

Eplerenone

Concise evaluated information to support the managed entry of new medicines in the NHS

Summary

- Eplerenone is a selective aldosterone receptor antagonist. It is licensed as add-on treatment for left ventricular dysfunction and heart failure after recent myocardial infarction (MI), to reduce the risk of cardiovascular (CV) morbidity and mortality.
- The licence is based on a large randomised controlled trial in over 6000 patients (EPHESUS), which found additional reductions in all cause mortality and in CV mortality and morbidity among patients with left ventricular dysfunction and heart failure post MI, when eplerenone was added to standard therapy. The authors estimated a numbers needed to treat (NNT) of 50 to save one life in one year and an NNT of 33 to prevent one death from CV causes or one hospitalisation for a CV event in one year.
- There is no evidence for a beneficial effect of eplerenone on morbidity and mortality in severe or chronic heart failure; such evidence does exist for spironolactone.
- Unlike spironolactone, eplerenone selectively blocks the mineralocorticoid receptor. Eplerenone has a similar incidence of gynaecomastia to placebo, whereas the incidence of gynaecomastia with spironolactone is approximately 10%. However, eplerenone has a significant potential for drug interactions. No long-term, direct comparative studies of eplerenone and spironolactone have been carried out in heart failure.
- Patients prescribed eplerenone need to be carefully selected and monitored to avoid serious hyperkalaemia, in the same way as those taking spironolactone.
- Eplerenone is 20 times more expensive than spironolactone.

Introduction

Eplerenone is a selective aldosterone receptor antagonist. Unlike spironolactone, it selectively blocks the mineralocorticoid receptor and has minimal affinity for the glucocorticoid, androgen or progestogen receptors.^{1,2} Aldosterone is involved in several mechanisms that lead to the development and progression of heart failure. There is increasing evidence that aldosterone blockade is effective in reducing mortality and morbidity rates in patients with heart failure caused by systolic left ventricular dysfunction that may be due to ischaemic or non-ischaemic causes.³ Eplerenone is licensed as an adjunct to standard therapy for stable patients with left ventricular dysfunction and clinical evidence of heart failure after recent myocardial infarction (MI), to reduce the risk of cardiovascular morbidity and mortality.⁴

Evidence

The licence for eplerenone was granted on the basis of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy Survival Study (EPHESUS), a multicentre, international, randomised, double-blind, placebo-controlled trial.⁵ The study included 6632 patients 3-14 days (mean 7 days) after MI, with a left ventricular ejection fraction (LVEF) of $\leq 40\%$ and clinical symptoms of heart failure; patients with diabetes and a LVEF of $\leq 40\%$ were considered high risk and were included in the study, even if asymptomatic. Important exclusion criteria were use of potassium-sparing diuretics, serum creatinine concentrations $>220\mu\text{mol/l}$ or serum potassium $>5.0\text{mmol/l}$. Patients were randomised to eplerenone (25mg per day initially, titrated to a maximum of 50mg per day (n=3319) or placebo (n=3313) in addition to optimal medical therapy [including ACE inhibitors or angiotensin II – receptor blockers (86%), beta-blockers (75%), diuretics (60%), aspirin (88%) and statins (47%)].

The study was designed to enrol 6200 patients and to continue until 1012 deaths had occurred. The primary endpoints were time to death from any cause and time to death from cardiovascular causes or first hospitalisation for a cardiovascular event, including heart failure, recurrent acute MI, stroke or ventricular arrhythmia. After a mean follow up of 16 months, 478 deaths (14.4% of patients) occurred in the

Brand Name, (Manufacturer): Inspra® (Pfizer)

BNF Therapeutic Class: Aldosterone antagonists

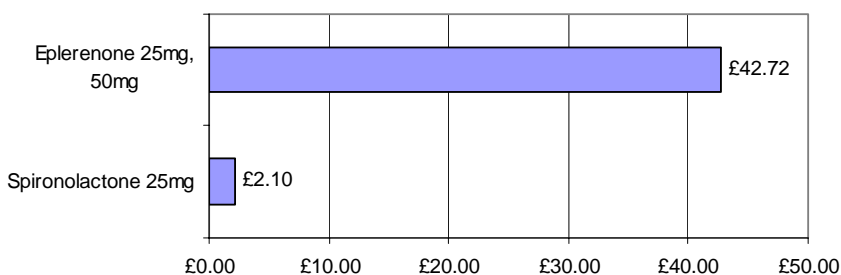
Licensed Indications: Reduction of risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (left ventricular ejection fraction of $\leq 40\%$) and clinical evidence of heart failure after recent myocardial infarction, in addition to standard therapy including beta-blockers

Dosage and Administration: Starting dose of 25mg daily titrated to the recommended maintenance dose of 50mg daily according to serum potassium levels – see Summary of Product Characteristics (SPC)

Marketed: November 2004

Cost Comparisons:

Cost for 28 days treatment - MIMS October 2004; Drug Tariff September 2004.
NB eplerenone costs are the same regardless of tablet strength



NB. Spironolactone is not licensed for the same indication as eplerenone
Doses shown for general comparison and do not imply therapeutic equivalence

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eplerenone group vs. 554 (16.7% of patients) in the placebo group (relative risk, RR 0.85; 95% CI 0.75–0.96). Of these deaths, 407 (12.3%) in the eplerenone group and 483 (14.6%) in the placebo group were attributed to cardiovascular causes (RR 0.83; 95% CI 0.72–0.94). The combined endpoint of death from cardiovascular causes or hospitalisation for cardiovascular events was reduced by eplerenone (RR 0.87; 95% CI 0.79–0.95). The authors have calculated a number needed to treat (NNT) of 50 to save one life in one year, and an NNT of 33 to prevent one death from cardiovascular causes or one hospitalisation for a cardiovascular event in one year.

Eplerenone is only licensed for patients meeting EPHEUS inclusion criteria. A wider indication would be for the treatment of severe or chronic heart failure, and for this indication it would compete with spironolactone, the use of which is supported by the RALES⁶ trial (see below). Only preliminary comparative data for eplerenone and spironolactone are available at this time. In a 12 week randomised study⁷ (published in abstract form only) in 321 patients with stable NYHA Class II-IV heart failure, eplerenone 25-100mg daily, spironolactone 25mg daily or placebo was added to standard therapy (ACE inhibitor, diuretic + digoxin). A significant reduction in brain natriuretic peptide (a surrogate marker for heart failure) occurred in all the treatment groups, except eplerenone 25mg daily, compared with placebo ($P < 0.05$). There was no significant change in NYHA class with either the eplerenone or the spironolactone groups compared with placebo.

Safety (see table 2)

The most common adverse effects of eplerenone are gastrointestinal disorders and predictably, hyperkalaemia.^{1,2,4} In EPHEUS the incidence of serious hyperkalaemia (serum potassium concentration ≥ 6.0 mmol/l) was 5.5% in the eplerenone group and 3.9% in the placebo group ($p=0.002$), with the risk being greatest in patients with a creatinine clearance < 50 ml/min. Serious hypokalaemia (serum potassium < 3.5 mmol/l) occurred less frequently in the eplerenone group compared with placebo (8.4% vs 13.1%). The incidence of GI disorder was 19.9% for eplerenone and 17.7% for placebo ($p=0.02$). The

rates of gynaecomastia, impotence and breast pain were similar in the eplerenone and placebo groups.⁵ The incidence of gynaecomastia with spironolactone is approximately 10%.⁸ In the preliminary comparative study⁷ (see above) hyperkalaemia (> 6.0 mmEq/L) was seen in 12% of the eplerenone 100mg group vs. 8.7% in the spironolactone group. Testosterone levels were increased in men prescribed spironolactone, as compared to those given eplerenone.

Eplerenone is metabolised primarily via CYP3A4, which means it has a significant potential for drug interactions⁴ (see Risk Management Issues).

Place in Therapy

No long-term studies directly comparing spironolactone and eplerenone in heart failure have been conducted. RALES⁶ - a study of spironolactone as add-on therapy in severe heart failure - and EPHEUS cannot be compared directly as they were conducted at different times with different endpoints in different patient populations (see Table 1). In EPHEUS 75% of patients were on beta blockers. In RALES 10.5% of patients were on beta blockers and 75% of patients were on digoxin. (The percentage of patients taking digoxin in EPHEUS was not stated). Mean LVEF was lower in RALES than in EPHEUS (25% and 33% respectively). One year mortality among the placebo group was 25% in RALES and 13.6% in EPHEUS. The difference in mortality may reflect the variations in the severity of heart failure at enrolment, the level of systolic dysfunction (which was more profoundly depressed in RALES) or the number of additional effective therapies administered (a higher number in EPHEUS).^{9,10}

There is evidence that following the publication of RALES there was an increase in the inappropriate prescribing of spironolactone in heart failure without consideration of the patients' functional class or ejection fraction and without optimisation of background treatment with ACE inhibitors and beta-blockers. This was accompanied by an increase in the rates of hyperkalaemia-associated morbidity and mortality.^{9,11,12} Patients prescribed eplerenone should be carefully selected, screened and monitored using the same criteria as those employed in EPHEUS. This will

include monitoring of renal function and serum electrolytes and ensuring that patients are screened for left ventricular dysfunction before eplerenone is prescribed and before the patient is discharged from hospital.⁹

Further studies are needed to determine whether eplerenone will also prove efficacious in patients with chronic heart failure, with varying degrees of heart failure, and in those with heart failure due to mainly diastolic dysfunction.

Key Paper

5. Pitt B, Remme W, Zannad F, et al (for EPHEUS Study Investigators). Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348**: 1309–1321.

Appendix I : Bibliography Appendix II : Tables comparing EPHEUS & RALES

Risk Management Issues:

Periodic monitoring of serum potassium is recommended especially in patients at risk of hyperkalaemia eg elderly, those with mild renal impairment, (eplerenone is contra-indicated if GFR < 50 ml/min), diabetes and concurrent therapy with other drugs which can cause hyperkalaemia. Prescribers should beware of potential drug interactions. Concomitant administration of eplerenone with strong CYP3A4 enzyme inhibitors e.g. ketoconazole, clarithromycin, or strong CYP3A4 enzyme inducers e.g. rifampicin, carbamazepine, St Johns Wort, is contra-indicated. Eplerenone may be given with mild to moderate inhibitors of CYP3A4 e.g. amiodarone, fluconazole, at a dose not exceeding 25mg daily.⁴



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The information contained in this document will be superseded in due course.

Appendix I

Bibliography

References

1. Zillich A J, Carter B. Eplerenone — a novel selective aldosterone blocker. *Ann Pharmacother* 2002; **36**: 1567–76
2. Anon. Eplerenone Pharmacy and Therapeutics Review (Updated 2002 Evaluation). Facts and Comparisons, December 2002: 409–16
3. Pitt B. Aldosterone blockade in patients with systolic left ventricular dysfunction. *Circulation* 2003; **108**: 1790-94
4. Inspra SPC Pfizer 5th August 2004
5. Pitt B, Remme W, Zannad F, et al (for EPHEBUS Study Investigators). Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003; **348**: 1309–21
6. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999; **341**: 709–717
7. Pitt B, Roniker B. Eplerenone, a novel selective aldosterone receptor antagonist (SARA): dose-finding study in patients with heart failure (abstract). *JACC* 1999; 188A: Abstract 825–4
8. Aggarwal A. Eplerenone in patients with left ventricular dysfunction. *New Engl J Med* 2003; **349**: 88-9
9. Jessup M. Aldosterone blockade and heart failure. *N Engl J Med* 2003; **348**: 1380-82
10. Nolan PE Jr. Integrating traditional and emerging treatment options in heart failure, in : Role of aldosterone blockade in managing heart failure: New and emerging treatment options. Ed. Aforismo JF. Role of aldosterone blockade in managing heart failure: New and emerging treatment options. *Am J Health-Syst Pharm* 2004; **61** (S2): S14-S22
11. Juurlink DN, Mamdani MM et al. Rates of hyperkalaemia after publication of the randomized aldactone evaluation study. *New Engl J Med* 2004; **351**: 543-51
12. Mc Murray JVJ and O'Meara E. Treatment of heart failure with spironolactone – trial and tribulations. *N Engl J Med* 2004; **351**: 526-28
13. Eplerenone UKMi/NPC New Drugs in Clinical Development: 3/03/05. December 2003

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Appendix II

Table 1. Differences in characteristics in RALES and EPHEBUS studies^{5,6,13}

Baseline Population Characteristics	RALES	EPHEBUS
Eligibility for enrolment	Patients had NYHA class IV heart failure within the six months before enrolment, and were either class III or IV at enrolment. Patients had been given a diagnosis at least 6 weeks before enrolment. For 55% of patients in the spironolactone group the cause of heart failure was defined as ischaemic.	Patients with left ventricular dysfunction were eligible for randomisation three to fourteen days after the index acute myocardial infarction. 45% of patients had reperfusion or revascularisation therapy. No NYHA classification stated. Evidence of heart failure was required, except for patients with diabetes when evidence of SLVD alone was accepted.
% Patients with diabetes	Not stated	32%
Age	65 ± 12 years	64 ± 11 years
% Patients taking beta- blockers	Approx 11%	Approx 75%
% Patients taking ACE-inhibitors	Approx 95%	Approx 86%
% Patients taking aspirin	Approx 36%	Approx 88%
% Patients taking statins	Not stated	47%
% Patients taking diuretics	100%	Approx 60%
Mean LVEF (%)	25.6 ± 6.7	33.0 ± 6.0
One year mortality in those assigned to placebo	25%	13.6%

Table 2. Comparison of tolerability of eplerenone & spironolactone in EPHEBUS & RALES^{5,6}

	RALES		EPHEBUS	
	Spironolactone	Placebo	Eplerenone	Placebo
Discontinuation rate due to adverse effects	8%	5%	4.4%	4.5%
% Patients with gynaecomastia	9%	1%	0.5%	0.6%
% Patients with serious hyperkalaemia (serum potassium ≥ 6 mmol/litre ⁵)	2%*	1%*	5.5%	3.9%
% Patients with serious hypokalaemia (serum potassium < 3.5 mmol/litre ⁵)	Not stated		8.4%	13.1%

*definition of serious hyperkalaemia not given