

eplerenone 25, 50mg film-coated tablets (Inspra®) SMC No. (793/12)

Pfizer Ltd

08 June 2012

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 full submission

eplerenone (Inspra®) is accepted for use within NHS Scotland.

Indication under review: in addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF $\leq 30\%$).

In the pivotal phase IIIb study, addition of eplerenone to standard optimal therapy significantly reduced the composite of death from cardiovascular causes or hospitalisation for heart failure (primary outcome) and both the risk of cardiovascular death and the risk of hospitalisation (secondary outcomes) in patients with mild heart failure (NYHA class II) and LVEF $\leq 30\%$.

Overleaf is the detailed advice on this product.

**Chairman,
Scottish Medicines Consortium**

Indication

In addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure AND left ventricular systolic dysfunction (LVEF $\leq 30\%$).

Dosing Information

Initially, 25 mg once daily then titration to the target dose of 50mg once daily preferably within 4 weeks; taking into account the serum potassium level.

After initiation, the dose should be adjusted based on the serum potassium level.

Product availability date

19 April 2012

Summary of evidence on comparative efficacy

Eplerenone is an aldosterone-receptor antagonist (also known as a mineralocorticoid receptor antagonist), with a similar mechanism of action to spironolactone, but with greater selectivity for the aldosterone receptor. Inhibiting the binding of aldosterone influences the regulation of blood pressure and the pathophysiology of cardiovascular disease.

SMC has previously accepted eplerenone for use 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. The indication under review is an extension to the marketing authorisation for the use of eplerenone in the tightly defined population of patients with chronic systolic heart failure associated with NYHA class II symptoms and LVEF $\leq 30\%$.

The evidence to support the extension to the marketing authorisation comes from a large, phase IIIb, placebo-controlled randomised clinical study (EMPHASIS-HF)¹, which recruited 2737 patients aged ≥ 55 years with LVEF $\leq 30\%$ (or LVEF $\leq 35\%$ with a QRS interval $>130\text{ms}$) and a recent (within 6 months) hospitalisation for a cardiovascular reason. A small proportion of patients without recent hospitalisation ($\sim 14\%$ in each group) were recruited on the basis of a high B-type natriuretic peptide (BNP) or N-terminal proBNP level in addition to the other inclusion criteria.

At baseline, patients were receiving treatment with optimal target or maximally-tolerated doses of an angiotensin-converting enzyme (ACE) inhibitor and/or angiotensin-receptor blocker (ARB) and a beta-blocker (unless contra-indicated). Patients were randomised to eplerenone ($n=1364$) or matching placebo ($n=1373$) at a dose of 25mg daily or 25mg every other day and after 4 weeks, this dose increased to 50mg daily or 25mg daily respectively, with dosing dependent on pre-specified estimated glomerular filtration rate (eGFR) values. Serum potassium and renal function were monitored at each study visit and the dose of eplerenone was adjusted according to pre-specified limits for both serum potassium and eGFR.

The primary endpoint was a composite of death from cardiovascular causes or hospitalisation for heart failure, defined as either the first occurrence of heart failure hospitalisation or cardiovascular death, and was analysed in the intent-to-treat population. The time-to-event distributions were summarised by treatment group using Kaplan-Meier estimates of cumulative incidence. To test the consistency of effect, the primary endpoint was analysed in 20 pre-specified sub-groups e.g. age, gender, heart rate. There were two planned interim analyses of the primary endpoint: after the accrual of 271 and 542 primary events. After 542 events had occurred, the Data Safety Monitoring Committee could recommend termination of the study if either overwhelming benefit or harm was demonstrated.

The study was stopped early, after a median follow-up of 21 months, after crossing a pre-specified stopping boundary for overwhelming benefit (two-sided $p < 0.001$ in favour of eplerenone). The primary endpoint was reached by 18% (249/1364) of patients in the eplerenone group compared with 26% (356/1373) of patients in the placebo group; adjusted hazard ratio (HR) 0.63 (95% confidence interval [CI]: 0.54 to 0.74; $p < 0.001$). The number of patients who would need to be treated to prevent one primary outcome event was 19.

A large number of secondary endpoints were pre-specified and included the individual components of the primary endpoint and other measures of cardiovascular hospitalisation and causes of death; these were also significantly reduced in the eplerenone group. The composite secondary endpoint of death from any cause or hospitalisation for heart failure was reported in 270 (19.8%) eplerenone patients compared with 376 (27.4%) placebo patients (adjusted HR 0.65 (95% CI: 0.55 to 0.76), $p < 0.001$); hospitalisation for heart failure in 164 (12.0%) eplerenone patients compared with 253 (18.4%) placebo patients (adjusted HR 0.58 (95% CI: 0.47 to 0.70), $p < 0.001$); and death from cardiovascular causes in 147 (10.8%) eplerenone patients compared with 185 (13.5%) placebo patients (adjusted HR 0.76 (95% CI: 0.61 to 0.94), $p = 0.01$) and death from any cause in 171 (12.5%) eplerenone patients compared with 213 (15.5%) placebo patients (adjusted HR 0.76 (95% CI: 0.62 to 0.93).

Summary of evidence on comparative safety

There are no comparative adverse event data available in this patient population but no new unexpected adverse events were reported in the EMPHASIS-HF study¹.

The most frequently reported treatment emergent adverse event in the study was hyperkalaemia, which occurred in 8.0% of patients in the eplerenone group, compared with 3.7% in the placebo group ($p < 0.001$). Hyperkalaemia is an expected adverse event, due to the renal tubular effects of aldosterone receptor blockade.

Overall, a serum potassium level > 5.5 mmol/L was reported in 158 of 1336 (11.8%) eplerenone and 96 of 1340 (7.2%) of placebo patients ($p < 0.001$) and a serum potassium of > 6.0 mmol/L in 33 of 1336 patients (2.5%) in the eplerenone group and 25 of 1340 patients (1.9%) in the placebo group ($p = 0.29$).

Gynecomastia or other breast disorders were reported in 10 patients (0.7%) in the eplerenone group and 14 patients (1.0%) in the placebo group in the EMPHASIS-HF study ($p = 0.54$).

Summary of clinical effectiveness issues

In the pivotal phase IIIb study, EMPHASIS-HF¹, eplerenone in addition to standard optimal therapy (an ACE inhibitor +/- an angiotensin-receptor blocker and a beta-blocker) reduced both the risk of cardiovascular death and the risk of hospitalisation in patients with mild heart failure (NYHA class II) and low ejection fraction. The authors acknowledged that all-cause mortality as a primary endpoint would have been more robust. However, they argued that as eplerenone is not expected to have any effect on non-cardiovascular deaths, this endpoint might have diluted the expected benefit together with a loss of power, requiring an even larger sample size, and that their chosen outcome is frequently used in studies of heart failure. Death from any cause was reported as a secondary outcome and was also significantly reduced in the eplerenone group. The study was terminated early, in accordance with pre-specified criteria, because of overwhelming benefit for eplerenone over placebo. The study authors acknowledged that the early stopping may have overestimated the magnitude of the treatment effect. In addition, the median follow-up at the end of the study was 21 months, so there remains some uncertainty about whether the treatment benefit persists over a longer time-period.

The study population was aged ≥ 55 years (mean age in both groups was 69 years) and had a history of recent hospitalisation (within the previous 6 months) for a cardiovascular reason or a high BNP or N-terminal proBNP level and there is some uncertainty about whether the study population reflects the population likely to be eligible in Scotland. There is also some uncertainty about the most appropriate comparator for eplerenone in this indication. The submitting company considers that current standard treatment with an ACE inhibitor and a beta-blocker is the most appropriate comparator in this patient population. The other available aldosterone antagonist, spironolactone, is licensed as add-on therapy to treatment with an ACE inhibitor and a beta-blocker in patients with more severe (NYHA class III-IV) heart failure^{2,3}; but it has not been studied in the NYHA class II heart failure population covered in this submission. The NYHA heart failure classification is based on the patient's symptoms at the time of assessment and is likely to vary over the course of the disease. The ARB, candesartan, is indicated as add-on therapy to an ACE inhibitor and a beta-blocker in patients with class II-III heart failure who remain symptomatic but the combination of ACE inhibitor, ARB and beta-blocker is rarely used in clinical practice, and only a very small number of patients (n=85; 3.1%) in the EMPHASIS-HF study were receiving this treatment combination¹

Eplerenone is an aldosterone antagonist and is associated with a risk of hyperkalaemia. In the EMPHASIS-HF study¹, hyperkalaemia was reported as an adverse event in 8.0% of patients in the eplerenone arm. The eplerenone Summary of Product Characteristics recommends regular monitoring of serum potassium, with adjustment of the dose if necessary, dependent on the potassium level. Serum potassium was monitored closely in the EMPHASIS-HF study and patients with any pre-existing and ongoing significant co-morbid condition were excluded from the study. In clinical practice, the addition of eplerenone to the standard current therapy for heart failure in eligible patients is likely to result in an increased incidence of hyperkalaemia in this group of patients and possibly a requirement for additional monitoring.

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis comparing eplerenone as adjunctive therapy to standard optimal therapy compared to standard optimal therapy alone in patients with NYHA class II heart failure and left ventricular systolic dysfunction (left ventricular ejection fraction $\leq 30\%$). Standard optimal therapy for the majority of patients consists of the optimal dose of an angiotensin-converting enzyme (ACE) inhibitor in addition to a beta-blocker. The time horizon for the model was lifetime.

The model used was a discrete evaluation model that took into account mortality due to both cardiovascular and non-cardiovascular risk, hospitalisation due to heart failure and other cardiovascular causes. The clinical data were taken primarily from the EMPHASIS-HF study. Other pre-specified secondary events including death from any cause, hospitalisation for any reason and fatal or non-fatal myocardial infarction were also taken into account. The main effect from treatment with eplerenone was a reduction in mortality when compared with current treatment alone.

Utility values were taken from a subset of a clinical study, EPHESUS. The patient population was considered to be similar to that of the EMPHASIS-HF clinical study on which the model is based.

The base case cost-effectiveness ratio was a cost per quality adjusted life year (QALY) of £3,140 based on a QALY gain of 1.21 and an incremental cost of £3,822.

Sensitivity analysis was conducted, and the results were found to be relatively robust when eplerenone was used in addition to current treatment. For example, when the model took into account trial data only, and did not extrapolate the data, the cost per QALY estimate increased to £8,894. Also, when the distributional parameters for the number of HF hospitalisations were changed, the cost per QALY increased to approximately £4,500. A scenario where the price of eplerenone was adjusted was also provided as eplerenone becomes generic in 2014. In this scenario, the cost per QALY decreased to £1,724.

Given the analysis submitted, the economic case was considered to have been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The National Institute for Health and Clinical Excellence (NICE) published clinical guideline (CG) 108 “Chronic Heart Failure” in August 2010⁴. This guideline recommends that both ACE inhibitors and beta-blockers licensed for heart failure should be offered to all patients with heart failure due to left ventricular systolic dysfunction. Specialist advice should be sought before offering second-line treatment to patients with heart failure due to left ventricular systolic

dysfunction. Consider adding one of the following if a patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta-blocker:

- an aldosterone antagonist licensed for heart failure (especially if the patient has moderate to severe heart failure [NYHA class III–IV] or has had an MI within the past month) or
- an angiotensin II receptor antagonist (ARB) licensed for heart failure¹⁷ (especially if the patient has mild to moderate heart failure [NYHA class II–III]) or
- hydralazine in combination with nitrate (especially if the patient is of African or Caribbean origin¹⁸ and has moderate to severe heart failure [NYHA class III–IV]).

European Society of Cardiology (ESC) published “Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008”. This guideline recommends:

- an ACE inhibitor (or if not tolerated, an angiotensin receptor blocker) in all patients with symptomatic heart failure and a left ventricular ejection fraction $\leq 40\%$.
- a beta-blocker in all patients with symptomatic heart failure and an left ventricular ejection fraction $\leq 40\%$.
- that an aldosterone antagonist should be considered in all patients with an left ventricular ejection fraction $\leq 35\%$ and severe symptomatic heart failure, i.e. currently NYHA functional class III or IV, in the absence of hyperkalaemia and significant renal dysfunction.
- an angiotensin receptor blocker in patients with heart failure and a left ventricular ejection fraction $\leq 40\%$ who remain symptomatic despite optimal treatment with an ACE inhibitor and beta-blocker, unless also taking an aldosterone antagonist.

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline number 95 “Management of Chronic Heart Failure” in February 2007. This guideline recommends that ACE inhibitors should be considered in patients with all NYHA functional classes of heart failure due to left ventricular systolic dysfunction and that beta-blocker therapy should be started as soon as their condition is stable in these patients (unless contraindicated by a history of asthma, heart block or symptomatic hypotension). Patients with chronic heart failure due to left ventricular systolic dysfunction alone, or heart failure, left ventricular systolic dysfunction or both following MI who are intolerant of ACE inhibitors should be considered for an angiotensin receptor blocker. Patients with heart failure due to left ventricular systolic dysfunction who are still symptomatic despite therapy with an ACE inhibitor and a beta blocker may benefit from the addition of candesartan, following specialist advice. Also following specialist advice, patients with moderate to severe heart failure due to left ventricular systolic dysfunction should be considered for spironolactone unless contraindicated by the presence of renal impairment or a high potassium concentration. In patients who develop gynaecomastia, eplerenone can be substituted for spironolactone. Patients who have suffered a MI and with left ventricular ejection fraction $\leq 40\%$ and either diabetes or clinical signs of heart failure should be considered for eplerenone unless contraindicated by the presence of renal impairment or a high potassium concentration. The SIGN website indicates that a review of this guideline is being considered.

Additional information: comparators

Relevant comparators include candesartan, spironolactone, and ivabradine has recently received a marketing authorisation for use in this indication.

Cost of relevant comparators

Drug	Dose Regimen	Cost per year (£)
Eplerenone	25 to 50mg once daily	555
Candesartan	4 to 32mg once daily	127 to 210
Ivabradine	5 to 7.5mg twice daily	522
Spirolactone	25 to 50mg once daily	20 to 27

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 30 March 2012. Note: there are differences between these medicines in the specific licensed indication for heart failure.

Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 7,457 in year 1 and 7,536 in year 5. Based on an estimated uptake of 5% in year 1 (349 patients) rising to 15% in year 5 (1,057 patients), the impact on the medicines budget was estimated at £194.1k in year 1 and £588.6k in year 5 with no adjustment to the price to reflect that eplerenone is assumed to become generic in year 3. The submitting company provided a further estimate showing an anticipated reduction in list price of eplerenone in years 3 to 5 due to the anticipation that it will become generic, in which the impact on the medicines budget would be £194.1k in year 1 and £147.2k in year 5. As heart failure is a common condition the company's estimated uptake may be conservative.

References

The undernoted references were supplied with the submission.

1. Zannad F, McMurray J, Krum H, van Veldhuisen D, Swedburg K, Shi H, Vincent J, Pocock S, Pitt B. Eplerenone in patients with systolic heart failure and mild symptoms. N Eng J Med. 2011; 364(1):11-21.
2. Scottish Intercollegiate Guidelines Network (SIGN). Guideline number 95: Management of Chronic Heart Failure, February 2007.
3. Pharmacia Ltd. Spironolactone Aldactone® summary of product characteristics, medicines.org.uk, 15/09/2011.
4. National Institute for Health and Clinical Excellence (NICE). Clinical Guideline (CG) 108: Chronic Heart Failure, August 2010.
5. Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology (ESC). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008". Eur Heart J 2008; 29: 2388–2442.

This assessment is based on data submitted by the applicant company up to and including 14 May 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

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.