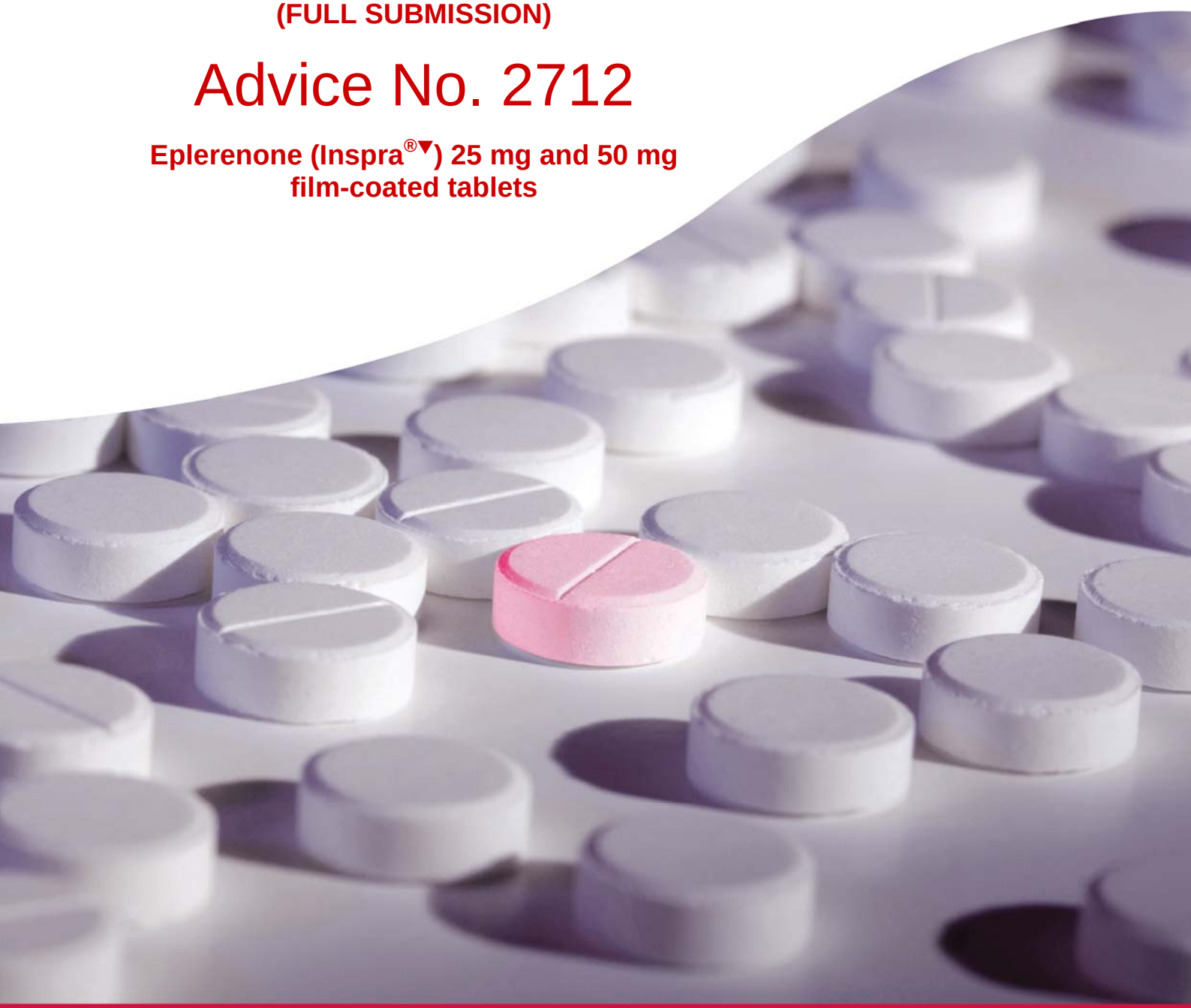
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

(FULL SUBMISSION)

Advice No. 2712

Eplerenone (Inspra®▼) 25 mg and 50 mg film-coated tablets



In collaboration with the Centre for Health Economics & Medicines Evaluation, Bangor University

AWMSG Secretariat Assessment Report – Advice No. 2712
Eplerenone (Inspra®▼) 25 mg and 50 mg film-coated tablets

This assessment report is based on evidence submitted by Pfizer Ltd on 18 March 2012[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Eplerenone (Inspra®▼) is indicated in addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in adult patients with New York Heart Association (NYHA) class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤ 30%)[2].
Dosing	Treatment should be initiated at a dose of 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within four weeks; taking into account the serum potassium level. Patients with a serum potassium level > 5.0 mmol/l should not be started on eplerenone. See Summary of Product Characteristics (SPC) for details[2].
Marketing authorisation date	Date of licence extension 16 February 2012[1] (originally licensed for use in addition to standard optimal therapy, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction and clinical evidence of heart failure after recent myocardial infarction on 21 September 2004)[2].

2.0 DECISION CONTEXT

2.1 Background

Structural or functional abnormalities of the heart, leading to impairment of cardiac function, give rise to the complex syndrome of symptoms known as heart failure (HF), which commonly includes breathlessness, fatigue and ankle swelling[3]. Approximately half the patients with HF have left ventricular systolic dysfunction (LVSD), which is associated with a reduced left ventricular ejection fraction (LVEF)[3]. Goals of treatment are prevention of premature death, reduced hospitalisation and reduction in symptoms[4].

In 2010–11, 29,029 people in Wales were reported as having HF, and of these 16,102 exhibited LVSD[5]. A 2001 study of West Midlands primary care patients by Davies et al reported that 36% of LVSD patients presented as NYHA class II (classified as ordinary physical activity results in breathlessness; see Glossary for further details)[6].

The prognosis for patients with HF remains poor. The National Heart Failure Audit 2010 found that 32% of patients had died within a year of admission for HF[7]. However, it is reported in the National Institute for Health and Clinical Excellence (NICE) Clinical Guideline for chronic HF that the prognosis for HF has improved over the last 10 years[3]. Morbidity and mortality rates due to HF have fallen due to the cumulative effects of several classes of treatment including angiotensin converting enzyme (ACE) inhibitors, beta-blockers, aldosterone antagonists, combined arterial and venous dilators and angiotensin receptor blockers (ARBs)[3]. Reduced cardiac output in HF leads to compensatory mechanisms involving activation of many neurohormonal

pathways, including the renin-angiotensin-aldosterone system (RAAS). Eplerenone competitively inhibits the binding of aldosterone and is used to moderate the aldosterone response to over-activation of the RAAS[4].

2.2 Comparators

The comparator requested by the All Wales Therapeutics and Toxicology Centre (AWTTC) was standard optimal therapy[3].

2.3 Guidance and related advice

- European Society of Cardiology (ESC). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure (2012)[8].
- NICE. Chronic heart failure pathway (2011)[9].
- NICE. Clinical Guideline 108. Chronic heart failure: full guideline (2010)[3].
- Welsh Medicines Resource Centre bulletin. Treatment of chronic heart failure (2008)[10].
- Scottish Intercollegiate Guidelines Network. Management of chronic heart failure (2007)[11].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company submission presents the Eplerenone in Mild Patients Hospitalisation And Survival Study in Heart Failure (EMPHASIS-HF), which evaluated eplerenone for the treatment of NYHA class II chronic HF (CHF) patients with LVSD[12]. The Eplerenone Postacute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), compared eplerenone with placebo as a treatment for patients after acute myocardial infarction (MI)[13]. EPHESUS will not be further discussed as it relates specifically to patients treated following acute MI. Other smaller trials have been conducted using eplerenone in CHF patients but they did not report results on class II patients separately and will not be discussed further[14,15].

3.1 EMPHASIS-HF study

The EMPHASIS-HF study was a multicentre, randomised, placebo-controlled trial of 2,737 NYHA class II CHF patients with LVSD[12]. Patients were randomised to receive either eplerenone (n = 1,364) or placebo (n = 1,373) in addition to their current standard CHF medication, which could include an ACE inhibitor or ARB (or both) and a beta-blocker. Eplerenone was initiated at a dose of 25 mg once daily and increased to 50 mg daily after four weeks; patients with impaired renal function were initiated on 25 mg eplerenone on alternate days, escalating to 25 mg daily after four weeks. Serum potassium levels were measured every four months and the eplerenone dose was decreased if serum potassium was 5.5–5.9 mmol/l and withheld if levels were ≥ 6.0 mmol/l. Potassium serum levels were remeasured within 72 hours after dose reduction and eplerenone treatment was recommenced once the serum levels were < 5.0 mmol/l[12].

The study included patients with LVEF ≤ 35%; patients having an LVEF between 30% and 35% (n = 96 [3.5%]) were included if they had a QRS time > 130 ms on electrocardiography. The trial population included only patients ≥ 55 years who had recently been hospitalised for cardiovascular (CV) reasons (within six months) or who had elevated levels of either B- type Natriuretic Protein (BNP) or N-terminal pro BNP. The main exclusion criteria were NYHA class III or IV or serum potassium level > 5.0 mmol/l. Patients with an acute MI were excluded unless the event occurred more than 30 days prior to screening. The patient group had a mean age of 69 years and was 78% male[12].

The study was terminated prematurely after a median follow-up of 21 months, according to a pre-specified stopping guideline, which allowed study conclusion following observed benefits of eplerenone. The primary endpoint was the composite endpoint of time to first occurrence of either death due to CV causes or hospitalisation for HF. After termination, the composite endpoint was reached by 18.3% (n = 249) of the eplerenone patients and 25.9% (n = 356) of the placebo patients (p < 0.001; see Table 1). The incidences of MI were higher for eplerenone compared to placebo but the difference was not statistically significant. The primary endpoint was supported by secondary endpoint analysis, including death from any cause and hospitalisation for any reason (see Table 1 for further analyses)[12].

Table 1. Results for primary endpoint, selected secondary endpoints and other outcomes from EMPHASIS-HF[12].

Endpoint	Eplerenone (n = 1,364)	Placebo (n = 1,373)	Unadjusted hazard ratio (95% confidence interval)	Unadjusted p value
Primary endpoint				
Death from CV causes or hospitalisation for HF	249 (18.3%)	356 (25.9%)	0.66 (0.56–0.78)	< 0.001
Secondary endpoints and ancillary analysis				
Death from any cause	171 (12.5%)	213(15.5%)	0.78 (0.64–0.95)	0.01
Death from CV causes	147 (10.8%)	185 (13.5%)	0.77 (0.62-0.96)	0.02
Hospitalisation for any reason	408 (29.9%)	491 (35.8%)	0.78(0.69–0.89)	< 0.001
Hospitalisation for CV causes	304 (22.3%)	399 (29.1%)	0.72 (0.62-0.83)	< 0.001
MI	45 (3.3%)	33 (2.4%)	1.34 (0.86–2.10)	0.20
Sudden cardiac death	60 (4.4%)	76 (5.5%)	0.77 (0.55–1.08)	0.12
Death from worsening HF	45 (3.3%)	61 (4.4%)	0.71 (0.48–1.04)	0.08

3.2 Comparative safety of eplerenone

During the EMPHASIS-HF study, 979/1,360 (72.0%) eplerenone-treated patients and 1007/1,369 (73.6%) placebo group patients reported adverse events (AEs); these AEs led to treatment discontinuation in 188 (13.8%) and 222 (16.2%) patients respectively[12]. Hyperkalaemia (associated with an increase in the plasma potassium level above 5.5 mmol/l) was significantly more prevalent in the eplerenone arm (109/1,360 [8.0%]) than the placebo arm (50/1,369 [3.7%]). However, treatment discontinuation due to hyperkalaemia was comparable between groups (1.1% versus 0.9% respectively) and hospitalisation due to increased serum potassium levels occurred in 4/1,360 patients receiving eplerenone and 3/1,369 patients receiving placebo. A serum potassium level > 6.0 mmol/l occurred in 33 (2.5%) patients and 25 (1.9%) patients treated with eplerenone and placebo respectively. The incidence of hypokalaemia (associated with a serum potassium level below 4.0 mmol/l) was significantly lower for eplerenone-treated patients (1.2%) than for placebo patients (2.2%).

Occurrence of gynaecomastia and other breast disorders was slightly reduced in the eplerenone group compared with the placebo arm (10 [0.7%] patients versus 14 [1.0%] patients)[12].

3.3 AWTTC critique

- In the pivotal study EMPHASIS-HF, eplerenone-treated CHF patients demonstrated significantly reduced rates of mortality and hospitalisation when

compared to placebo[12]. However, the study included some patients (3.5%) with an LVEF 30–35% if they had a QRS time > 130 ms although eplerenone is licensed for the treatment of NYHA class II CHF patients with LVEF ≤ 30%. Additionally, eligibility criteria included patients aged ≥ 55 years with recent hospitalisation for CV reasons (or elevated levels of either BNP or N-terminal pro BNP); these factors are known to increase CV risk. In the study, 50.3% (686/1,384) eplerenone patients and 50.6% (695/1,373) placebo-treated patients reported having had a MI more than 30 days prior to initial screening[12]. It is not known whether the results in this specific group of patients would be applicable to all patients with NYHA class II chronic HF and LVEF≤ 30%.

- NICE guidance recommends that for patients taking aldosterone antagonists as second-line treatments, potassium levels, creatinine levels and estimated glomerular filtration rate (eGFR) should be closely monitored and that specialist advice should be sought if the patient develops hyperkalaemia or if the renal function deteriorates[3].
- Early termination of the trial, although required due to the pre-specified protocol, may have overestimated the magnitude of the difference between eplerenone and placebo[12].
- Current NICE guidance for treatment of HF recommends considering adding aldosterone antagonists especially for moderate to severe HF (NYHA class III and IV) if a patient remains symptomatic despite optimal therapy with an ACE inhibitor and a beta blocker, or if the patient has had a MI in the past month[3]. A clinical expert contacted by AWTTC stated that spironolactone is not used in clinical practice for NHYA class II patients[16], despite its broad indication for congestive HF which is not restricted to any HF class[17]. The RALES study reported on the effectiveness of spironolactone in HF NYHA class III or IV[18] and experts have speculated on the efficacy of spironolactone on class II CHF patients and commented on the need for a trial to demonstrate the relative performance of spironolactone and eplerenone[16,19–21].
- ESC guidelines for the diagnosis and treatment of acute and chronic heart failure published after the EMPHASIS-HF study recommend an aldosterone antagonist for all patients with persisting symptoms (NYHA class II to IV) and an EF ≤ 35% despite treatment with an ACE inhibitor (or an ARB if an ACE inhibitor is not tolerated) and a beta blocker, to reduce the risk of HF hospitalisation and the risk of premature death[8].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost utility analysis (CUA) of eplerenone in its licensed indication, in addition to standard optimal therapy, to reduce the risk of CV mortality and morbidity in adult patients with NYHA class II CHF and LVSD (LVEF ≤ 30%)[1]. The comparator used in the evaluation is standard therapy alone, which includes an ACE inhibitor (or an ARB) in combination with a beta-blocker given at optimal dose.

The analysis is based on a discrete event simulation model which models time to clinically and economically important events using patient-level data from the EMPHASIS-HF randomised controlled trial (RCT)[12]. The model uses a cohort of 25,000 patients for each of eplerenone and standard optimal therapy. In the base case, a lifetime analytical time horizon is used. See Appendix 1 for further details.

4.1.2 Results

Table 2. Results of the company's base case analysis.

	Eplerenone	Standard therapy	Difference
Cost of CV hospitalisations	£1,627	£1,629	-£2
Cost of HF hospitalisations	£1,840	£2,301	-£461
Cost of active treatment	£3,410	£0	£3,410
Cost of concomitant treatment	£1,773	£1,426	£347
Cost of device implantation	£1,987	£1,683	£304
Cost of disease management	£3,433	£2,761	£672
Cost of AEs	£113	£83	£31
Total costs	£14,184	£9,882	£4,302
Total LYG	7.74	6.23	1.51
Total QALYs gained	6.19	4.98	1.21
ICER	**£3,534 per QALY gained**		
ICER: incremental cost-effectiveness ratio; LYG: life-year gained; QALY: quality-adjusted life-year gained.			

The company model estimates the incremental cost per QALY gained to be £3,534, based on additional costs of £4,302 and a gain of 1.21 QALYs for eplerenone added to standard therapy over a lifetime horizon of analysis. Probabilistic sensitivity analysis (PSA) based on 100 simulations indicates that 100% of modelled simulations fall below a threshold of £20,000–£30,000 per QALY gained.

One way sensitivity analyses indicate the model is most sensitive to the distributional parameters for: CV mortality, number of HF hospitalisations and the number of CV hospitalisations (all when no previous hospitalisations have been experienced) followed by the utility decrements associated with age. For all the parameter values explored, the ICER remained below £6,000 per QALY gained. The base case ICER remains similar in sub groups of patients with or without diabetes, ischaemic heart disease or renal impairment. The model is sensitive to the time horizon over which costs and outcomes are considered, the ICER increasing to £37,300 per QALY gained at the extreme of one year. See Appendix 1 for further details.

Further to requests from AWTTC, scenario analyses showing the impact of varying the assumption relating to extrapolation of treatment benefit in terms of hospitalisations and CV mortality beyond the trial time horizon were provided by the company. These assumed convergence of the HF hospitalisation and CV mortality curves at three, five and ten years. The impact of using a different parametric function for extrapolation of HF hospitalisation beyond the trial period was also examined. The results showed that ICER estimates ranged from £2,846 per QALY (when assuming benefits maintained over lifetime horizon) to £31,047 per QALY (when no benefit beyond that of standard care is assumed from 3 years). However, the company contends that the worst case scenario is that in which eplerenone patients would do as well as patients in the standard care arm after the trial period, resulting in an ICER of £7,492.

4.1.3 AWTTC critique

It is unclear whether or not the base case model provides the most plausible estimate of the cost-effectiveness of eplerenone, due to the limitations listed below. However,

the ICER remained below the £30,000 per QALY gained threshold in the majority of the sensitivity and scenario analyses presented by the company, with the exception of a scenario in which eplerenone offers no benefit beyond that afforded by standard care alone, after three years.

Strengths of the economic evidence include:

- Direct comparative data are used to model efficacy in the licensed population for eplerenone against standard care.
- The discrete event simulation model takes into account patient clinical history, which is known to alter the risk of future events.
- A range of scenario and sensitivity analyses are reported, to explore the impact of changing assumptions underlying the model.

Limitations of the economic evidence include:

- The EMPHASIS-HF trial was terminated early due to observed benefits of eplerenone treatment, and the modelled clinical and economic outcomes are extrapolated from these early-terminated data. Long-term data are lacking.
- The EMPHASIS-HF trial population were required to have had a CV- related hospital admission prior to entry in the trial, which is not specified in the licensed indication and may not be the case in practice.
- The model may overestimate the rate of recurrent hospitalisations compared with the available trial data. However, supplementary analyses provided by the company suggest the influence of recurrent event rates is minimal. Two additional scenario analyses were provided, one assuming that no patients experience a recurrent event, resulting in an ICER of £4,218 per QALY gained; the other assuming that the risk of experiencing a future hospitalisation is not increased by experiencing a previous one, which resulted in an ICER of £3,859 per QALY gained.
- There appears to be a lack of utility data specific to the patient population in the model, which has required a number of different sources of utility data to be brought together. However, supplementary sensitivity analyses provided by the company indicate the model is relatively robust to the assumed values.
- The model provided by the company is computationally demanding, which precludes verification of the PSA.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC have not identified any published evidence on the cost-effectiveness of eplerenone within the licensed indication currently under appraisal by AWMSG.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

Based on the Wales Quality and Outcomes Framework data for 2010–2011, the company reports that the prevalence of all HF in Wales is 29,029 patients[5]. As data relating to the incidence of HF in Wales are reportedly lacking, UK figures are extrapolated to the Welsh population, giving an estimated 2,912 incident cases per year. This population includes patients with preserved and with reduced LVEF and patients with all NYHA classes. An annual population growth rate of 1.8%, based on Office of National Statistics (ONS) data for Wales, is used, and an annual mortality rate of 7.1% for patients with NYHA class II HF is taken from a Swiss study[22].

Based on published estimates, the company estimates that 50% of all HF patients would have LVSD and that 36% of these patients would have NYHA class II symptoms[6,23]. Hence, the net number of eligible patients is estimated to be 5,225 patients in year 1, rising to 5,830 patients in year 5. Market share estimates are informed by the observed uptake of eplerenone in post MI patients, and are expected to be 5% in year 1, rising linearly to 15% in year 5. Total eplerenone treatment cost is calculated based on British National Formulary (BNF) prices and recommended doses. Direct costs relating to CV- and HF- related hospitalisation rates, and AEs, are derived from the modelled rates over five years as determined from the company's economic model. Scenarios representing different numbers of patients eligible for treatment and uptake of eplerenone are also reported.

5.1.2 Results

The company anticipates that the use of eplerenone will result in an overall net cost of £99,225 in year one rising to £332,651 in year 5, as detailed in Table 3 below.

Table 3. Budget impact analysis results.

	Year 1 (2012)	Year 2 (2013)	Year 3 (2014)	Year 4 (2015)	Year 5 (2016)
Number of eligible patients	5,225	5,378	5,530	5,681	5,830
Uptake (%)	5%	7.5%	10%	12.5%	15%
Treated patients	261	403	553	710	875
Net costs per patient					
Primary care	£145,347	£224,425	£307,958	£395,389	£487,275
Secondary & tertiary care	-£46,122	-£71,215	-£97,722	-£125,466	-£154,624
Overall net cost for whole population	£99,225	£153,210	£210,236	£269,923	£332,651

Alternative estimates of eligible patient numbers and uptake have the expected impacts, with net costs being proportional to the numbers treated.

5.1.3 AWTTC critique of the budget impact analysis

- The company has made reasonable efforts to define the epidemiology of CHF in Wales; however, the source of data used for calculating the incidence of CHF is dated and assumptions are made in relation to likely numbers meeting the specific licensed indication for eplerenone and its uptake. The number of patients likely to receive eplerenone is therefore subject to uncertainty.
- The cost savings from reduced hospitalisations are derived from the economic model. Limitations of the economic model, outlined above, may also be applicable to the budget impact estimates, although the company notes that early mortality data are derived directly from the trial data.
- Collectively, the net budget impact estimates are subject to uncertainty.

5.2 Table of comparative unit costs

The NICE clinical guideline on HF indicates that in patients who remain symptomatic despite optimal ACE inhibitor and beta-blocker therapy, options include the addition of an aldosterone antagonist licensed for use in HF (especially if the patient has moderate to severe HF [NYHA class III-IV]), addition of an angiotensin II receptor antagonist (ARB) licensed for HF (especially if the patient has mild to moderate HF [NYHA class II-III]), or addition of hydralazine in combination with a nitrate (especially if the patient is of African or Caribbean origin and has moderate to severe HF [NYHA class III-IV])[3]. Although reportedly not used routinely at present in patients with (NYHA class II) HF,

spironolactone is licensed for use in any class of HF[17]. The ARB candesartan is licensed for use in patients with LVEF ≤ 40%[24], while hydralazine is licensed only for use in moderate to severe HF[25]. Table 4 includes example acquisition costs of agents with licensed indications that may be inferred to overlap that of eplerenone. As doses need to be individually tailored to response, the doses and costs in this table are illustrative only.

Table 4. Comparative unit costs of agents licensed for use in addition to ACE inhibitor and beta-blocker therapy in patients with heart failure.

Drug	Example regimen	Approximate annual cost
Eplerenone (Inspra®▼) 25 and 50 mg oral tablets	25 mg once daily to be increased to 50 mg once daily after approximately four weeks	£557
Spironolactone (Non-proprietary) 25 mg, 50 mg oral tablets	25 mg once daily, increased to 50 mg once daily as clinically indicated	£20–£31
Candesartan (Amias®) 2 mg, 4 mg, 8 mg, 16 mg, 32 mg oral tablets	4 mg once daily, titrated up to 32 mg if tolerated	£202–£210
Costs based on MIMS list prices[26] and eDrug Tariff as of 09 May 2012[27]. See all relevant Summary of Product Characteristics for full licensed indications and dosing details. This table does not imply therapeutic equivalence of the stated drugs or doses.		

6.0 ADDITIONAL INFORMATION

6.1 Appropriate place for prescribing

AWTTC is of the opinion that if recommended, eplerenone may be appropriate for prescribing by all prescribers within NHS Wales for the indication under consideration.

6.2 Ongoing studies

The company expects that additional analyses on EMPHASIS-HF regarding blood pressure and hyperkalaemia will become available in the 6 to 12 months following submission[1]. The company submission states that there are no other ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review

This assessment report will be considered for review three years from the date of Ministerial ratification (as disclosed in the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 13 April 2012
Date range of evidence search: No date limits were applied to database searches.

GLOSSARY

New York Heart Association (NYHA) classification

The amount of exertion required to produce symptoms has been used to grade heart failure into four different classes in the New York Heart Association (NYHA) classification system (see Table 5)[3,11].

Table 5. NYHA classification of heart failure symptoms.

Class	Symptoms
I	Ordinary physical activity does not cause symptoms
II	Ordinary physical activity results in breathlessness
III	Less than ordinary physical activity causes symptoms
IV	Symptoms present at rest

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Appendix 1. Additional health economic information

Table 1. Health economic model detail.

	Base case model	Appropriate?
Comparator(s)	Eplerenone oral tablets (25 and 50 mg) in addition to standard optimal therapy are compared to standard optimal therapy alone. Standard optimal therapy includes an ACE inhibitor (or an ARB) in combination with a beta-blocker given at optimal dose. Eplerenone oral tablets are given as 25 mg once daily and increased to 50 mg once daily after four weeks or as 25 mg every other day and increased to 25 mg once daily after four weeks, if the estimated GFR is 30–49 ml/min/1.73 m^2.	Yes, as requested by AWTTC. Neither spironolactone nor ARBs are considered appropriate as comparators as they are not routinely used in Welsh clinical practice for treatment of NYHA class II HF.
Population	Patients with chronic systolic HF with NYHA class II symptoms and LVEF ≤ 30% (or, if 30–35%, a QRS duration of >130 ms on electrocardiography), in line with the patient population in the EMPHASIS-HF RCT.	The population in the EMPHASIS-HF RCT, as modelled, is wider than the licensed indication population as it also includes patients with LVEF > 30% to 35%. The company reports that this group of patients represented approximately 3.5% of the trial population[12].
Model type and description	Cost utility analysis (CUA) based on discrete event simulation using patient-level data from EMPHASIS-HF is reported. A cohort of 25,000 patients is used for eplerenone and standard optimal therapy.	Yes, CUA is the preferred type of analysis. The discrete event simulation model reflects the trial population clinical pathway.
Perspective	NHS Wales and social services.	Yes.
Time horizon	Lifetime analytical horizon assumed with one, two and five year time horizons explored in sensitivity analyses.	Yes, appropriate for life-long treatment to capture the survival benefits and costs beyond the trial time horizon.
Discount rate	3.5% discount rate for costs and outcomes, with 0% and 6% explored in sensitivity analyses.	Yes, appropriate.

Table 1. Continued.

	Base case model	Appropriate?
Efficacy	Survival analysis of patient-level data from EMPHASIS-HF trial is used to derive risk equations for clinical events occurring in the model: mortality (due to CV and non-CV causes), single or recurring hospitalisations for HF and for other CV causes, diagnosis of atrial fibrillation (AF), and implantation of defibrillator or cardiac resynchronisation device. Weibull or exponential parametric models, based on goodness of fit and prediction error estimates, were used to extrapolate these data to a lifetime time horizon. The risk of treatment discontinuation is calculated from the trial data in addition to a time-dependent discontinuation rate not linked to events in the model.	The EMPHASIS-HF RCT provides direct comparative efficacy estimates using patient level data for the comparison of interest. However, it was terminated prematurely after a median follow-up period of 21 months, due to an observed benefit of eplerenone at interim analyses. Comparison of the modelled event rates versus actual event rates at 21 months demonstrates that the model over predicts hospitalisation (and adverse) events in both the eplerenone and standard care arms, which the company attributes to the effects of censoring of trial data (therefore the censoring of patients in the trial who experience events precludes their inclusion in analyses of further/recurrent events). The company has provided supplementary analyses to explore this effect, by removing the impact of the occurrence of cardiovascular events on the risk of future hospitalisations. These are reported to demonstrate that the base case ICER increases only marginally to around £4,000 per QALY gained. The durability of treatment effect beyond the time horizon of the EMPHASIS-HF trial has been subjected to scenario analysis. In the base case, it is assumed that the effects of eplerenone on clinical events and survival continue at the rates determined from modelling the trial data for the remainder of patients' lives. Scenario analyses examining the impact of varying this assumption to consider diminution of effect at three, five and ten years were provided by the company in response to a request by AWTTC. Alternative parametric models for extrapolating the data have also been explored in sensitivity analyses.
Adverse effects	Costs and utilities relating to AEs are incorporated in the model as a weighted average of the five main AEs observed in the EMPHASIS-HF trial. These are: gynaecomastia or other breast disorders, hyperkalaemia, hypokalaemia, hypotension and renal failure. Only hyperkalaemia occurred significantly more frequently in the eplerenone group. Weibull curves are fitted to the trial data to extrapolate beyond the trial follow-up period.	The AEs reported represent the main AEs reported in the EMPHASIS-RCT trial. For pragmatic reasons, these have been bundled together into a weighted average AE, the costs and utilities for which are applied to any AE.

Table 1. Continued.

	Base case model	Appropriate?
Utility values	A targeted review to identify studies reporting utility values in HF patients with NYHA class II, based on patient characteristics and the number of hospitalisations, retrieved one study[28]. This study measured EQ-5D values for the EPHESUS trial of eplerenone for the reduction of mortality and morbidity among patients with acute MI complicated by LVSD and HF. Utility decrements associated with hospitalisation are derived from the data relating to a subset of the EPHESUS trial population who have chronic HF. Lifetime utility decrement for a diagnosis of AF is based on a model reported in another European study[29] based on data from the Euro heart survey. Utility decrement for renal failure is derived from a systematic review while that for gynaecomastia is taken from the catalogue of EQ-5D scores for the UK[30]. Utility decrement for hyperkalaemia and hypokalaemia are assumed to be zero, based on clinical opinion. Baseline utility of 0.84, calculated based on the patient characteristics in the EMPHASIS-HF trial, is used in the model. Age-dependent utility decrements are also applied for patients aged ≥ 69years.	The assumed utility values are a source of uncertainty. Several different sources have been used to provide utility values for different clinical events, including company-sought expert opinion. Supplementary sensitivity analyses, provided by the company suggest the model is relatively robust within the range of the utility values explored.
Resource use and costs	Resource use data are taken primarily from the EMPHASIS-HF RCT. The combined total rates of hospitalisations and device implantation for both of the trial arms are used, given the lack of significant difference in the distribution between the two arms. The lifespan of the device implanted is taken into account. Costs attached to hospitalisation and device implantation are taken from NHS reference costs (2009/2010)[31] and Personal Social Services Research Unit (PSSRU) Unit Costs for Health and Social Care[32]. A sensitivity analysis using the national payment by results tariff[33] is also reported. Concomitant medication costs are calculated based on the recommended daily doses given by the BNF[34] and NICE guidelines for diuretics use. The proportions of patients using each of these medications are taken from EMPHASIS-HF. A sensitivity analysis considered usage according to company market research data on use of concomitant medication in 2011 (data on file). Eplerenone cost is calculated using its recommended dosing schedule and current price. AE costs are also included based on a weighted average cost of the five main AEs reported in the EMPHASIS-HF RCT. Routine monitoring and follow up costs are also included in the model.	The costs of CV hospitalisations were calculated as a weighted average of all possible CV hospitalisation costs. The company acknowledges the presence of significant difference between eplerenone and placebo arms in certain types of hospitalisation (for MI, angina and other chest pain), which occurred more often in the eplerenone arm. However, the impact of this was examined in a scenario analysis and showed no effect on the ICER. The doses for eplerenone and background regimens assumed in the model are based on the recommended rather than the mean doses used in the RCT, which effectively assumes full adherence and dose intensity, in contrast to that observed in EMPHASIS HF. The company notes this is a conservative assumption.

Table 1. Continued.

	Base case model	Appropriate?
Uncertainty	A range of one-way sensitivity and scenario analyses, and probabilistic sensitivity analysis (PSA), is reported. Subgroup analysis is also reported for gender, diabetes status at baseline, renal function at baseline, type of disease (ischaemic or non-ischaemic). The deterministic analysis is carried out using 95% confidence interval range, minimum and maximum values or +/- 30%. Scenario analyses relating to the time horizon, source of unit costs, source of data for the calculation of concomitant medication use and utility decrements used are reported among others.	The one-way sensitivity analyses suggest that the ICER is largely insensitive to changes in the parameters examined within the specified ranges, with all estimates remaining below £6,000 per QALY gained. The most influential parameters are the distributional parameters for: CV mortality, number of HF hospitalisations and the number of CV hospitalisations (all when no previous hospitalisations have been experienced) followed by utility decrements associated with age. PSA results are reported to show that at a cost-effectiveness threshold of > £10,000 per QALY gained the probability that eplerenone being cost -effective is 100%. However, the number of simulations used in the PSA (n = 100) is low due to the time taken to run the model. The stability of the model to outputs has therefore not been confirmed. The scenario analyses show that shorter analytical time horizons increase the ICER: when using a one-year time horizon (an extreme), the ICER is around £37,000 per QALY gained. Results from subgroup analyses show that the ICER is largely the same for all subgroups of patients with values ranging between £3,187 and £3,907 per QALY gained. Analyses of different scenarios relating to the durability of treatment effect beyond the time horizon of EMPHASIS-HF were provided, using different parametric functions for extrapolation of treatment effects over a lifetime horizon. These resulted in ICER estimates ranging from £2,846 to £31,047 per QALY gained. The two scenarios which generated ICERs over £30,000 per QALY gained assume no survival differences after the end of the trial.
Model Provided?	Yes.	Parameter values and outputs of deterministic analyses appear to be consistent with those described in the company's submission, although PSA have not been verified due to the time taken to run the model.

ACE: angiotensin converting enzyme; AF: atrial fibrillation; ARB: angiotensin receptor blocker; AWTTC: All Wales Therapeutics and Toxicology Centre; BNF: British National Formulary; CUA: cost utility analysis; CV: cardiovascular; EQ-5D: EuroQoL - 5 Dimensions health outcome measure; GFR: glomerular filtration rate; HF: heart failure; ICER: Incremental cost-effectiveness ratio; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; MI: myocardial infarction; NICE: National Institute for Health and Clinical Excellence; NYHA: New York Heart Association; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life years; RCT: randomised controlled trial.