cause mortality compared with placebo was 30% (18% to 40%) and in death or hospitalisation for cardiovascular causes was 32% (22% to 41%). These risk reductions are larger than those observed with eplerenone in patients who have heart failure 314 days post-MI and the differences between the two drugs may be explained in part by the different patient populations recruited to the studies. In another study, spironolactone, given immediately after revascularisation procedures and continued for one month, demonstrated benefits on left ventricular function relative to placebo in the treatment of patients who had suffered their first anterior MI. It significantly improved left ventricular ejection fraction (7.2% vs. 4.5%) and reduced the increase in left ventricular end diastolic volume index observed post-MI (4 vs. 19 ml/m²).

No studies directly compare long-term outcomes with aldosterone antagonists, eplerenone and spironolactone, in patients with chronic heart failure post MI. Thus their relative efficacy and safety with respect to these outcomes in this population is uncertain.

Summary of comparative health economic evidence

In comparison with no treatment, data from the EPHESUS trial suggest that eplerenone is likely to have acceptable costs per life year gained or QALY gained:

£6,000 per life year gained (95% CI £3,200 to £18,700)

£9,000 per QALY gained (95% CI £4,600 to £32,800)

Budget impact

Using eplerenone in this indication is likely to cost NHSScotland up to £400,000 in the first year rising to up to £4m in five years, depending on the rate of heart failure arising from MI and the percentage of patients treated with eplerenone.

Guidelines and protocols

The 1999 SIGN guideline (number 35) on diagnosis and treatment of heart failure due to left ventricular systolic dysfunction recommends that patients already treated with diuretics, an ACE-inhibitor and/or digoxin, who are in NYHA classes III or IV, should be considered for treatment with low dose (25mg daily) spironolactone.

The 2000 SIGN guideline (number 41) on secondary prevention of coronary heart disease following MI recommends the use of low dose aspirin, ACE-inhibitors, beta-blockers and, if necessary, lipid-lowering agents for the treatment of patients after a MI.

The 2001 NICE guideline (inherited guideline A) on prophylaxis for patients who have experienced a myocardial infarction recommends that patients who have had a MI and have moderate to severe heart failure, NYHA grade III or IV, should be given spironolactone.

Additional information

At its October 2004 meeting, after consideration of a full submission, the Scottish Medicines Consortium recommended that “eplerenone should be accepted for restricted use within NHS Scotland in addition to standard therapy including beta blockers, to reduce the risk of cardiovascular mortality and morbidity after recent myocardial infarction (MI) in stable patients with left ventricular dysfunction (left ventricular ejection fraction $\leq 40\%$) and clinical evidence of heart failure.

“Its use should be restricted to patients who cannot tolerate spironolactone due to sex hormone mediated adverse effects. Eplerenone is the second aldosterone antagonist marketed in the UK. It reduces all-cause mortality and cardiovascular-related mortality and hospitalisation in patients with heart failure post-MI. However, there are no data on its clinical and cost effectiveness in this population compared to the other aldosterone antagonist marketed in the UK, which also reduces mortality and morbidity in patients with heart failure and is considerably cheaper. “

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 9 February 2005.

Drug prices are those available at the time the papers were issued to SMC for consideration.

The reference numbers in this document refer to the under-noted references. Those shaded grey are additional to those supplied with the submission.

Pitt B, Remme W, Zannad F et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; 348: 1309-21

Pitt B, Williams G, Remme W et al. The EPHEsus trial: eplerenone in patients with heart failure due to systolic dysfunction complicating acute myocardial infarction. *Cardiovascular Drugs and Therapy* 2001; 15: 79-87

Pitt B, Roniker B. for the Eplerenone Heart Failure Investigators. Eplerenone, a novel selective aldosterone receptor antagonist (SARA): dose finding study in patients with heart failure. *JACC* (1999) 33 (2) Suppl 1:188A

Synopsis of study EPL023. Final report for a dose-ranging study of eplerenone versus placebo and spironolactone in patients with symptomatic heart failure. 4th June 2001, Pfizer data-on-file

Food and Drug Administration. Eplerenone medical review. www.fda.gov/cder/foi/nda/2002/21-437_Inspra.htm

Pitt B, Zannad F, Remme WJ et al. for the Randomised Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; 341: 709-17

Hayashi M, Tsutamoto T, Wada A et al. Immediate administration of mineralocorticoid receptor antagonist spironolactone prevents post-infarct left ventricular remodelling associated with suppression of a marker of myocardial collagen synthesis in patients with first anterior acute myocardial infarction. *Circulation* 2003; 107: 2559-65

McMurray JV and O'Meara E. Treatment of heart failure with spironolactone – trial and tribulations. *New Engl J Med* 2004; 351: 526-8

Funder JW. Aldosterone resurgens-letter from Ephesus. *J Clin Endocrinol Metab* 2003; 88: 2373-5