On the Horizon
Future Medicines

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Eplerenone▼ for patients with NYHA class II chronic heart failure

Summary

Background

- Eplerenone▼ (Inspra ®) is currently licensed, in addition to standard therapy, for stable patients with left ventricular dysfunction and clinical evidence of heart failure after recent myocardial infarction. An application for a licence extension will be submitted shortly for the proposed indication of reduction in mortality and morbidity, including heart failure hospitalisation, in patients with New York Heart Association [NYHA] class II chronic heart failure. This indication would be as add-on therapy to standard care including beta-blockers, ACE inhibitors and angiotensin-II receptor blockers, with or without diuretics.

Recent data

- EMPHASIS-HF (n=2,737) studied high-risk patients with a history of chronic systolic heart failure, mild symptoms (NYHA class II) and a left ventricular ejection fraction of ≤ 30% (or, if between 30 and 35%, a QRS duration of > 130msec on electrocardiography). Patients were randomised to eplerenone or matching placebo in addition to recommended doses, or maximally tolerated doses, of standard heart failure medicines. The composite primary efficacy outcome of death from cardiovascular causes or first hospitalisation for heart failure, in the intention-to-treat population, occurred in 18.3% of patients receiving eplerenone vs. 25.9% in the placebo group (adjusted hazard ratio [HR] 0.63, 95% confidence interval [CI] 0.54 to 0.74, P<0.001), number needed to treat (NNT) of 13 over a median duration of follow-up of 21 months.

- There were no statistically significant differences between the incidence of overall adverse effects or adverse events leading to discontinuation between eplerenone and placebo, but hyperkalaemia was more common in patients taking eplerenone: 8.0% vs. 3.7%, P<0.001.

Impact

- The results from EMPHASIS-HF are for a specific patient group and the results may not be applicable to all patients with “mild symptoms” of heart failure. It is unknown whether substituting spironolactone would produce similar results in these patients, but at significantly lower cost. Eplerenone costs £555 per year compared to £19 for spironolactone.

- The manufacturer estimates that approximately 230,000 patients in the UK may fall within NYHA class II and that half that number could be eligible for eplerenone for this new indication. However, based on previous uptake of the drug, they anticipate only a small proportion of patients may be prescribed it.

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Action required

If the drug should receive a licence extension, local decision-making groups may wish to consider whether:

- eplerenone should be the first line aldosterone antagonist used in patients in line with its licensed indication
- eplerenone should be the first line aldosterone antagonist for patients who fulfil the eligibility criteria for EMPHASIS-HF

or

- spironolactone should be the first line aldosterone antagonist at all stages of heart failure with eplerenone used in patients who have side effects with spironolactone e.g. gynaecomastia, or perhaps a significant fear of gynaecomastia. This would be on the basis that spironolactone has high quality, randomised controlled trial evidence of effectiveness from the RALES study in heart failure NYHA class III or IV, established data for hyperkalaemia risks, it is likely (but not known) that spironolactone would also be effective at other stages of heart failure as well as NYHA III and IV, and it has a broad licence for congestive cardiac failure which is not restricted to any heart failure class.

Eplerenone is proposed for the reduction in mortality and morbidity, including heart failure hopitalisation, in patients with NYHA class II chronic heart failure. This would be as add-on to standard care.

INTRODUCTION

Patients with heart failure have a reduced quality of life and have frequent admissions to hospital. In 2009/10 in England there were just over 59,000 hospital admissions for heart failure, with a mean length of stay of 12 days [1]. A non-elective admission to hospital in a patient with co-morbidities and complications costs £3,833 [2]. The prognosis for patients with heart failure remains poor [3]. The National Heart Failure Audit 2010 found that 32% of patients had died within a year of admission for heart failure.

Reduced cardiac output in heart failure leads to compensatory mechanisms involving activation of many neurohormonal pathways [4]. One such pathway is the renin-angiotensin-aldosterone system (RAAS). Eplerenone▼ and spironolactone competitively inhibit the binding of aldosterone. They are used in chronic heart failure due to left ventricular systolic dysfunction (LVSD) to moderate the aldosterone response to over-activation of the RAAS.

Many patients have heart failure due to LVSD, which is associated with a reduced left ventricular ejection fraction (LVEF) [5]. Goals of treatment in systolic heart failure are prevention of premature death, reduced hospitalisation and reduction in symptoms [6]. NICE guidance recommends ACE inhibitors plus beta-blockers licensed for heart failure as first line treatments in patients with systolic heart failure [5]. Clinical judgement should be used to decide which drug to start first. If symptoms persist despite optimal first line treatment, specialist advice should be sought before offering second line treatment. Options include spironolactone or eplerenone, within licensed indications or an angiotensin-II receptor blocker (ARB) licensed for heart failure.

Aldosterone antagonists have shown a significant reduction in total mortality in patients with chronic heart failure when added to ACE inhibitors, but ARBs have not [7]. In a systematic review of 19 randomised, controlled trials (n=10,807) in heart failure and acute myocardial infarction (MI), aldosterone antagonists were associated with a 20% reduction in all-cause mortality (relative risk [RR] 0.80, 95% confidence interval [CI] 0.74 to 0.87) [8].

Further information is available on NHS Evidence and in the NPC's e-learning materials on heart failure.

PROPOSED INDICATION, PRESENTATION AND MARKETING

Eplerenone (Inspra®) is currently licensed, in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular (CV) mortality and morbidity in stable patients with left ventricular dysfunction and clinical evidence of heart failure after recent MI [9]. 25mg and 50mg tablets are available. An application for a licence extension will be submitted shortly. The proposed indication is reduction in mortality and morbidity, including heart failure hospitalisation, in patients with New York Heart Association [NYHA] class II chronic heart failure [Personal communication Pfizer, April 2011]. This would be as add-on therapy to standard care including beta-blockers, ACE inhibitors and ARBs, with or without diuretics. The dose and frequency are likely to depend on estimated glomerular filtration rate (eGFR) and serum potassium levels.

TREATMENT COSTS		
Drug	Example maintenance dose	Example cost per patient (year)
Spironolactone (generic)	25mg daily.[a]	£18.59
Eplerenone▼ (Inspra®)	50mg daily	£555.36

[a] Doses for spironolactone should be individually determined and titrated as appropriate. The range for maintenance dose can be from 25 to 200mg daily. See individual Summary of Product Characteristics.

Reference sources: Drug Tariff June 2011/ BNF No 61 March 2011.

EFFICACY

The EMPHASIS-HF study was a randomised, double-blind trial which compared eplerenone with placebo in high-risk patients with a history of chronic systolic heart failure and mild symptoms (NYHA class II) [10]. Patients were aged ≥ 55 years (mean age 69 years) and had an LVEF ≤ 30%, or if between 30 and 35% a QRS duration on ECG of more than 130 msec (mean LVEF was 26%). 27% of patients had left bundle-branch block. Patients were on recommended doses, or maximally tolerated doses, of standard heart failure medicines. Similar proportions of patients in each group were on standard medication for heart failure. Overall, 87% of patients were taking beta-blockers, 85% diuretics, and 93% an ACE inhibitor, ARB or both. 22% of patients had cardiac implantable devices and/or resynchronisation therapy.

Randomisation had to occur within six months of hospitalisation for a CV reason (or some patients were enrolled on B-type natriuretic peptide [BNP] measures). Exclusion criteria included acute MI, NYHA class III or IV heart failure, a serum potassium > 5mmol/L, an eGFR less than 30ml/min/1.73m^2 or a need for a potassium-sparing diuretic.

Patients were randomised to eplerenone (n=1,364) or matching placebo (n=1,373). Starting doses were 25mg daily, increased after four weeks to 50mg daily. If eGFR was 30 to 49ml/min/1.73m^2 patients were started on 25mg on alternate days and increased to 25mg daily. Doses were only increased if serum potassium levels were no more than 5mmol/L. Doses were reduced or stopped if necessary depending on potassium levels.

The trial was stopped early after protocol-specified interim analyses showed benefit. The primary efficacy outcome, a composite of death from CV causes or first hospitalisation for heart failure in the intention-to-treat population, occurred in 18.3% of patients in the eplerenone group and in 25.9% of patients receiving placebo; hazard ratio (HR) 0.63 (95%CI 0.54 to 0.74), P<0.001. The number needed to treat (NNT) was 13 over a median duration of follow-up of 21 months. The HR was adjusted for baseline prognostic factors such as age. Hospitalisation for heart failure was 12.0% and 18.4% in the eplerenone and placebo groups, respectively; adjusted HR 0.58 (95%CI 0.47 to 0.70), P<0.001. Eplerenone was also associated with reduced all-cause mortality: 12.5% vs. 15.5%, respectively, adjusted HR 0.76 (95%CI 0.62 to 0.93), P=0.008. Further details are shown in the **table** on page 4.

When the trial was stopped, all patients were eligible to transfer into an open-label extension involving continuation of treatment with eplerenone for 12 months. This extension arm is currently ongoing [11].

SAFETY

There were no statistically significant differences between the incidence of overall adverse effects or adverse events leading to discontinuation between groups [10]. Hyperkalaemia was more common in patients taking eplerenone: 8.0% vs. 3.7%, P<0.001 (number needed to harm [NNH] 23), but there were no differences in the rate of withdrawal from the trial or risk of hospitalisation due to hyperkalaemia.

The current Summary of Product Characteristics for eplerenone states that serum potassium should be measured before starting eplerenone, within the first week and one month after the start of treatment or dose adjustment, and periodically thereafter [9]. Doses should be adjusted accordingly. The concomitant use of potassium supplements or potassium-sparing diuretics is not recommended, due to an increased risk of hyperkalaemia. Potent inhibitors of CYP3A4 (such as itraconazole) are contra-indicated with eplerenone because they may increase eplerenone concentrations [9].

CURRENT DRUG USAGE

During the year April 2010 to March 2011 just less than two million items of spironolactone were prescribed at a cost of approximately £3.8 million. Approximately 130,000 items of eplerenone were prescribed at a cost just under £6 million (Personal communication, NHSBSA Prescription Services. June 2011).

ESTIMATED IMPACT AND PLACE IN THERAPY

Data for the current indication for eplerenone come from the EPHESUS study [12]. This study included patients who had recently had an acute MI, with a LVEF ≤ 40% and signs or symptoms of heart failure. Eplerenone (n=3,319) or placebo (n=3,313) were given in addition to optimal treatment for heart failure, including ACE inhibitors, ARBs and beta-blockers. Death occurred in 14.4% of patients given eplerenone and 16.7% of placebo patients, RR 0.85 (95%CI 0.75 to 0.96), P=0.008, NNT 44 over 16 months.

Spironolactone is licensed for congestive cardiac failure [13]. Data for its use comes from the RALES study [14] which involved a different patient population to the EMPHASIS-HF trial. Patients in NYHA classes III or IV with a LVEF ≤ 35% and taking an ACE inhibitor and loop diuretic were given either spironolactone (n=822) or placebo (n=841). Spironolactone reduced all-cause mortality, death from cardiac causes and hospitalisation for cardiac reasons. All-cause mortality (the primary end point) occurred in 34.5% vs. 45.9% of patients, respectively, RR 0.70 (95%CI 0.60 to 0.82), P<0.001, NNT 9 over 24 months.

Spironolactone has been associated with gynaecomastia, which is normally reversible when the drug is stopped [13]. In RALES, gynaecomastia or breast pain was reported by 10.1% of men in the spironolactone group (61/603) and 1.5% in the placebo group (9/614), P<0.001 [14].
The manufacturer has estimated that, with a prevalence of 1.5%, 930,000 patients are expected to have chronic heart failure in the UK and that:

- Approximately half are likely to have systolic heart failure (approximately 465,000 patients)

Table: Main outcomes from EMPHASIS-HF trial [10]

		Eplerenone (n=1,364)	Placebo (n=1,373)	Adjusted HR (95%CI)	Adjusted P value
		No. of patients (%)			
Primary efficacy outcome:	Death from CV causes or hospitalisation for heart failure	249 (18.3)	356 (25.9)	0.63 (0.54 to 0.74)	<0.001
Examples of secondary outcomes:	Death from CV causes	147 (10.8)	185 (13.5)	0.76 (0.61 to 0.94)	0.01
	All-cause mortality	171 (12.5)	213 (15.5)	0.76 (0.62 to 0.93)	0.008
	Hospitalisation for heart failure	164 (12.0)	253 (18.4)	0.58 (0.47 to 0.70)	<0.001
	Hospitalisation for hyperkalaemia	4 (0.3)	3 (0.2)	1.15 (0.25 to 5.31)	0.85
	Hospitalisation for worsening renal function	9 (0.7)	8 (0.6)	0.97 (0.37 to 2.58)	0.95

- Of these, half again are likely to fall within NYHA class II (approximately 232,000 patients)

- After taking into account the percentage of patients diagnosed with NYHA class II heart failure and treated, the manufacturer estimates that the number above will reduce to approximately 127,000 patients [Personal communication, Pfizer, April 2011].

If we apply these figures to an average GP practice of 6,600 patients [15], then within that practice there may be approximately 13 patients diagnosed with NYHA class II heart failure and treated. Based on previous uptake of eplerenone, the manufacturer expects only a small proportion of these patients to be prescribed the drug for this new indication. If we assume that 10% might receive eplerenone this would be approximately 2 patients per average practice or 30 patients/100,000 population.

NICE Clinical Guideline (CG108) on chronic heart failure noted the existence of the EMPHASIS trial (p108) but did not comment upon it because, at the time of production, data was not published.

Eplerenone costs £555 a year compared to £19 for spironolactone. If the drug should receive a licence extension, local decision-making groups may wish to consider whether:

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or

- spironolactone should be the first line aldosterone antagonist at all stages of heart failure with eplerenone used in patients who have side effects with spironolactone e.g. gynaecomastia, or perhaps a significant fear of gynaecomastia. This would be on the basis that spironolactone has high quality, randomised controlled trial evidence of effectiveness from the RALES study in heart failure NYHA class III or IV, established data for hyperkalaemia risks, it is likely (but not known) that spironolactone would also be effective at other stages of heart failure as well as NYHA III and IV, and it has a broad licence for congestive cardiac failure which is not restricted to any heart failure class.

Points to consider in determining the place of eplerenone in the management of patients with systolic heart failure and mild symptoms:

- Aldosterone antagonists, used appropriately within their licensed indications, are an appropriate option to consider in patients who are symptomatic despite optimal treatment with an ACEI and a beta-blocker licensed for HF. Specialist advice should be sought before offering second line treatment.
- EMPHASIS-HF has shown a benefit of eplerenone on both reducing hospitalisation due to heart failure and early death from CV causes. This was in a very specific patient group and the results may not be applicable to all patients with left ventricular dysfunction and mild symptoms of heart failure. Only patients similar to those included in EMPHASIS-HF should be considered for eplerenone for this indication.
- There are no head-to-head studies of eplerenone versus spironolactone on patient-oriented outcomes in chronic heart failure.
- RALES and EPHESUS used different patient populations, so comparisons with EMPHASIS-HF are difficult. However, the relative benefits (as seen by the RRs) provided by spironolactone and eplerenone are similar for the populations studied.
- Clinicians need to explain to patients the need for regular monitoring of serum potassium levels and renal function, especially in patients with renal insufficiency or diabetes. They should ensure that such monitoring of patients is routinely carried out.

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