Australian Public Assessment Report for Eplerenone

Proprietary Product Name: Inspra

Sponsor: Pfizer Australia Pty Ltd

October 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

· The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.

· TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

· The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

· The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

· To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

· An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.

· AusPARs are prepared and published by the TGA.

· An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.

· An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.

· A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACE-I	angiotensin converting enzyme inhibitors
ARB	Angiotensin II receptor blocker
bpm	Beats per minute
CHF	Chronic Heart Failure
CI	Confidence interval
CMI	Consumer Medicines Information
CRT	resynchronization therapy
CSR	Clinical Study Report
CV	Cardiovascular
DBP	Diastolic blood pressure
DSMC	Data Safety Monitoring Committee
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration rate
EMA	European Medicines Agency
ESC	Executive Steering Committee
EU	European Union
e.g.	Exempli gratia; for example
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HF	Heart failure
HR	Heart rate
ICD	implantation of cardiac defibrillator
i.e.	Id est; that is
L	Litre
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
Mg	Milligram
mL	Millilitre
msec	milliseconds
NYHA	New York Heart Association
PI	Product Information

Abbreviation	Meaning
SAE	Serious adverse event
SD	Standard Deviation
SBP	Systolic blood pressure
TEAE	Treatment emergent adverse event
TGA	Therapeutic Goods Administration
U	Units
US	United States of America
³	At or greater than
£	At or lesser than
>	Greater than
<	Less than
vs.	Versus

I. Introduction to product submission

Submission details

Type of submission	Extension of Indications
Decision:	Approved
Date of decision:	23 May 2013
Active ingredient:	Eplerenone
Product name:	Inspra
Sponsor's name and address:	Pfizer Australia Pty Ltd
	38-43 Wharf Road, West Ryde NSW 2114
Dose form:	Tablet
Strengths:	25 mg and 50 mg
Container:	Blister pack
Pack sizes:	10s, 30s, 50s and 60s
Approved therapeutic use:	*Inspra is indicated 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 ≤30% or LVEF ≤35% in addition to QRS duration of >130 msec) in addition to standard optimal therapy (see Clinical Trials).[1]*
Route of administration:	Oral
Dosage:	Patients with eGFR ≥ 50 mL/min/1.73 m^2 (CKD stages 1,2 and partly 3) - Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks, taking into account serum potassium levels.
ARTG numbers:	100162 and 100163

Product background

Inspra (eplerenone) is a mineralocorticoid receptor antagonist with weak binding to androgen, glucocorticoid and progesterone receptors. It prevents the binding of aldosterone.

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[1] The full Indications are now:
Inspra is indicated to reduce the risk of cardiovascular death in combination with standard therapy in patients who have evidence of heart failure and left ventricular impairment within 3-14 days of an acute myocardial infarction (see Clinical Trials and Dosage and Administration) 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 ≤30% or LVEF ≤35% in addition to QRS duration of >130 msec) in addition to standard optimal therapy (see Clinical Trials).

Inspra has been considered previously by the Advisory Committee on Prescription Medicines (ACPM) on one occasion (238th (2005/1) meeting in 2005) prior to its initial registration for the currently approved indication.[1]

The proposed indications submitted with this application are as follows:

> *Inspra is indicated 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 ≤35%) in addition to standard optimal therapy*

There were no new data relating to quality, pharmaceutical chemistry or nonclinical (toxicology) issues submitted with this application.

The relevant European Union (EU) Guidelines (beside the general guidelines) to this application are as follows:

- CPMP/EWP/235/95 Rev 1 (pdf,63kb)
  Note for Guidance on the Clinical Investigation of Medicinal Products in the Treatment of Cardiac Failure. Published: TGA Internet site. Effective: 23 February 2001

- CPMP/EWP/2986/03 (pdf,210kb)
  Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure. Addendum on CPMP/EWP/235/95 Rev 1. Published: TGA Internet site. Effective: 1 February 2007

- pp. 127 - 132 of Rules 1998 (3C) - 3CC6a (pdf,27kb)
  Clinical Investigation of Medicinal Products for Long-Term Use. Replaces: pp. 163 - 165 of Rules 1989. Effective: 12 February 2002

See also: pp. 121 - 125 of Rules 1998 (3C) - 3CC5a (Adopted by TGA with conditions)

- – CPMP/EWP/908/99 (pdf,210kb)
    Points to Consider on Multiplicity Issues in Clinical Trials. Published: TGA Internet site. Effective: 23 June 2005

- – CPMP/EWP/2330/99 (pdf,51kb)
    Points to Consider on Application with
    1. Meta-Analyses;
    2. One Pivotal Study
    Published: TGA Internet site. Effective: 27 March 2002
    Adopted by the TGA with the following notation:"Sponsors are reminded that they should submit all available new safety data that are relevant to the intended treatment population."

Regulatory status

The product received initial ARTG Registration on 26 June 2006.

With respect to its international regulatory status, similar applications have been approved in The Netherlands and Canada (see Table 1 below).

Table 1. International regulatory status

Country	Submission date	Approval date	Indications
Canada	04 November 2011	31 August 2012	INSPRA (eplerenone) is indicated as an adjunct to standard therapy to reduce the risk of cardiovascular mortality and hospitalization for heart failure in patients with NYHA class II systolic chronic heart failure and left ventricular systolic dysfunction. In patients 75 years and older a reduction in cardiovascular mortality was not observed with INSPRA (see WARNINGS AND PRECAUTIONS - Special Populations - Geriatrics, and CLINICAL TRIALS – EMPHASIS-HF Study). INSPRA (eplerenone) is indicated as an adjunct to standard therapy to reduce the risk of mortality and hospitalization for heart failure following myocardial infarction in clinically stable adult patients who have evidence of heart failure and left ventricular systolic dysfunction (ejection fraction $\leq$40%). In patients 75 years and older a reduction in mortality was not observed with INSPRA (see WARNINGS AND PRECAUTIONS - Special Populations - Geriatrics, and CLINICAL TRIALS – EPHESUS Study).
European Union	Not submitted – Mutual Recognition Procedure with The Netherlands as RMS (see next row)	-	-
Netherlands RMS	5 April 2011	16 February 2012	Eplerenone is indicated: - in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF $\leq$40%) and clinical evidence of heart failure after recent myocardial infarction. - 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%) (see section 5.1).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The submission contained 1 pivotal efficacy/safety study with 3 sets of company study reports (CSRs):

· An amended primary CSR,

· A supplementary CSR and

· An Open-Label Extension Phase report.

The reason for and the contents of the 3 sets of CSRs will be described below.

Pharmacokinetics

No new data submitted.

Pharmacodynamics

No new data submitted.

Efficacy

Proposed additional indication of reducing the risk of cardiovascular mortality and morbidity in adult patients with NYHA Class II heart failure and left ventricular systolic dysfunction in addition to standard optimal therapy.

A single clinical trial, Study A6141079 (study acronym: EMPHASIS-HF), was submitted with this application and involved 3 sets of CSRs:

· amended Primary CSR (amended pCSR),

· Supplemental CSR (sCSR), and

· Open-label extension (OLE) report.

The trial was originally planned to continue until 813 primary endpoints had occurred but after the protocol-specified second interim analysis on 6 May 2010, when a total of 501 adjudicated primary endpoint events were reviewed by the Data Safety Monitoring Committee (DSMC), the DSMC and the Executive Steering Committee (ESC) recommended that the study be stopped based on pre-specified stopping rules in the study design regarding early attainment of positive efficacy results and that all subjects be offered eplerenone. Consequently, enrolment into the study was stopped on 26 May 2010 and a 12 month open-label phase was added where consenting subjects who were participating in the double-blind phase of the study were offered the opportunity to receive open-label eplerenone treatment once appropriate regulatory and ethics committee approvals had been obtained. Although enrolment into the study was halted on 26 May 2010, the double-blind phase of the study continued until all active patients were able to be transitioned into the OLE phase of the study. The OLE phase of the study was ongoing at the time of submission to the TGA.

All double-blind data collected from study start (30 March 2006) to 25 May 2010 were included in the initial primary CSR. However, since enrolled subjects continued in the double-blind phase after 25 May 2010, individual subject data were not unblinded in this initial primary CSR. After the complete transition of consenting patients into the OLE phase of the study and the double-blind phase had ended, subject-level data were released and the initial primary CSR was amended (this is the first of the 3 sets of CSRs submitted to the TGA, labelled as "amended pCSR"). All data from the double-blind phase collected after 25 May 2010 up until completion of the double-blind phase (18 March 2011) are reported in the supplemental CSR (sCSR). The sCSR reported efficacy and safety data on 2 datasets: double-blind data from termination of enrolment (26 May 2010) to end of double-blind phase (18 March 2011) and the complete double-blind data from study initiation (30 March 2006) to end of double-blind phase (18 March 2011). All safety data collected in the OLE phase up to the submission cut-off point date of 14 June 2011 are reported in the OLE report. The content and scope of the three sets of CSRs included in this submission are summarised in Table 2 below.

Table 2. Summary of A6141079 Clinical Study Reports included in TGA Application

Clinical Study Report	Description	Period/Patients Covered
Amended Primary CSR (pCSR)	Efficacy and safety data from study initiation to termination of enrolment, including subject level data listings and serious adverse event narratives.	*Data from the double blind phase only (up to 25 May 2010)* Data for all subjects from study initiation (30 March 2006) to termination of enrolment (25 May 2010)[a]
Supplemental CSR	Summary of efficacy and safety data covering period from termination of enrollment to end of the double blind phase. Also includes a summary of the full double blind phase from study initiation to end of double blind phase.	*Data from the double blind phase only* Data for all subjects still in double blinded treatment from termination of enrolment (26 May 2010) to end of double blind phase (18 March 2011)[a] Also includes an overall summary of all double blind data from the double blind phase: from study initiation (30 March 2006) to end of double blind phase (18 March 2011)[a]
Open label extension (OLE) report	Interim analysis of available safety data from ongoing open label phase of study.	*Open Label period data only* Data from all subjects in OLE phase i.e. from end of their double blind phase to submission cut-off point (14 June 2011)[b].

[a] Does not include data from the OLE phase of subjects already enrolled in OLE.
[b] Does not include data from the double blind phase of subjects in overlapping double blind phase.

In the sCSR, the efficacy data were summarised as descriptive statistics for each treatment group and no p values for treatment group comparisons were reported. The sponsor has stated that the OLE report submitted is an interim synopsis type study report presenting a snapshot of the safety data from the OLE phase up to the submission cut-off point date of 14 June 2011. No efficacy analysis was done in the OLE phase and only safety data was reported in the OLE report. The sponsor has also stated that in order to present the most current interim safety update for this submission, data cleaning of the OLE report was still ongoing when a database snapshot was made on 14 June 2011 and hence the database was not fully reconciled at the time of the data snapshot.

In this evaluation report, the amended pCSR will be evaluated as a pivotal efficacy study report. The sCSR will be summarised and presented below. The OLE report does not contain any efficacy analysis and will be presented in the safety section of this report.

Evaluator's conclusions on clinical efficacy for the proposed additional indication

To reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA Class II heart failure and left ventricular systolic dysfunction in addition to standard optimal therapy.

Overall, the study design and study inclusion and exclusion criteria were appropriate and consistent with the TGA adopted EU guidelines on the clinical investigation of drugs for treatment of cardiac failure, and aimed to recruit a study population of adult patients ≥55 years of age with chronic heart failure and New York Heart Association (NYHA) class II[2] functional capacity, on standard heart failure (HF) medications and reduced left ventricular ejection fraction (LVEF). The selection of patients with concomitant standard HF treatment is consistent with the TGA-adopted EMA guidelines on the clinical investigation of drugs for treatment of cardiac failure[3] and in keeping with the proposed indication. However, no rationale was given for why patients with estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m[2], were included when the currently approved Australian PI for eplerenone stated that "*Inspra should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance <50mL/min)*". In the sponsor's Clinical Overview included with this submission, the sponsor has stated that "*This is the first large study with an aldosterone antagonist that included subjects with moderate renal impairment (eGFR 30 to 49 mL/min/1.73 m[2]). Unlike in the EPHESUS trial where patients were excluded with moderate renal impairment, the present study enrolled subjects with mild and moderate renal impairment.*" It appeared to the evaluator that the sponsor had meant that the inclusion of subjects with eGFR of 30 to 49 mL/min/1.73 m[2] was planned prospectively with the intention of evaluating the efficacy and safety in this group of patients. However, this was not clearly stated in the study protocol or study report and was not included in the objective of the study.

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[2]Doctors usually classify patients' heart failure according to the severity of their symptoms. The list below describes the most commonly used classification system, the New York Heart Association (NYHA) Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity.

Class Functional Capacity: How a patient with cardiac disease feels during physical activity

I Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.

II Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.

III Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.

IV Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

[3]Note for Guidance on Clinical Investigation of Medicinal products for the Treatment of cardiac Failure. CPMP/EWP/235/95 Rev 1. <http://www.tga.gov.au/pdf/euguide/ewp023595en.pdf>

The starting dose of eplerenone and the subsequent titration schedule according to serum potassium levels for subjects with eGFR ≥50 mL/min/1.73 m² are appropriate and consistent with the dosing recommendation in the currently approved PI for eplerenone. However, the rationale for the dosing regimen for subjects with eGFR between 30 to 49 mL/min/1.73 m² was not given.

The primary and secondary efficacy endpoints were appropriate. The TGA-adopted EU guidelines on the clinical investigation of drugs for treatment of cardiac failure[3] recommend that the preferred primary endpoint of heart failure treatment studies be all-cause mortality, but that "*provided that a deleterious effect on mortality is ruled out, improvement in symptoms and correlation of haemodynamic improvement with clinical findings can be accepted as evidence of efficacy*". This is based on the principle that that main objectives are to demonstrate improvement in cardiovascular morbidity and clinical symptoms and no adverse effect on overall mortality. Although the study primary endpoint differs from the recommended preferred primary endpoint of all-cause mortality, it allows a composite assessment of effect on cardiovascular (CV) mortality and HF morbidity (as assessed by HF hospitalisation). The secondary endpoints allowed composite assessment of effect on all-cause mortality and HF morbidity as well as individual mortality endpoints (all-cause, CV and HF deaths) and morbidity endpoints (all-cause, CV and HF hospitalisation). Together with the primary endpoint, these allow evaluation of whether there would be improvement in cardiovascular morbidity with no adverse effect on overall mortality of eplerenone compared to placebo.

In the double-blind phase data up to 25 May 2010, the baseline demographic and disease characteristics were comparable between treatment groups. The study population, with a mean age of about 69 years and where the aetiology of HF was mainly ischaemic, was reflective of the targeted clinical HF patient population. The baseline demographic and disease characteristics in the post-cut off dataset and the complete double-blind phase dataset were also comparable between treatment groups, as well as comparable to those presented for the double-blind phase up to 25 May 2010.

Overall, in the double-blind phase data up to 25 May 2010, efficacy analysis results showed a 37% relative risk reduction in the incidence of the primary composite endpoint of CV mortality or hospitalisation for HF in the eplerenone group compared to the placebo group and this reduction was found to be statistically significant at p <0.0001. The results also showed that there was a statistically significant relative risk reduction of 23.9% in all-cause mortality for eplerenone compared to placebo, as well as statistically significant relative risk reductions of 42% in hospitalisation for HF and of 31% in CV hospitalisation for eplerenone compared to placebo. Although the difference in CV mortality between treatment groups was not statistically significant, there was a relative risk reduction of 24.3% in favour of eplerenone and the p-value was close to the level of significance (p=0.0120). Analyses in the complete double-blind phase dataset were consistent with the results in the amended pCSR.

Subgroup analyses of the mortality endpoints of all-cause death and CV death showed that there was no statistically significant greater risk of all-cause or CV mortality in the eplerenone group compared to placebo across the subgroups. Subgroup analyses of the morbidity endpoints showed that there was no obvious pattern indicating that eplerenone was definitively less effective in certain subgroups across the endpoints, except for the subgroups of subjects with prior beta-blocker plus angiotensin-converting-enzyme inhibitor (ACE-I) plus angiotensin II receptor blockers (ARB) use, subjects without prior beta-blocker use, subjects without prior ACE-I or ARB use, subjects with baseline Left bundle branch block (LBBB) and subjects with prior hospitalisation of ≥180 days. However, it is noted that the sample size in these subgroups were all small, except for that of subjects with baseline LBBB which had 888 subjects. In the subgroup of subjects with baseline LBBB, analyses of all endpoints yielded results that showed no statistically

significant difference between treatment groups. The sponsor did not provide any explanation regarding the lack of efficacy in this particular subgroup of subjects with baseline LBBB, and this will be raised as a clinical question (see Clinical Question below). However, it is noted that analyses in the subgroup of subjects with baseline QRS[4] >130 msec (n=871) showed statistically significant relative risk reduction for eplerenone over placebo for the morbidity endpoints of all-cause hospitalisation and CV hospitalisation.

Safety

Studies providing evaluable safety data

Only one study (A6141079), with 3 sets of CSRs (as previously described above) has been submitted; amended pCSR, sCSR and OLE report. In this safety evaluation, the amended pCSR will be evaluated as the pivotal CSR.

Patient exposure

The summary of study medication dose titration and drug exposure in the amended pCSR were presented in the submission. At Month 5, the mean dose of eplerenone was 39.5 mg and of placebo was 41.1 mg. At study cut off date, the mean final dose was 37.4 mg in the eplerenone group and 39.2 mg in the placebo group. The median duration of treatment from study start to study cut off was comparable between treatment groups (533.0 days and 494.0 days in the eplerenone and placebo groups, respectively).

The summary of study medication dose titration and drug exposure in the sCSR for the post-cut off dataset and for the complete double-blind phase dataset were presented in the submission. In the post-cut off dataset, at Month 5, the mean dose of eplerenone was 39.5 mg and of placebo was 40.9 mg. At the end of the double-blind phase, the mean final dose was 40.0 mg in the eplerenone group and 41.9 mg in the placebo group. The median duration of treatment in the post-cut off dataset was 141 days and 139 days in the eplerenone and placebo groups, respectively.

In the complete double-blind phase dataset, at Month 5 the mean dose of eplerenone was 39.1 mg and of placebo was 41.0 mg. At the end of the double-blind phase, the mean final dose was 37.4 mg in the eplerenone group and 39.2 mg in the placebo group. The median duration of treatment in the complete double-blind phase dataset was 675.0 days and 615.0 days in the eplerenone and placebo groups, respectively.

The extent of drug exposure and median duration of treatment in the OLE phase was not reported in the OLE report. A total of 1155 subjects were enrolled in the OLE phase. There

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[4]A graphic tracing of the variations in electrical potential caused by the excitation of the heart muscle and detected at the body surface is shown below. The normal electrocardiogram is a scalar representation that shows deflections resulting from cardiac activity as changes in the magnitude of voltage and polarity over time and comprises the P wave, QRS complex, and T and U waves.
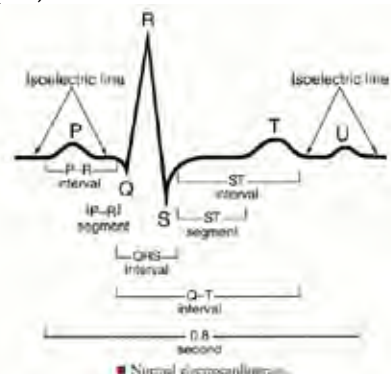
were a total of 58 (5.0%) subjects who discontinued from the study prior to the data snapshot date of 14 June 2011.

Comments: Overall, the study drug exposure in the double-blind phase was adequate to assess if the safety profile is consistent with that reported in the Product Information.

Postmarketing experience

No detailed postmarketing data was provided. The sponsor has stated that in support of this submission, Pfizer's postmarketing safety database was searched cumulatively for all medically confirmed, nonclinical study eplerenone cases reported through 31 January 2011. This was briefly summarised in the sponsor's Clinical Overview. It showed that the most frequently reported adverse event (AE) was hyperkalemia and that the overall postmarketing analyses were consistent with the known safety profile of eplerenone.

The proposed Product Information (PI) contains data regarding postmarketing experience which is unamended from the currently approved PI, and states that

"In post-marketing experience, the following additional undesirable effects have been reported: Skin and subcutaneous tissues disorders Angioneurotic oedema, rash".

Evaluator's overall conclusions on clinical safety

Overall, the incidence of all-causality AEs and all-causality serious AEs (SAEs) was comparable between the 2 treatment groups. However, the incidences of treatment-related AEs and treatment-related SAEs were higher in the eplerenone group than in the placebo group (20.6% versus 15.9%, and 2.7% versus 2.2%, respectively).

The safety results of the study were consistent with the known adverse effects of eplerenone. The AEs elicited in this study are known adverse effects of eplerenone stated in the currently approved Australian PI for eplerenone. Safety results in the complete double-blind phase dataset and in the OLE phase were consistent with those of the double-blind phase up to 25 May 2010.

The most commonly occurring treatment-related AE in the eplerenone group was hyperkalemia, which is a known adverse effect of eplerenone stated in the currently approved Australian PI. The incidence of hyperkalemia reported as treatment-related AE with administration of eplerenone was 8.0% (compared with 3.7% in the placebo group) in the double-blind phase up to 25 May 2010 and 8.7% (compared with 4.0% in the placebo group) in the complete double-blind phase. This incidence is higher compared to that in the EPHESUS study, the registration study for eplerenone, where the incidence of hyperkalemia with administration of eplerenone was 3.4% (compared with 2.0% in the placebo group)[5]. However, the study population in EPHESUS was different from that of Study A6141079 and involved patients randomised 3 to 14 days after an acute myocardial infarction, and who were on different concomitant medications compared to the study patients in Study A6141079. It is noted that in Study A6141079 the majority of hyperkalemia reported as treatment-related AEs were mild in severity[6]. It is also noted by the evaluator that in the proposed PI, the sponsor has added the precaution of increased risk of hyperkalemia when eplerenone is used in combination with ACE-Is or ARBs. In addition, although the incidence of serum potassium >5.5 mEq/L was statistically significantly higher in the eplerenone group compared to placebo group, there was no

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[5] Currently approved PI in Australia for eplerenone

[6] In the double-blind phase up to 25 may 2010, out of the 90 subjects in the eplerenone group who had treatment-related AE of hyperkalaemia, 62 were of mild severity, 21 moderate and 7 severe. In the complete double-blind phase, out of the 95 subjects in the eplerenone group who had treatment-related AE of hyperkalaemia, 67 were of mild severity, 21 moderate and 7 severe.

statistically significant difference between treatment groups in the incidence of serum potassium >6 mEq/L. Efficacy results in the double-blind phase up to 25 May 2010 had also shown that there were no statistically significant difference in the occurrence of hospitalisation for hyperkalemia between eplerenone group and placebo group.

The observed increase in serum creatinine with eplerenone is also a known adverse effect of eplerenone listed in the currently approved PI as "*renal function abnormal*". It is noted that the mean change from baseline in serum creatinine at the final follow-up assessment in the eplerenone group, although statistically significantly more compared to the placebo group, was small (about 0.1 mg/dL). The associated mean decrease from baseline in eGFR at the final follow-up assessment in the eplerenone group was also small (up to about -4 ml/min/1.73m^2). There were also no obvious trends in mean change from baseline in serum creatinine or eGFR with time in the eplerenone group. Efficacy results in the double-blind phase up to 25 May 2010 had also shown that there was no statistically significant difference in the occurrence of hospitalisation for worsening renal function between eplerenone group and placebo group.

The observed drop in systolic blood pressure (SBP) and diastolic blood pressure (DBP) with eplerenone is a known adverse effect of eplerenone listed in the currently approved PI as "*hypotension*". Although the mean changes from baseline in SBP and DBP at final follow-up assessment in the eplerenone group were small (mean change from baseline of up to -2.8 mmHg in SBP and -2.2 mmHg in DBP), the sponsor did not provide an analysis of the responder rates in terms of the degree of reduction in SBP and DBP, which would allow better evaluation of the hypotensive effect of eplerenone on the study population (see Question 8 under *List of Clinical Questions*). The incidence of death in the safety analysis supported the efficacy results that there was no increased risk of overall mortality compared to placebo. However, although the sponsor provided a list of deaths for all 3 sets of CSRs, it was not clearly summarised or indicated as to which deaths were considered related to study treatment and the incidence of each cause of death was not summarised. As a result the incidence of treatment-related deaths and of each cause of death could not be compared between the eplerenone and placebo groups. This will be raised as a clinical question (see Question 5 under *List of Clinical Questions*).

Overall safety analyses results in the subgroup of patients aged ≥75 years were consistent with those in the overall study population. Safety analyses in the subgroup of patients aged ≥75 years showed that the incidences of all-causality AEs, treatment-related AEs, all-causality SAEs and treatment-related SAEs were higher in this subgroup of patients in the eplerenone group compared to those in the overall study population and to those aged <75 years. However the incidences of these AEs and SAEs were also higher in the placebo group in the subgroup of patients aged ≥75 years compared with the respective placebo groups in the overall study population and in the subgroup of patients aged <75 years. This suggests that the higher incidences of these AEs and SAEs seen in the eplerenone groups in the subgroup of patients aged ≥75 years might be reflecting the generally higher incidence of AEs or SAEs in the more elderly age group, rather than an actual adverse effect of eplerenone on the subgroup of elderly patients.

The profile of the most commonly reported AEs and SAEs in the eplerenone group in this subgroup of patients aged ≥75 years is comparable with that in the overall study population and that in the subgroup of patients aged <75 years. The mean changes from baseline in serum potassium, serum creatinine and eGFR at the final follow-up assessment in the eplerenone group were also comparable between the subgroup of patients aged ≥75 years and in the overall study population. In addition, the incidence of serum potassium levels of >5.5 mEq/L in the eplerenone group in the subgroup of patients aged ≥75 years (12.42%) was similar to that in the overall study population (11.80%) and that in the subgroup of patients aged <75 years (11.64%). Consistent with the results in the overall

population, there was no statistically significant difference between treatment groups in the incidence of potassium levels of >6 mEq/L in this subgroup of patients aged ≥75 years.

The mean change from baseline in SBP at final follow-up assessment in the eplerenone group in the subgroup of patients aged ≥75 years (-4.75 mmHg) was greater compared to the overall study population (-2.47 mmHg) and in the subgroup of patients aged <75 years (-1.75 mmHg). Although the mean change from baseline in DBP at final follow-up assessment in the subgroup of patients aged ≥75 years was not statistically significantly different between treatment groups, it was also greater in this subgroup of patients aged ≥75 years (-3.19 mmHg) compared to the overall study population (-1.83 mmHg) and in the subgroup of patients aged <75 years (-1.40 mmHg). The sponsor did not provide an analysis of the responder rates in terms of the degree of reduction in SBP and DBP in this subgroup of patients, which would allow better evaluation of the hypotensive effect of eplerenone on this elderly study population (see Question 8 under *List of Clinical Questions*).

List of clinical questions

Efficacy

1. Please provide the rationale for the inclusion criterion of eGFR ≥30 mL/min/1.73 m² in study A6141079 (Emphasis-HF Study).

Rationale for this question:

As commented above, the currently approved Australian PI for eplerenone stated that "*Inspra should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance <50mL/min)*". No clear rationale was given by the sponsor as to why patients with eGFR ≥30 mL/min/1.73 m² were included in the Emphasis-HF study.

It is noted by the evaluator that in the sponsor's Clinical Overview included with this submission, the sponsor has stated that "*This is the first large study with an aldosterone antagonist that included subjects with moderate renal impairment (eGFR 30 to 49 mL/min/1.73 m²). Unlike in the EPHESUS trial where patients were excluded with moderate renal impairment, the present study enrolled subjects with mild and moderate renal impairment.*" It appeared to the evaluator that the sponsor had meant that the inclusion of subjects with eGFR of 30 to 49 mL/min/1.73 m² was planned prospectively with the intention of evaluating the efficacy and safety in this group of patients. However, this was not clearly stated in the study protocol or study report, and was not included in the objective of the study.

2. Please justify the dosing regimen for subjects with eGFR between 30 to 49 mL/min/1.73 m2 of 25mg eplerenone every other day.

Rationale for this question:

As commented above, in the study, the starting dose of eplerenone and the subsequent titration schedule according to serum potassium levels for subjects with eGFR ≥50 mL/min/1.73 m² were consistent with the dosing recommendation in the currently approved Australian PI for eplerenone. However, the rationale for the dosing regimen for subjects with eGFR between 30 to 49 mL/min/1.73 m² was not given in the CSRs. The references to dosing in patients with renal impairment in the currently approved PI are restricted to that "*Inspra should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance <50mL/min)*", that "*No initial dose adjustment is required in patients with mild renal impairment*" and that "*Inspra is contraindicated in patients with severe renal insufficiency*".

*3. **Please provide information for the pivotal study report (that is, amended pCSR) on the number of subjects in each treatment group with each category of protocol deviations.***

Rationale for this question:

As commented above, in the amended pCSR, information regarding the number of subjects in each treatment group with each category of protocol deviations was not provided. This information is important to assess whether the incidence of protocol deviations was comparable between treatment groups.

*4. **Please put forward possible explanations for the subgroup analysis results which showed no statistically significant difference between treatment groups across all efficacy endpoints in the subgroup of subjects with baseline LBBB.***

Rationale for this question:

As noted above, subgroup analyses of the morbidity endpoints showed that there was no obvious pattern indicating that eplerenone was definitely less effective in certain subgroups across the endpoints, except for the subgroups of subjects with prior beta-blocker plus ACE-I plus ARB use, subjects without prior beta-blocker use, subjects without prior ACE-I or ARB use, subjects with baseline LBBB, and subjects with prior hospitalisation of ≥180 days. It is noted that the sample size in these subgroups were all small, except for that of subjects with baseline LBBB, which had 888 subjects. In the subgroup of subjects with baseline LBBB, analyses of all endpoints yielded results that showed no statistically significant difference between treatment groups. The sponsor did not provide any explanation regarding the lack of efficacy in this particular subgroup of subjects with baseline LBBB.

Safety

*5. **Please provide a tabulation or summary of the incidences of treatment-related deaths as well as of the incidence of each cause of death, for the amended pCSR, sCSR and OLE report.***

Rationale for this question:

As commented above, although the sponsor has provided a list of the deaths for all 3 sets of CSRs, it was not clearly summarised or indicated as to which deaths were considered related to study treatment, and the incidence of each cause of death was not summarised. As a result the incidence of treatment-related deaths and of each cause of death could not be compared between the eplerenone and placebo groups.

*6. **Please provide a tabulation or summary of the incidences of treatment-related SAEs for the amended pCSR and the sCSR.***

Rationale for this question:

As noted previously in this evaluation, in both the amended pCSR and the sCSR, a list of the most frequently reported treatment-related SAEs was not clearly tabulated or summarised.

*7. **Please provide additional safety analyses for the subgroup of patients with baseline LBBB present.***

Rationale for this question:

As commented previously, subgroup efficacy analyses showed that for the subgroup of subjects with baseline LBBB, analyses of all efficacy endpoints yielded results that showed no statistically significant difference between treatment groups. It was recommended that

a safety analysis be done in this subgroup in order to evaluate the risk-benefit profile for the use of eplerenone in this subgroup.

8. Please provide analysis of the responder rates in terms of reductions in SBP and DBP in the overall study population as well as in the age-stratified subgroups (≥75 years and <75 years).

As noted previously, decreases in systolic and diastolic blood pressure were statistically significantly more in the eplerenone group compared to the placebo group in the overall study population. Although this is a known adverse effect of eplerenone, it was recommended that further analysis comparing the responder rates in terms of reductions in SBP and DBP be done and presented to allow better evaluation of the hypotensive effect of eplerenone. In particular, analyses in the subgroup of patients aged ≥75 years showed that the mean decrease from baseline in SBP and DBP at final follow-up assessment in the eplerenone group in this subgroup was greater compared to the overall study population and to the subgroup of patients aged <75 years. It was recommended that further analysis comparing the responder rates in terms of reductions in SBP and DBP in these age-stratified subgroups(≥75 years and <75 years) be done and presented in order to fully evaluate if eplerenone has a greater risk of hypotension in the elderly patient population. This would allow evaluation on the need for a precaution to be added in the proposed PI with regards to risk of hypotension or necessity for closer blood pressure (BP) monitoring in the elderly patients.

The clinical evaluator also posed two questions regarding the proposed PI and Consumer Medicines Information documents:

PI and CMI Question 1: the sponsor was asked for a safety analysis of the sub-group of patients with an eGFR of 30-59 mL/min/1.73 m2 to justify relaxation of the contra-indications from 'moderate to severe renal insufficiency' to 'severe renal insufficiency'.

PI and CMI Question 2: the sponsor was asked to justify the proposal that patients with mild to moderate renal impairment should be started at 25 mg daily.

These issues and the sponsor's responses are discussed by the Delegate under *VI. Overall conclusion and risk/benefit assessment, Second Round Evaluation of Clinical Data Submitted in Response to Questions* below.

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The benefits of eplerenone in the proposed usage are:

· Potential reduction in the risk of cardiovascular mortality and morbidity in adult patients with NYHA Class II chronic heart failure when used in addition to standard heart failure therapy

According to statistics gathered by the Australian Institute of Health and Welfare (AIHW) and the National Heart Foundation of Australia (NHFA)[7], at least 300 000 Australians had chronic heart failure, with 30,000 new cases diagnosed each year. Heart failure accounted for 9.5% of hospitalisations for heart, stroke and vascular diseases and was the third largest cause of death from heart, stroke and vascular diseases in Australia. There is thus

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[7] Australian Institute of Health and Welfare (AIHW) and the National Heart Foundation of Australia (NHFA). Heart, stroke and vascular diseases—Australian facts 2004.

potential benefit in the availability of a drug that can reduce mortality or morbidity arising from chronic heart failure.

The TGA adopted EU guideline on the clinical investigation of drugs for treatment of cardiac failure[3] recommends that the preferred primary endpoint of heart failure treatment studies be all-cause mortality, but that "*provided that a deleterious effect on mortality is ruled out, improvement in symptoms and correlation of haemodynamic improvement with clinical findings can be accepted as evidence of efficacy*". This is based on the principle that that the main objective is to demonstrate improvement in cardiovascular morbidity and clinical symptoms and no adverse effect on overall mortality. Overall, the efficacy results of Study A6141079 had managed to demonstrate improvement in cardiovascular morbidity and no adverse effect on overall mortality.

Efficacy analysis results showed that there was a statistically significant 37% relative risk reduction in the incidence of the primary composite endpoint of CV mortality or hospitalisation for HF in the eplerenone group compared to the placebo group. There was statistically significant relative risk reduction of 23.9% in all-cause mortality for eplerenone compared to placebo, as well as statistically significant relative risk reductions of 42% in hospitalisation for HF and of 31% in CV hospitalisation for eplerenone compared to placebo.

Subgroup analyses[8] of the mortality endpoints of all-cause death and CV death showed that there was no statistically significant greater risk of all-cause or CV mortality in the eplerenone group compared to placebo across the subgroups. Subgroup analyses[13] of the morbidity endpoints were difficult to interpret in certain subgroups with small sample sizes but in general showed that there was no obvious indication that eplerenone was less effective in certain subgroups across the endpoints, except for the subgroup of subjects with baseline LBBB, where analyses of all efficacy endpoints yielded results that showed no statistically significant difference between treatment groups. This needs to be evaluated in the context of the safety profile for this subgroup of patients (see Question 7 under *List of Clinical Questions*).

First round assessment of risks

The risks of eplerenone in the proposed indication are:

· hyperkalemia,

· increase in serum creatinine and associated decrease in eGFR

· drop in systolic and diastolic blood pressure

The safety results of the study were consistent with the known adverse effects of eplerenone stated in the currently approved Australian PI. The potential risks of eplerenone listed above were all known adverse effects of eplerenone.

The most commonly occurring treatment-related AE in the eplerenone group in this study was hyperkalemia. However, the majority of AEs of hyperkalemia reported as treatment-related AEs were mild in severity. In addition, although the incidences of serum potassium >5.5 mEq/L was statistically significantly higher in the eplerenone group compared to placebo group, there was no statistically significant difference between treatment groups in the incidence of serum potassium >6 mEq/L. It also needs to be taken into consideration that this adverse effect of eplerenone can be monitored by routine laboratory assessment.

With regards to changes in serum creatinine and eGFR, the mean changes from baseline in serum creatinine and of eGFR at the final follow-up assessment in the eplerenone group were small and not clinically significant. There were also no obvious trends in mean

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[8] Including for the subgroup of patients of age ≥ 75 years.

change from baseline in serum creatinine or eGFR with time in the eplerenone group. It is also noted that these adverse effects of eplerenone can also be monitored by routine laboratory assessment.

Although decreases in systolic and diastolic blood pressure were statistically significantly more in the eplerenone group compared to the placebo group, this is a known adverse effect of eplerenone and is an adverse effect that can be assessed with non-invasive blood pressure monitoring. In addition, it is noted that the incidence of hypotension reported as treatment-related AE in the overall study population in the pivotal CSR (that is, amended pCSR) was low (eplerenone versus placebo: 1.1% versus 0.3%).

Overall safety analyses results in the subgroup of patients aged ≥75 years were consistent with those in the overall study population and did not indicate significantly greater safety concerns in this age group with the use of eplerenone. Although the incidences of all-causality AEs, treatment-related AEs, all-causality SAEs and treatment-related SAEs were higher in this subgroup of patients in the eplerenone group compared to those in the overall study population and to those aged <75 years, the incidences were also higher in the placebo group in the subgroup of patients aged ≥75 years compared with the respective placebo groups in the overall study population and in the subgroup of patients aged <75 years. This suggests that the higher incidences of these AEs and SAEs seen in the eplerenone groups in the subgroup of patients aged ≥75 years might be reflecting the generally higher incidence of AEs or SAEs in this more elderly age group rather than an actual adverse effect of eplerenone in the subgroup of elderly patients. The profile of the most commonly reported AEs and SAEs, mean changes from baseline in serum potassium, serum creatinine and eGFR at the final follow-up assessment and incidence of serum potassium levels of >5.5 mEq/L in the eplerenone group in this subgroup of patients aged ≥75 years were all comparable with that in the overall study population and that in the subgroup of patients aged <75 years.

However, the mean change from baseline in SBP and DBP at final follow-up assessment in the eplerenone group in the subgroup of patients aged ≥75 years was greater compared to the overall study population and to the subgroup of patients aged <75 years. Although it is noted that the incidence of hypotension reported as treatment-related AE in the subgroup of patients aged ≥75 years in the pivotal CSR (that is, amended pCSR) was low (eplerenone versus placebo; ≥75 years old: 0.9% versus 0.3%; <75 years old: 1.8% versus 0.3%), further analysis comparing the responder rates in terms of reductions in SBP and DBP in age-stratified groups, is needed to fully evaluate if eplerenone has a greater risk of hypotension in the elderly patient population (see Question 8 under *List of Clinical Questions*).

First round assessment of benefit-risk balance

The benefit-risk balance of eplerenone given the proposed usage was considered to be favourable.

Efficacy results of Study A6141079 demonstrated improvement in cardiovascular morbidity and no adverse effect on overall mortality. Efficacy results showed a statistically significant relative risk reduction of 23.9% in all-cause mortality for eplerenone compared to placebo, as well as statistically significant relative risk reductions of 42% in hospitalisation for HF and of 31% in CV hospitalisation for eplerenone compared to placebo.

The safety results of the study were consistent with the known adverse effects of eplerenone stated in the currently approved Australian PI. The potential risks of eplerenone elicited in Study A6141079 were hyperkalemia, increase in serum creatinine and associated decrease in eGFR, and drop in systolic and diastolic blood pressure, which

were all known adverse effects of eplerenone and could be monitored by routine laboratory assessment or non-invasive blood pressure monitoring.

First round recommendation regarding authorisation

It was recommended that the application for extension of indication of eplerenone for treatment of adult patients with NYHA Class II chronic heart failure, as an addition to standard optimal therapy, be approved.

This is subject to a satisfactory response to the recommended changes in the PI and CMI and to the clinical questions raised (see *List of Clinical Questions*). In addition it was noted that the sponsor has stated that the OLE report provided in this submission was a snapshot of the safety data from the OLE phase up to the 14 June 2011 data snapshot and that in order to present the most current interim safety update for this submission, data cleaning was still ongoing while a database snapshot was made on 14 June 2011 and the database was not fully reconciled at the time of the data snapshot. It is recommended that the sponsor provide to the TGA the final OLE CSR based on a complete and validated OLE database as soon as this becomes available.

Second round evaluation of clinical data submitted in response to questions

Overall, the sponsor has adequately addressed all the questions posed in the first round of evaluation. The evaluator was in disagreement with the sponsor's conclusion in relation to *Efficacy Question 4* but it does not impact the recommendation for this submission. Evaluation of the additional clinical data submitted by the sponsor in response to *Safety Question 8* raised some concern on the effect of eplerenone on the blood pressure of elderly patients, triggering a recommendation to amend the proposed PI (this will be described under the subheading "*Safety Question 8*"). The responses by the sponsor to the other questions did not raise new efficacy or safety concerns.

This section summarises the evaluation of the sponsor's responses to the questions posed in the first round of evaluation.

Efficacy question 1

The response by the sponsor adequately clarified that the inclusion of subjects with eGFR of 30 to 49 mL/min/1.73 m[2] had been planned prospectively with the intention of evaluating the efficacy and safety in this group of patients. The Executive Steering Committee for the Emphasis-HF Study had made the decision to evaluate prospectively patients with moderate renal impairment at a lower dose of eplerenone, based on post-hoc analysis results from the EPHESUS trial.

Efficacy question 2

The response by the sponsor has satisfactorily addressed the question. The dose had been chosen empirically with the aim of being an efficacious dose while avoiding the risk of hyperkalemia, which was a known adverse effect of eplerenone. A post-hoc analysis of the EPHESUS trial evaluating the effect of eplerenone in patients receiving either 25 mg daily or 25 mg every other day suggested that eplerenone at a dose of 25 mg every other day, could be efficacious[9].

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[9] Banas et al. Favorable outcomes with 25 mg of eplerenone in patients with post-AMI heart failure: Results from the EPHESUS Trial. J Card Fail 2005;1(Suppl):S156, Abstract 249

Efficacy question 3

The sponsor provided data which showed that the number of subjects with each category of protocol deviations was comparable between treatment groups.

Efficacy question 4

The sponsor has stated that the total number of subjects with left bundle branch block (LBBB) at baseline was 688 and not 888, as described in the first round evaluation report. On review, the evaluator acknowledged that the figure should be 688. However, the figure of 888 had been drawn from Figure 6 on page 70 of the amended pCSR submitted by the sponsor [not in this AusPAR]. It is recommended that the sponsor make the relevant amendment to Figure 6 in the amended pCSR.

The sponsor had reproduced the subgroup efficacy tables previously submitted in the amended pCSR and which had been previously evaluated, and had stated that "*For the secondary endpoint of all-cause mortality or heart failure hospitalization, 84 (24.8%) in the eplerenone group (n=339), and 111 (31.8%) in the placebo group (n=349) met this endpoint, resulting in a significant relative risk reduction of 25.4% (p<0.0344, CI 0.562, 0.991). Similarly, for the secondary endpoint of all-cause mortality, 46 (13.6%) in the eplerenone group (n=339) and 68 (19.5%) in the placebo group (n=349) met this endpoint, resulting in a significant relative risk reduction of 33.3% (p<0.0344; CI 0.459, 0.971)*".

The evaluator would like to bring to attention that, for the secondary endpoint of all-cause mortality or heart failure hospitalisation, the p value was 0.0430 and not <0.0344. It should also be noted that in accordance with the description in the study statistical methods, results were considered statistically significant if a p-value <0.049 was obtained for the primary endpoint and p-value <0.01 for the secondary endpoints. Hence, the results for the 2 secondary endpoints quoted by the sponsor were not considered statistically significant.

The results of the subgroup analyses on the primary and secondary efficacy endpoints in the amended pCSR had been summarised in the first round evaluation report and the relevant part concerning the subgroup of baseline LBBB present versus not present is reproduced below in Table 3 (with the sample size amended). Results showed that in the subgroup of subjects with LBBB at baseline, analyses of the primary and main secondary endpoints had all yielded results which were not statistically significant, compared to those in the subgroup of subjects without LBBB at baseline, where results were mostly statistically significant in favour of eplerenone and this had prompted the question to the sponsor in the first evaluation report.

Table 3. Primary and main secondary endpoints in the subgroups of subjects with and without LBBB at baseline, study A6141079 (amended pCSR)

| | Baseline LBBB present | | | |
| Endpoints | Yes N=688 | | No N=2048 | |
	Hazard Ratio	P value	Hazard Ratio	P value
HF hospitalisation or CV death (Primary endpoint)	0.751	0.0541	0.623	<0.0001
All-cause mortality or HF hospitalisation	0.746	0.0430	0.649	<0.0001
All cause mortality	0.667	0.0344	0.824	0.1141
CV mortality	0.671	0.0521	0.811	0.1118
All-cause hospitalisation	0.891	0.3678	0.747	0.0002
HF hospitalisation	0.869	0.4255	0.523	<0.0001
All-cause death or all-cause hospitalisation	0.794	0.0520	0.753	0.0001
HF death or HF hospitalisation	0.869	0.4255	0.527	<0.0001
CV hospitalisation	0.713	0.0177	0.717	0.0002

Values that are underlined and blue are statistically significant.

It is acknowledged that the study was not powered for the subgroup analyses and that the sample size for the subgroup of subjects with LBBB at baseline was relatively small compared to the subgroup of subjects without LBBB at baseline. The question had been raised as a matter of academic curiosity, to explore if the sponsor had any possible explanations for this observation. The sponsor's response to "*Safety Question 7*" regarding the safety results in the subgroup of subjects with LBBB at baseline (described later), showed that there were no major safety concerns in this subgroup of subjects. Hence, although the evaluator disagreed with the sponsor's conclusion that "*subjects with left bundle branch block (LBBB) at baseline experienced a significant benefit from treatment with eplerenone*" this does not affect the recommendation for this submission.

Safety question 5

The additional data provided by the sponsor in response to this question did not raise any significant safety concerns. The sponsor had stated in their response that as the sCSR contained the full double-blind dataset, their response will be directed towards the sCSR and the OLE only. This is deemed by the evaluator to be appropriate. The sponsor did not provide a direct summary of the incidences of treatment-related deaths and of the incidence of each cause of death but had provided a summary of the incidences of all-cause SAEs and treatment-related SAEs occurring within 14 days of a death and of deaths due to unknown cause as surrogate information. The sponsor did not state clearly in their response regarding why direct data was not provided. It is assumed by the evaluator that

this was not recorded during the study and hence unavailable. In the absence of direct data, the surrogate information provided was deemed acceptable.

In the full-double-blind dataset in the sCSR, the number of all-cause SAEs reported within 14 days prior to a death was comparable between treatment groups (346 and 442 in the eplerenone and placebo group, respectively). The most commonly reported SAE in the eplerenone group was cardiac failure and the incidence was comparable between treatment groups (40.5% [83/205] and 35.6% [90/253] in the eplerenone and placebo group, respectively). The number of treatment-related SAEs reported within 14 days prior to a death was also comparable between treatment groups (7 and 6 in the eplerenone and placebo group, respectively). The most commonly reported SAE in the eplerenone group was hyperkalemia (1.0% [2/205] versus 0.0% [0/253] in the placebo group). Of the subjects who died during the double blind phase of the study, 2 deaths in the placebo group and 1 death in the eplerenone group were reported with cause unknown and therefore attributed to the study medication by the sponsor.

In the OLE dataset, there were 78 all-cause SAEs reported within 14 days prior to a death. The most commonly reported SAE was cardiac failure, reported in 11 subjects (19.6%; 11/56). Three treatment-related SAEs in 3 subjects were reported within 14 days prior to a death in the OLE dataset. Two of these were in the preferred term of "deaths", and 1 in the preferred term of "*malignant neoplasm of ampulla of Vater*". Of the subjects who died during the OLE phase of the study, 2 deaths were reported with "*cause unknown*" and therefore attributed to the eplerenone treatment, and one death was reported with cause "*Other*," and therefore was not attributed to the study treatment.

Safety question 6

The additional data provided by the sponsor in response to this question did not raise any significant safety concerns.

In the pCSR 37 (2.7%) subjects in the eplerenone group had 50 treatment-related SAEs compared to 30 (2.2%) subjects in the placebo group who reported 38 treatment-related SAEs. The most-frequently reported treatment-related SAEs in the eplerenone group were hyperkalemia (0.9% [12/1360] versus 0.2% [3/1369] in the placebo group), cardiac failure (0.4% [5/1360] versus 0.2% [3/1369]) and renal impairment (0.4% [5/1360] versus 0.4% [5/1369]).

For the complete double-blind phase in the sCSR, 39 (2.9%) subjects in the eplerenone group had 52 treatment-related SAEs compared to 29 (2.1%) subjects in the placebo group who reported 36 treatment-related SAEs. The most-frequently reported treatment-related SAEs in the eplerenone group were hyperkalemia (0.9% [12/1364] versus 0.2% [3/1372] in the placebo group), renal impairment (0.4% [5/1364] versus 0.4% [5/1372]) and cardiac failure (0.3% [4/1364] versus 0.2% [3/1372]).

Safety question 7

The additional data provided by the sponsor in response to this question did not raise any significant safety concerns for this subgroup of subjects. The safety results in this subgroup of subjects were generally comparable with those for the overall study population (see Table 4 below).

In the complete double-blind phase, there were 339 subjects in the eplerenone group and 349 in the placebo group with LBBB at baseline. In this subgroup, 257 subjects (75.8%) in the eplerenone group and 262 subjects (75.1%) in the placebo group experienced 930 and 932 AEs of any cause, respectively. The most commonly reported all-causality AEs in the eplerenone group were cardiac failure (eplerenone versus placebo: 22.1% versus 24.6%), hyperkalemia (9.1% versus 3.7%) and renal impairment (5.0% versus 2.9%). In this

subgroup of subjects with LBBB at baseline, 79 subjects (23.3%) in the eplerenone group and 58 subjects (16.6%) in the placebo group experienced 116 and 91 treatment-related AEs, respectively. The most commonly reported treatment-related AEs in the eplerenone group were hyperkalemia (eplerenone versus placebo: 8.3% versus 2.6%), hypotension (1.8% versus 0.0%) and renal impairment (1.5% versus 1.4%).

With regards to all-cause SAEs, 147 subjects (43.4%) in the eplerenone group and 173 subjects (49.6%) in the placebo group experienced 326 and 392 all-causality SAEs, respectively. The most commonly reported SAEs in the eplerenone group were cardiac failure (eplerenone versus placebo: 20.1% versus 20.9%), pneumonia (2.7% versus 1.7%), and renal impairment (2.7% versus 1.7%). With regards to treatment-related SAEs 11 subjects (3.2%) in the eplerenone group and 9 subjects (2.6%) in the placebo group experienced 14 and 12 treatment-related SAEs, respectively. The most commonly reported SAEs in the eplerenone group were hyperkalemia (eplerenone versus placebo: 1.8% versus 0.0%), cardiac failure (0.9% versus 0.3%) and renal impairment (0.6% versus 0.9%).

Table 4. Summary of safety results in the complete double-blind phase dataset in the overall population and in the subgroup of subjects with LBBB at baseline

	Complete double-blind phase dataset(sCSR), subgroup of subjects with LBBB at baseline		Complete double-blind phase dataset (sCSR), overall population	
	Eplerenone N=339	Placebo N=349	Eplerenone N=1364	Placebo N=1372
Incidence of all-causality AEs	75.8%	75.1%	76.8%	78.1%
Incidence of treatment-related AEs	23.3%	16.6%	21.3%	17.1%
Incidence of all-causality SAEs	43.4%	49.6%	43.0%	50.0%
Incidence of treatment-related SAEs	3.2%	2.6%	2.9%	2.1%
Most commonly reported all-causality AEs in the eplerenone group	Cardiac failure (22.1% versus 24.6% in the placebo group) Hyperkalemia (9.1% versus 3.7% in the placebo group) Renal impairment (5.0% versus 2.9% in the placebo group).		Cardiac failure (20.5% versus 23.8% in the placebo group) Hyperkalemia (8.7% versus 4.0% in the placebo group) Dyspnoea (5.0 % versus 5.5% in the placebo group) Renal impairment (5.0% versus 3.2% in the placebo group)	
Most commonly reported treatment-related AEs in the eplerenone group	Hyperkalemia (8.3% versus 2.6% in the placebo group)		Hyperkalemia (7.0% versus 2.9% in the placebo group)	
Most commonly reported all-causality SAEs in the eplerenone group	Cardiac failure (20.1% versus 20.9% in the placebo group)		Cardiac failure (16.0% versus 19.7% in the placebo group)	
Most commonly reported treatment-related SAEs in the eplerenone group	Hyperkalemia (1.8% versus 0.0% in the placebo group) Cardiac failure (0.9% versus 0.3% in the placebo group) Renal impairment (0.6% versus 0.9% in the placebo group)		Hyperkalemia (0.9% versus 0.2% in the placebo group) Renal impairment (0.4% versus 0.4% in the placebo group) Cardiac failure (0.3% versus 0.2% in the placebo group).	

Safety question 8

The additional data provided by the sponsor suggested that eplerenone may be associated with a greater drop in systolic BP in patients aged ≥75 years.

The sponsor did additional post-hoc analyses in the complete double-blind phase database on the maximum reduction from baseline in SBP and DBP measured at any time post

randomisation and presented results of incidences in the categories of no reduction, reductions of 1-5 mmHg, reductions of 6–10 mmHg, reductions of 11– 20 mmHg, greater than 20 mmHg reduction and missing values. These post-hoc analyses results provided by the sponsor showed that among subjects aged <75 years the proportion of subjects with each category of reductions in SBP and DBP was generally comparable between the eplerenone and the placebo group (see Table 5). Among subjects aged ≥75 years, the proportion of subjects in each category of reductions in SBP and DBP was also generally comparable between the eplerenone and the placebo group, except for the category of reductions >20 mmHg, for both SBP and DBP (see Table 6). In the category of reductions in SBP >20 mmHg, the incidence in the eplerenone group was 37.9% compared with 24.4% in the placebo group, while in the category of reductions in DBP >20 mmHg, the incidence in the eplerenone group was 14.2% compared with 8.8% in the placebo group. Comparing the results between age groups (<75 years versus ≥75 years), the proportion of subjects in each category of reductions in SBP and DBP was generally comparable between the 2 age groups in both the eplerenone and the placebo treatment groups except for the category of reductions >20 mmHg for SBP, where the incidence in the eplerenone group was 37.9% for subjects aged ≥75 years, compared with 28.3% for subjects aged <75 years. For the placebo group, the proportion of subjects in this category of reductions >20 mmHg for SBP was comparable between the 2 age groups (24.4% for subjects aged ≥75 years, and 23.9% for subjects aged <75 years).

Table 5. Maximum systolic/diastolic blood pressure reduction from baseline - patients age <75 (based on complete DB phase database), study A6141079

| | Systolic BP | | Diastolic BP | |
| | Inspra | Placebo | Inspra | Placebo |
Maximum Reduction (mmHg)	(N=1037)	(N=1048)	(N=1037)	(N=1048)
No reduction	181 (17.5)	193 (18.4)	253 (24.4)	267 (25.5)
1 - 5	91 (8.8)	121 (11.5)	127 (12.2)	144 (13.7)
>5 - 10	181 (17.5)	196 (18.7)	255 (24.6)	266 (25.4)
>10 - 20	275 (26.5)	270 (25.8)	263 (25.4)	248 (23.7)
>20	293 (28.3)	250 (23.9)	123 (11.9)	105 (10.0)
Missing	16 (1.5)	18 (1.7)	16 (1.5)	18 (1.7)

Table 6.Maximum systolic/diastolic blood pressure reduction from baseline - patients age >=75 (based on complete DB phase database), study A6141079

| | Systolic BP | | Diastolic BP | |
| | Inspra | Placebo | Inspra | Placebo |
Maximum Reduction (mmHg)	(N=330)	(N=328)	(N=330)	(N=328)
No reduction	47 (14.2)	65 (19.8)	56 (17.0)	66 (20.1)
1 - 5	22 (6.7)	21 (6.4)	51 (15.5)	42 (12.8)
>5 - 10	46 (13.9)	57 (17.4)	71 (21.5)	95 (29.0)
>10 - 20	85 (25.8)	98 (29.9)	100 (30.3)	89 (27.1)
>20	125 (37.9)	80 (24.4)	47 (14.2)	29 (8.8)
Missing	5 (1.5)	7 (2.1)	5 (1.5)	7 (2.1)

The sponsor also did a categorical assessment of the incidence of subjects with measured blood pressures at any time post randomisation of less than 90 mmHg systolic or 50 mmHg diastolic, regardless of symptom presentation. The results showed that the incidences were comparable between the age groups of <75 years and ≥75 years (see Table 7 below).

Table 7. Incidence of patients exhibiting SBP <90 or DBP <50 post-baseline (based on complete DB phase database), study A6141079

Age Group	Inspra (N=1367)	Placebo (N=1376)
All patients	120 (8.8)	72 (5.2)

Age Group	Inspra (N=1037)	Placebo (N=1048)
Age <75	92 (8.9)	54 (5.2)

Age Group	Inspra (N=330)	Placebo (N=328)
Age >=75	28 (8.5)	18 (5.5)

The sponsor acknowledged in their response that there "*may be an age related component. As is often the case, in the absence of definitive data, there may be a greater sensitivity to treatment in older individuals, with appropriate clinical monitoring and oversight potentially prudent based on individual clinical presentation*". However, the sponsor stated that the term "*hypotension*" has been included in the proposed PI as "*Common*" in the *Adverse Effects* section and that they would therefore not be proposing to add a "*Precaution*" related to these post hoc observations "*given the current proposed product information already informs of relative incidence of the AE from the study, which is more clinically relevant than the post hoc numerical reductions discussed here*".

The evaluator noted that hypotension has been included as a common adverse event in the proposed PI. However, although these post-hoc observations were not definitive, they suggested that eplerenone may be associated with a greater drop in systolic BP in patients aged ≥75 years. Clinicians prescribing eplerenone will be guided by the PI in deciding the frequency of monitoring of BP. Given that these observations suggested that there may be greater sensitivity to treatment in older patients who may therefore need closer BP monitoring, it is recommended that a statement stating that "*post-hoc analyses in the EMPHASIS-HF study suggested that there may be a greater sensitivity to treatment in older individuals and thus potentially greater reductions in blood pressure with the use of eplerenone compared to younger individuals*" be added as a precaution to the heading of "*Use in elderly*" in the proposed PI.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of eplerenone in the proposed usage are unchanged from those identified in the First Round Evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of eplerenone in the proposed usage are unchanged from those identified in the First Round Evaluation.

Second round assessment of benefit-risk balance

The benefit-risk balance of eplerenone, given the proposed usage, was considered to be favourable.

Second round recommendation regarding authorisation

It is recommended that the application for extension of indication of eplerenone for treatment of adult patients with NYHA Class II chronic heart failure, as an addition to standard optimal therapy, be approved.

This is subject to a satisfactory response to the recommended changes in the PI recommend to the Delegate by the evaluator.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 8.

Table 8. Ongoing safety concerns as identified by the sponsor.

Type of risk	Risk
Important identified risks	Myocardial infarction
	Hyperkalemia
	Renal impairment
	Pruritus
Important potential risks	Rash

OPR reviewer comment

Pursuant to the evaluation of the nonclinical and clinical aspects of the safety specifications (SS), the above summary of the Ongoing Safety Concerns were considered acceptable.

Pharmacovigilance plan

Routine pharmacovigilance activities were proposed for all identified/potential safety concerns.

The sponsor states that a multi-tiered pharmacovigilance system is in place which includes 'an early alert safety database, the Pfizer Analytical and Statistical Tool (PfAST), product-specific data capture tools, periodic safety reports and regularly scheduled labelling reviews.'

The sponsor proposes the following activities pertaining to certain identified risks (outlined in Table 9):

Table 9. Overview of activities pertaining to certain identified risks as proposed by the sponsor.

Identified/potential safety concern	Action/assessment
Myocardial infarction	PSURs, DME reviews, TME reviews, RMCs, data mining
Hyperkalemia	PSURs, DME reviews, TME reviews, RMCs, data mining
Renal impairment	PSURs, DME reviews, TME reviews, RMCs, data mining
Pruritus	PSURs, DME reviews, TME reviews, RMCs
Rash	PSURs, DME reviews, TME reviews, RMCs

PSURs= Periodic Safety Update Report; DME=Designated Medical Event; TME= Targeted Medical Event;

RMC= Risk Management Committee

Currently, the sponsor activates the Periodic Safety update Report (PSUR) process every 3 years and states that this may revert to every 6 months once the new indication is approved (in accordance with Volume 9A of the Rules Governing Medicinal Products in the European Union[10]).

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

According to the submission by the sponsor, no studies were either ongoing or planned. The sponsor only mentions 3 completed studies regarding the use of eplerenone in patients with heart failure. The studies are: EMPHASIS-HF (Study A6141079; considered the use of eplerenone for mild to moderate heart failure), REMODEL (Study A6141078), and EPHESUS (Study A6141029; considered the use of eplerenone for left ventricular dysfunction post myocardial infarction).

The sponsor used mainly the EMPHASIS-HF study to identify risks of the drug by comparing the number of potential adverse events in the treatment group versus the placebo group. This was considered acceptable, as this identified the main risks.

Appropriateness of milestones

The proposed 6 month (or potentially 12 month) milestones for submission of PSURs are acceptable.

Risk minimisation activities

A summary of planned actions was provided by the sponsor. The sponsor proposed routine risk minimisation activities[11] for the safety concerns Myocardial infarction, Hyperkalemia, Renal Impairment, Pruritus and Rash.

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[10] <http://eudravigilance.ema.europa.eu/human/docs/vol9A_2007-04.pdf>
[11] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

OPR reviewer comment

The proposed measures are appropriate and feasible. The drug has been on the market since 2005. However, additional considerations should be taken into account regarding updating information in the PI and the CMI.

In regard to the proposed routine risk minimisation activities, it is noted that eplerenone is contraindicated in the EU Summary of Product Characteristics (SmPC) and Canadian product labelling in patients with a potassium level of >5.0mmol/L whereas in the Australian PI the level contraindicated is >5.5mmol/L. The sponsor is requested to provide robust justification of this apparent inconsistency or consider changing.

There are numerous omissions in the Australia PI with regards to interactions in comparison with those mentioned in the EU SmPC and Canadian documents. These differences require justification.

The sponsor should consider mentioning that eplerenone and lithium should not be co-administered (or a statement to that effect); the concomitant use of eplerenone and cyclosporin or tacrolimus should be avoided, but if needed, close monitoring of serum potassium and renal function should be performed (or a statement to that effect).

The sponsor should consider adding that the concomitant use of eplerenone and trimethoprim increases the risk of hyperkalemia and requires monitoring of serum potassium and renal function (or a statement to that effect).

In addition potential increases of the antihypertensive effects or postural hypotension may be observed in the concomitant use of eplerenone and the following drugs or drug groups: tricyclic anti-depressants, neuroleptics, amifostine, baclofene and alpha-1-blockers (or a statement to that effect).

More examples of CYP3A4 inhibitors in the PI, such as ritonavir, nelfinavir, clarithromycin, telithromycin, troleandomycin and nefazadone (or a statement to that effect) may be included.

In the '*Contraindications'* section, the sponsor should consider adding more examples of CYP3A4 inducers in the PI, such as rifampin, carbamazepine, phenytoin and phenobarbital (or a statement to that effect).

In the '*Dosage and Administration*' section, the sponsor should consider adding 'E*plerenone dosing should therefore not exceed 25 mg when mild to moderate inhibitors of CYP3A4 are co-administered with eplerenone*' and add examples of these drug (such as, erythromycin, saquinavir, amiodarone, diltiazem, verapamil and fluconazole) (or a statement to that effect).

The proposed Australian PI does not reflect the above issues.

In regard to the proposed routine risk minimisation activities, the draft consumer medicine information should be revised to reflect the approved product information, when finalised.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of a RMP satisfactory to the TGA is imposed as a condition of registration; and the submitted EU-RMP is applicable without modification in Australia unless so qualified and the draft product information and consumer medicine information documents should not be revised until the Delegates Overview has been received.

Further safety considerations

The sponsor should be aware that safety considerations may be raised by the nonclinical evaluator through the consolidated request for information from the TGA and/or the nonclinical evaluation report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the Risk Management Plan and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.

Pharmacovigilance milestones

The proposed 6 month (or potentially 12 month) pharmacovigilance milestones are acceptable. The Delegate may wish to consider whether 3 yearly updated PSURs are acceptable.

Proposed Product Information content

9. In regard to the proposed routine risk minimisation activities, it is noted that eplerenone is contraindicated in the EU SmPC and Canadian product labelling in patients with a potassium level of >5.0mmol/L whereas in the Australian PI the level contraindicated is >5.5 mmol/L. The sponsor is requested to provide robust justification for this apparent inconsistency.

10. In the proposed product information, overdosing and its management have been discussed to a satisfactory standard. Nevertheless the Poisons Information telephone number should be included in the PI.

11. In regard to the proposed routine risk minimisation activities, it is drawn to the Delegate's attention that the draft Product Information document is deficient in several areas, most notably in the Interactions section.

See also VI. Overall conclusions and risk/benefit assessment. Risk Management Plan below.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended that the extensions of indication sought by the sponsor should be approved.

Pharmacokinetics

No new data to be evaluated.

Pharmacodynamics

No new data to be evaluated.

Efficacy

There was a single, pivotal clinical trial [Study A6141079, EMPHASIS-HF] but there were 3 separate clinical study reports submitted. The trial was originally planned to continue until 813 primary endpoints had occurred but after the protocol-specified second interim analysis on 6 May 2010, when there were a total of 501 adjudicated primary endpoint events reviewed, it was recommended that the study be stopped. This decision was based on the pre-specified stopping rules regarding early attainment of positive efficacy results. Therefore enrolment into the study was stopped on 26 May 2010 and a 12 month open-label phase initiated. Although enrolment into the study was halted on 26 May 2010, the double-blind phase of the study continued until all actively participating subjects were able to be transitioned into the open-label extension phase.

The 3 separate clinical study reports were as follows:

·   The amended primary CSR (pCSR) which reported data for all subjects from study initiation on 30 March 2006 to termination of enrolment on 25 May 2010

·   The supplemental CSR which reported data for all subjects still in double-blind treatment from termination of enrolment (26 May 2010) to the end of the double-blind phase (18 March 2011); also included was an overall summary of all double-blind data from study initiation (30 March 2006) to the end of the double-blind phase (18 March 2011)

·   The open-label extension report which reported data from all subjects in the open-label extension phase, that is, from the end of their double-blind phase to the submission cut-off point (14 June 2011). It should be noted that this open-label extension report is not a final clinical study report. It does not contain any efficacy data, only safety data.

The most important of these 3 study reports is the amended primary CSR or pCSR, the report of Study A6141079 in its double-blind phase up to 25 May 2010. Study A6141079 was a multi-centre, randomised, double-blind, placebo-controlled, parallel-group trial whose primary objective was the evaluation of the efficacy and safety of eplerenone plus standard heart failure therapy versus placebo plus standard heart failure therapy on the cumulative incidence of cardiovascular mortality or hospitalisation for heart failure.

Subjects in the study were males or females of at least 55 years of age, with chronic systolic heart failure of either ischaemic or non-ischaemic aetiology and of duration of at least 4 weeks characterised by either LVEF ≤30% or LVEF ≤35% + QRS duration of at least 130 msec. All subjects had to have heart failure associated with a functional capacity of NYHA Class II and were already to be on standard heart failure therapy consisting of ACE inhibitors and/or angiotensin receptor blockers, beta-blockers and/or diuretics. Subjects were also required to have a serum potassium level ≤5.0 mmol/L and eGFR of at least 30 mL/min/1.73 m^2 within the 24 hours prior to randomisation. The currently approved PI contraindicates the administration of eplerenone to patients with moderate to severe renal insufficiency (creatinine clearance <50 mL/min). While creatinine clearance and eGFR are not precisely the same thing, the latter being a guide to the former, it is worth noting that subjects with moderate renal failure, that is, with eGFR between 30 and 49 mL/min/1.73m^2 were enrolled into the study. The clinical evaluator asked questions of the sponsor about the enrolment of this sub-group.

The primary efficacy endpoint was the composite of the first occurrence of cardiovascular mortality or hospitalisation for heart failure. In a response to the clinical evaluation report,

the sponsor explained that the definition of hospitalisation for heart failure includes a decision by the Endpoint Adjudication Committee that heart failure has to be the primary admitting diagnosis for the hospitalisation. Thus any occurrence of heart failure merely as a component of a hospitalisation did not qualify that hospitalisation as a primary endpoint event.

The main secondary efficacy endpoint was the composite endpoint of first occurrence of all-cause mortality or heart failure hospitalisation. There were a number of other secondary efficacy endpoints.

Subjects were randomised 1:1 to the two treatment arms, eplerenone + standard HF therapy versus placebo + standard HF therapy. Subjects received eplerenone 25mg or matching placebo once daily for the first 4 weeks of treatment. For subjects with an eGFR between 30 and 49 mL/min/1.73m^2, the initial dose of study drug was eplerenone 25 mg or matching placebo every second day for the first 4 weeks. Any later dose adjustments were according to serum potassium level.

Efficacy analyses were performed on the Full Analysis Set [FAS] composed of all randomised subjects. As noted previously, this was an endpoint-driven study with an estimate that a total of 813 primary endpoint events were required in order to have at least 80% power to detect an 18% reduction in the rate of the primary efficacy endpoint. As a result of a blinded data review on 28 March 2009, the annual event rate was estimated to be 12%, lower than the original estimate of 18%. In order to reach the 813 primary endpoints required for study completion, it was re-estimated that a sample size of 3100 subjects, 1550 per treatment arm, would be required. The Delegate requested that the sponsor to confirm that this re-estimation of a sample size of 3100 was based upon an event rate of 12%. The Delegate is not entirely certain, having read the clinical evaluation report, that the trial was stopped early on 25 May 2010, that is, slightly more than a year after the blinded data review of 28 March 2009 because there was a demonstrably better outcome in the eplerenone arm by 25 May 2010 or because the trial was going to take too long to enrol sufficient subjects. The sponsor was asked to clarify this issue in detail in its pre-ACPM response.

A total of 3027 subjects were screened and 2737 subjects were randomised, 1364 to the eplerenone group and 1373 to the placebo group. Given that the real event rate was 12% and not 18% as originally estimated and given that a sample size of 3100 (1550 in each treatment arm) would have been required for this real event rate of 12% rather than the 2737 subjects who were actually randomised, was the study actually powered appropriately for the outcomes sought? The baseline demographic and disease characteristics were comparable between treatment groups with the majority of subjects being male [77-78%] and White [82-83%]. The mean [standard deviation (SD)] age was 68.7 [7.7] in the eplerenone group and 68.6 [7.6] in the placebo group while the aetiology of the heart failure was ischaemic in the majority of subjects [approx. 69%].

Overall, 18.3% [249/1364] of subjects in the eplerenone group and 25.9% [356/1373] of subjects in the placebo group were reported as having a primary endpoint outcome, that is, either cardiovascular death or hospitalisation for heart failure. This represents an absolute risk reduction of 7.6% or relative risk reduction of 37.0% for the eplerenone group compared with the placebo group, the latter having been found to be statistically significant [p <0.0001]. The results for the primary efficacy endpoint and for each of its two components are displayed in Table 10 below.

Table 10. Survival analysis of heart failure hospitalisation or cardiovascular death (full analysis set), study A6141079, double-blind phase up to 25 May 2010

	Number (%) of Subjects		Hazard Ratio	P-value	95% CI for Hazard Ratio
	Eplerenone (N = 1364)	Placebo (N = 1373)			
HF hospitalization/CV death	249 (18.3)	356 (25.9)	0.630	<0.0001	0.535, 0.741
HF hospitalization	164 (12.0)	253 (18.4)	0.576	<0.0001	0.473, 0.702
CV death	147 (10.8)	185 (13.5)	0.757	0.0120	0.609, 0.941

Hazard ratio, 95% CI of hazard ratio, and p-value were based on a Cox proportional hazard model including treatment as the major factor, adjusting for age, eGFR, LVEF, BMI, hemoglobin, heart rate, SBP, diabetes, history of hypertension, prior MI, baseline LBBB and QRS, and atrial fibrillation as covariates.
CI = confidence interval; HF = heart failure; CV = cardiovascular; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; BMI = body mass index; SBP = systolic blood pressure; MI = myocardial infarction; LBBB = left bundle branch block; QRS = time from electrocardiogram Q wave to the end of the S wave corresponding to ventricle depolarization

For the primary endpoint component of hospitalisation for heart failure, the results were statistically significantly in favour of eplerenone. Although the rates of CV death were lower in the eplerenone group than in the placebo group, the extent of the reduction was not statistically significant. Components, being treated as secondary endpoints, had to satisfy a more stringent test of statistical significance, namely a p-value of less than 0.01, rather than less than 0.05.

Kaplan-Meier plots of time to first event for the primary endpoint and each of its components showed a clear and increasing separation between the treatment arms (less so as expected with the component of time to cardiovascular death).

Analysis of the rates of the main secondary efficacy endpoint of the first occurrence of all-cause mortality or heart failure hospitalisation and analyses of the rates of the minor secondary endpoints of all-cause mortality, all-cause hospitalisation, heart failure hospitalisation, all-cause death or all-cause hospitalisation, heart failure death or heart failure hospitalisation and cardiovascular hospitalisation all revealed statistically significant relative risk reductions in the eplerenone group compared with the placebo group. The Delegate did note that the minor endpoints from all-cause hospitalisation onwards were listed below the secondary endpoint of cardiovascular mortality in the table submitted. The latter endpoint was shown to be not statistically significant. Was there any pre-defined hierarchy in the analyses of the secondary endpoints? In other words did a non-statistically significant result for any particular parameter automatically mean that all parameters tested subsequently could not achieve statistical significance or were all secondary endpoint analysis results considered statistically significant if a p value less than 0.01 was obtained? The sponsor was asked to clarify this issue and justify whatever approach was taken for the statistical analysis of secondary endpoints.

Sub-group analyses on the primary efficacy endpoint showed that there was a statistically significant relative risk reduction in favour of eplerenone over placebo across the sub-groups, except for those subjects without prior beta-blocker use, subjects without prior ACE inhibitor or angiotension receptor blocker use, subjects with prior hospitalisation ≥180 days and subjects with baseline LBBB. All of these sub-groups, except the one with subjects with baseline LBBB, were small and the confidence intervals were correspondingly relatively wide. In the case of the group of subjects with baseline LBBB, it was a reasonably sized group of 888 and this is reflected in the confidence interval which one could regard as only modestly wide. Given the nature of LBBB, this is probably not a well defined group. Furthermore the upper limit of the confidence interval appears to be almost co-incident with 1.0. The Delegate requested that the ACPM to comment on this issue. The sponsor was also invited to comment on this issue.

Reassuringly, when the primary endpoint was analysed with respect to age, in particular comparing the group below the age of 75 years (n = 2080) with that aged at least 75 years

(n = 657), the point estimates of the primary endpoint hazard ratio for each sub-group appear to be the same with the only difference being a modest widening of the confidence interval for the older age group. This slight widening is consistent with the smaller size of that more elderly sub-group. The upper limit of that slightly wider confidence interval is clearly less than 1.0. However, the Delegate has noted that, while there were statistically significant reductions in the rates of both all-cause mortality and cardiovascular mortality in the group aged less than 75 years, the corresponding reductions in the group aged at least 75 years were not statistically significant. The Delegate requests the sponsor to provide, in its pre-ACPM response, the actual rates, both as percentages and as numerator/denominator, of all-cause mortality, cardiovascular mortality and heart failure death in the group aged less than 75 years and in the group aged at least 75 years.

Other efficacy analyses

The only other clinical study report to offer an analysis of efficacy was the report called the supplemental CSR [sCSR]. The latter presented efficacy data for 2 datasets, all data collected from 26 May 2010 to the end of the double-blind phase [18 March 2011], referred to as the "post-cut off dataset" and the complete double-blind data, that is, from 30 March 2006 to 18 March 2011, referred to as the "complete double-blind phase dataset".

In the complete double-blind phase dataset, a total of 1367 subjects were randomised to the eplerenone group and 1376 subjects to the placebo group. Of 1364 subjects treated with eplerenone, 826 (60.4%) completed the double-blind phase and of 1372 subjects treated with placebo, 771 (56.0%) completed the double-blind phase. The Delegate requests the sponsor to account for the extra subjects apparently left out of these calculations, that is, the 3 (1367-1364) extra in the eplerenone group and the 4 (1376-1372) extra in the placebo group. The Delegate assumed that the apparently low rates of completion of the double-blind phase are accounted for by earlier than expected transitioning to the open-label extension phase. The sponsor was requested to confirm whether or not this is the case. In its pre-ACPM response, the sponsor was requested to give a detailed overall accounting of the disposition and/or early transitioning of all patients which occurred throughout the study, an accounting summary which is to be transparent, logically set out and above all easily digestible and comprehensible.

As noted in the clinical evaluation report, overall, the baseline demographic and disease characteristics were comparable between treatment groups in both the post cut off dataset and the complete double-blind phase dataset and were also comparable with those presented for the double-blind phase up to 25 May 2010. The efficacy results in both the post-cut off dataset and the complete double-blind phase dataset were not analysed for statistical significance but the Delegate agreed with the clinical evaluator that the results of the complete double-blind phase were generally comparable with those of the double-blind phase up to 25 May 2010. With regard to the slightly smaller post cut off dataset, the one notable exception to a favourable comparison with the results of the double-blind phase up to 25 May 2010 involves of course the rates for the primary efficacy endpoint, 3.6% for the eplerenone group [n = 1041] versus 3.4% for the placebo group [n = 1006]. This lack of consistency in the results for the primary efficacy endpoint across the 3 populations was of concern to the Delegate and the sponsor was asked to comment on this issue. The ACPM was also asked to express its opinion as to whether this lack of consistency with regard to the primary efficacy endpoint undermines, to any significant degree, the robustness of the findings of the study overall. The Delegate has reproduced the table below.

Table11. Baseline demographic and disease characteristics, and main efficacy endpoints for double-blind phase up to 25 May 2010, post cut-off dataset, and complete double-blind phase dataset. Table continued across two pages.

	Double-blind phase up to 25 May 2010		Post cut-off database		Complete double-blind phase dataset	
	Eplerenone (N=1364)	placebo N=1373	Eplerenone N=1041	placebo N=1006	Eplerenone N=1367	placebo N=1376
Baseline demographic and disease characteristics						
Males (%)	77.3	78.1	76.4	78.2	77.4	78.1
White (%)	82.6	83.1	85.0	84.8	82.6	83.1
Mean age (SD) (years)	68.7 (7.7)	68.6 (7.6)	68.3 (7.5)	68.3 (7.7)	68.7 (7.7)	68.6 (7.6)
Ischaemic aetiology of HF (%)	69.7	68.1	67.4	66.9	NA	NA
Mean duration of ischaemic HF (years)	5.36	5.34	5.31	5.15	NA	NA
Primary efficacy endpoint CV mortality or hospitalisation for HF	18.3%	25.9%	3.6%	3.4%	21.1%	28.5%
Main secondary efficacy All-cause mortality or HF hospitalisation	19.8%	27.4%	3.7%	4.0%	22.8%	30.4%

	Double-blind phase up to 25 May 2010		Post cut-off database		Complete double-blind phase dataset	
	Eplerenone (N=1364)	placebo N=1373	Eplerenone N=1041	placebo N=1006	Eplerenone N=1367	placebo N=1376
Mortality secondary endpoints						
All-cause mortality	12.5%	15.5%	3.1%	4.0%	15.0%	18.4%
CV mortality	10.8%	13.5%	2.8%	3.0%	13.0%	15.6%
Morbidity secondary endpoints						
All-cause hospitalisation	29.9%	35.8%	4.5%	5.3%	33.9%	40.1%
HF hospitalisation	12.0%	18.4%	2.1%	2.1%	13.6%	20.1%
CV hospitalisation	22.3%	29.1%	3.5%	3.7%	25.3%	31.9%
All-cause mortality-morbidity composite secondary endpoint						
All-cause mortality or all-cause hospitalisation	33.9%	41.4%	5.6%	6.0%	38.8%	46.2%
HF mortality-morbidity composite secondary endpoint						
HF mortality or HF hospitalisation	12.5%	19.1%	2.3%	2.2%	14.2%	20.9%

Safety

As with the evaluation of efficacy, safety was evaluated in an amended primary CSR [pCSR] and a supplemental CSR [sCSR]. The major difference between the evaluations of efficacy and safety was that the open-label extension (OLE) CSR did actually provide safety data for analysis, safety data from all subjects in the OLE phase from the end of their double-blind phase to the submission cut-off point of 14 June 2011. The Delegate will focus on the data contained within the pCSR.

The median duration of treatment from study start to study cut-off was comparable between the treatment groups at 533.0 days and 494.0 days in the eplerenone and placebo groups, respectively.

As reported in the pCSR, in the eplerenone group, 979 patients reported 3431 AEs and in the placebo group 1007 patients reported 3530 AEs. The percentages of subjects with any AEs were 72.0% (979/1360) and 73.6% (1007/1369) in the eplerenone and placebo groups, respectively.

The most commonly reported treatment-emergent AEs [all causalities] occurring in ≥2% of subjects in either treatment group [pCSR] were as follows: in the eplerenone group cardiac failure (17.4% versus 21.8% in the placebo group), hyperkalemia (8.0% versus 3.7% in the placebo group), dyspnoea (4.3 % versus 5.1% in the placebo group), renal impairment (4.2% versus 2.6% in the placebo group) and dizziness (4.0% versus 4.4% in the placebo group). In the OLE phase a total of 246 (21.3%) subjects reported 415 AEs up to the data snapshot date. Therein the most commonly reported AEs were hyperkalemia (17 [1.5%] subjects), cardiac failure (15 [1.3%] subjects), nasopharyngitis (13 [1.1%] subjects) and chest pain (11 [1.0%] subjects).

In the eplerenone group [pCSR], 280 patients reported 436 treatment-related AEs and in the placebo group [pCSR] 218 patients reported 322 treatment-related AEs. The percentages of subjects with any treatment-related AEs were 20.6% (280/1360) and 15.9% (218/1369) in the eplerenone and placebo groups, respectively. Treatment-related AEs by preferred term that occurred in >1% of subjects in the eplerenone group were hyperkalemia (6.6% versus 2.8% in the placebo group) and renal impairment (1.4% versus 0.9% in the placebo group). Out of the 90 subjects in the eplerenone group who had treatment-related AE of hyperkalemia, 62 were of mild severity, 21 were moderate and 7 were severe. It is stated in the clinical evaluation report that in the open-label extension phase a total of 66 (5.7%) subjects reported 82 treatment-related AEs in the OLE phase up to the data snapshot date. The most commonly reported treatment-related AE was hyperkalemia, reported by 15 [1.3%] subjects. When the Delegate goes to the tables cited by the clinical evaluator as supporting these results, it was noted that the tables relate to treatment-emergent adverse events (all causalities and treatment-related). The Delegate would have assumed that the term 'all causalities' would have, by definition, included those events which were 'treatment-related'. The Delegate requests the sponsor to define precisely the term 'all causalities and treatment-related'. The Delegate further requests the sponsor to provide tables showing the frequencies/incidences of actual treatment-related events for the OLE phase.

The number of deaths reported and adjudicated [pCSR] was 171 (12.5%) in the eplerenone group and 213 (15.5%) in placebo group. The clinical evaluator noted that there had been no details provided in the data as to which deaths were considered related to study treatment and asked the sponsor to provide these details. The issue is discussed in the clinical evaluation report under *Safety Question 5*. It would appear that no 'direct data' allowing such attribution was collected. The Delegate was not satisfied by this explanation and requested the sponsor to clarify in detail the extent of the data available which would allow some estimation of the numbers of deaths which could be attributed to study treatment. There were a total of 22 (1.9%) deaths in the OLE phase prior to the data snapshot date.

Overall [pCSR], 37.4% of subjects (509/1360) in the eplerenone group reported 1105 SAEs and 44.9% of subjects (614/1369) in the placebo group reported 1349 SAEs. The most frequently occurring SAE in the eplerenone group by System Organ Class (SOC) was in the SOC of Cardiac disorders (22.5% versus 28.7% in the placebo group). The most frequently occurring SAEs in the eplerenone group by preferred term were cardiac failure (eplerenone vs placebo: 13.8% versus 17.8%), myocardial infarction (2.1% versus 2.1%) and death (1.9% versus 2.5%). The clinical evaluator asked the sponsor to clarify the

numbers of treatment-related SAEs and this was addressed under *Safety Question 6*. In the pCSR 37 (2.7%) subjects in the eplerenone group had 50 treatment-related SAEs compared to 30 (2.2%) subjects in the placebo group who reported 38 treatment-related SAEs. The most-frequently reported treatment-related SAEs in the eplerenone group were hyperkalemia (0.9% [12/1360] versus 0.2% [3/1369] in the placebo group), cardiac failure (0.4% [5/1360] versus 0.2% [3/1369]), and renal impairment (0.4% [5/1360] versus 0.4% [5/1369]). In the OLE phase, the most frequently occurring SAE by preferred term was cardiac failure, reported by 12 (1.0%) subjects.

A total of 188 (13.8%) and 222 (16.2%) of subjects in the eplerenone and placebo groups, respectively, permanently discontinued the study due to any AEs [pCSR]. Permanent study discontinuation due to treatment-related AEs occurred in 46 (3.4%) and 42 (3.1%) of subjects in the eplerenone and placebo groups, respectively. The sponsor was requested to provide, in its pre-ACPM response, details of the frequencies, in descending order, of the ten most common treatment-related AEs leading to permanent discontinuation in the pCSR for eplerenone and for placebo. If there were events in each list of ten which did not occur in both lists, then the sponsor was requested to report also the corresponding frequency from the other treatment arm. For the post cut-off and complete double-blind phase datasets, details of individual AE frequencies/incidences appear to have been given and involve small numbers of such events as blood creatinine increased, hyperkalemia and renal failure. A total of 28 (2.4%) subjects permanently discontinued the study in the OLE phase due to AEs, with 12 (1.0%) subjects discontinuing due to treatment-related AEs. The most frequently reported AEs leading to permanent discontinuation were cardiac failure/worsening heart failure, death and hyperkalemia, each reported by 3 subjects.

As noted by the clinical evaluator, there were no significant laboratory abnormalities of concern except for serum creatinine, eGFR and serum potassium.

The mean (SD) change from baseline in serum creatinine at the final follow-up assessment was 0.09 (0.37) mg/dL in the eplerenone group and 0.04 (0.40) mg/dL in the placebo group (p = 0.0157) [pCSR]. The sponsor was asked to provide, in its pre-ACPM response, details of the numbers/percentages of subjects who moved from normal renal function at baseline to impaired renal function (mild, moderate or severe–stratified if possible) at final follow-up, the numbers/percentages of subjects who moved from mildly impaired renal function at baseline to either moderately or severely impaired renal function (moderate or severe-stratified if possible) at final follow-up and the numbers/percentages of subjects who moved from moderate impairment of renal function at baseline to severe impairment of renal function at final follow-up. The serum creatinine should be used as the determinant of renal function. The Delegate requested also that this exercise be repeated using eGFR as the determinant of renal function. The Delegate also requested that both sets of results be stratified by age; <75 years and ≥75 years. For completeness, the Delegate also requested that all the calculations requested so far in this paragraph be repeated for the complete double-blind phase dataset, that is, sCSR.

The mean (SD) change from baseline in serum potassium at the final follow-up assessment was 0.16 (0.56) mEq/L in the eplerenone group and 0.05 (0.53) mEq/L in the placebo group (p <0.0001). The incidence of potassium levels of >5.5 mEq/L was statistically significantly higher in the eplerenone group compared to the placebo group (11.8% versus 7.16% p <0.0001). There was no statistically significant difference in the incidence of potassium levels of >6 mEq/L between treatment groups. For the group of subjects reported with a potassium level >5.5 mEq/L, the sponsor was requested to give details of the mean, median, interquartile range (showing lower and upper limits) and range (showing min and max) of serum potassium for eplerenone versus placebo. Likewise, for the group of subjects reported with a potassium level >6 mEq/L, the sponsor was requested to give details of the mean, median, interquartile range (showing lower and

upper limits and range (showing min and max) of serum potassium for eplerenone versus placebo.

Serum creatinine and eGFR were not assessed in the OLE phase. Analyses of serum potassium in the subjects in the OLE phase showed that 7.46% (82/1099) of subjects and 5.19% (57/1099) of subjects had serum potassium >5.5 mEq/L and >6 mEq/L, respectively.

There were statistically significantly greater mean reductions from baseline in the SBP and in the DBP in the eplerenone group compared to the placebo group [pCSR]. At the final follow-up assessment, the mean change from baseline in SBP was -2.47 mmHg in the eplerenone group and -0.25 mmHg in the placebo group. This difference was found to be statistically significant (p = 0.0005). The mean change from baseline in DBP at the final follow-up assessment was -1.83 mmHg in the eplerenone group and -0.71 mmHg in the placebo group. This difference was also found to be statistically significant (p = 0.0014). The median changes from baseline to last observation in SBP was -2.00 mmHg and 0.00 mmHg in the eplerenone and placebo group, respectively, and that in DBP were 0.00 mmHg in both treatment groups. As part of the consolidated request for information, the clinical evaluator asked the sponsor for analyses of the numbers/percentages of subjects in each group, that is, eplerenone versus placebo who, from baseline to final follow-up, experienced reductions of at least 5, 10, 15 and 20 mmHg in SBP, DBP and in both SBP and DBP. These results were also to be stratified by age; <75 years and ≥75 years. The sponsor's response to this request is discussed later in this overview. Tables 5 and 6 summarises the further analysis provided by the sponsor.

A search of Pfizer's postmarketing safety database showed that the most frequently reported adverse event was hyperkalemia. The overall postmarketing analyses were consistent with the known safety profile of eplerenone.

To satisfy a European Medicines Agency (EMA) imposed commitment, the safety data from the pivotal Study A6141079 were comprehensively analysed for the very elderly subjects in the study, that is, those subjects aged at least 75 years.

Safety analyses in the subgroup of patients aged ≥75 years showed that the incidences of all-causality AEs, treatment-related AEs, all-causality SAEs, and treatment-related SAEs were higher in this subgroup of patients in the eplerenone group compared to those in the overall study population and to those aged <75 years. The clinical evaluator noted that the incidences of these AEs and SAEs were also higher in the placebo group in the sub-group of patients aged ≥75 years compared with the respective placebo groups in the overall study population and in the sub-group of patients aged <75 years. The clinical evaluator suggested that the higher incidences of these AEs and SAEs seen in the eplerenone groups in the sub-group of patients aged ≥75 years might be reflecting the generally higher incidence of AEs or SAEs in the more elderly age group per se, rather than an actual adverse effect of eplerenone on the sub-group of elderly patients. While this argument has merit, it is difficult to state the precise extent to which it has merit. The ACPM was invited to comment on this issue.

As is known, the most commonly occurring treatment-related AE in the eplerenone group overall was hyperkalemia. The incidence of potassium levels of >5.5 mEq/L was statistically significantly higher in the eplerenone group compared to the placebo group in both age group categories. In subjects of age ≥75 years the incidences of potassium levels of >5.5 mEq/L were 12.42% and 6.60% in the eplerenone and placebo groups, respectively (p <0.0001). In subjects of age <75 years the incidences of potassium levels of >5.5 mEq/L were 11.64% and 7.34% in the eplerenone and placebo groups, respectively (p=0.0011). There was no statistically significant difference in the incidence of potassium levels of >6 mEq/L between treatment groups in both age group categories. For the groups of subjects reported with a potassium level >5.5 mEq/L, that is, the groups broken down

by age, the sponsor is requested to give details of the mean, median, interquartile range (showing lower and upper limits) and range (showing min and max) of serum potassium for eplerenone versus placebo. Likewise, for the groups of subjects reported with a potassium level >6 mEq/L, that is, the groups broken down by age, the sponsor was requested to give details of the mean, median, interquartile range (showing lower and upper limits) and range (showing min and max) of serum potassium for eplerenone versus placebo. This request is really an extension of the request already made above but this time stratifying the results by age.

In subjects ≥75 years of age, there was a statistically significant difference between the treatment groups in mean change from baseline in SBP at the final follow-up assessment (-4.75 mmHg in the eplerenone group and -0.70 mmHg in the placebo group [p = 0.0315]). There were no statistically significant differences between treatment groups in the mean change from baseline at the final follow-up assessment for DBP, pulse pressure or pulse rate in those subjects ≥75 years of age. The median changes from baseline to last observation in SBP was -5.00 mmHg and 0.00 mmHg in the eplerenone and placebo groups, respectively, and that in DBP were -3.00 mmHg and 0.00 mmHg, respectively. In subjects <75 years of age, there was a statistically significant difference between the treatment groups in mean change from baseline in SBP at the final follow-up assessment (-1.75 mmHg in the eplerenone group and -0.11 mmHg in the placebo group [p = 0.0058]), as well as for DBP (-1.40 mmHg in the eplerenone group and -0.54 mmHg in the placebo group [p = 0.0101]). In this subgroup, the median changes from baseline to last observation in SBP and DBP were 0.00 mmHg in both treatment groups. As noted by the clinical evaluator there was no analysis in the current submission of responder rates defined by the degree of reduction in SBP and DBP. To this end the evaluator asked the sponsor to provide such an analysis (*Safety Question 8* and the response to *Safety Question 4*).

Members of the ACPM were asked to peruse Tables 5 and 6. These tables were done as a *post hoc* analysis. Among subjects aged ≥75 years, the proportion of subjects in each category of reductions in SBP and DBP was also generally comparable between the eplerenone and the placebo group, except for the category of reductions >20 mmHg, for both SBP and DBP. In the category of reductions in SBP >20 mmHg, the incidence in the eplerenone group was 37.9% compared with 24.4% in the placebo group, while in the category of reductions in DBP >20 mmHg, the incidence in the eplerenone group was 14.2% compared with 8.8% in the placebo group. Comparing the results between age groups (<75 years versus ≥75 years), the proportion of subjects in each category of reductions in SBP and DBP was generally comparable between the 2 age groups in both the eplerenone and the placebo treatment groups, except for the category of reductions >20 mmHg for SBP, where the incidence in the eplerenone group was 37.9% for subjects aged ≥75 years, compared with 28.3% for subjects aged <75 years. For the placebo group, the proportion of subjects in this category of reductions >20 mmHg for SBP was comparable between the 2 age groups (24.4% for subjects aged ≥75 years and 23.9% for subjects aged <75 years). While, as argued by the sponsor, there may be a pure age-related component to these effects, the Delegate was of the view that the results in Tables 5 and 6 clearly demonstrate an age-related effect driven by eplerenone. The rates for placebo, both below and above the age of 75 years, for a maximum reduction of >20 mmHg in SBP are almost static (23.9% and 24.4%, respectively) whereas the corresponding rates for eplerenone show a marked difference (28.3% and 37.9%, respectively). The same effect, but to a lesser extent, can be observed in the results for DBP (in fact the rates for placebo decrease when moving from the younger to the older age group). While these tables show responder rates, they do not reveal information about the extent of the reductions above that maximum cut-off of 20 mmHg. The Delegate requested that the sponsor in its pre-

ACPM response, do the following analysis for each of the 8 sub-groups in Tables 5 and 6 who experienced maximum reductions in SBP/DBP >20 mmHg[12]:

- For each of those 8 groups, please provide the mean, median, interquartile range (showing lower and upper limits) and range (showing min and max) of those actual maximum reductions in SBP/DBP.

The Delegate strongly endorsed the request of the clinical evaluator for a precaution in the PI which draws attention to this increased sensitivity of the elderly to the blood pressure lowering adverse effects of eplerenone and requested the ACPM to express its opinion on this matter. Finally, with regard to this issue of reductions in SBP/DBP, there are 48 sets of results in Tables 5 and 6, 24 in each table (4 columns x 6 rows). The sponsor was requested to give tabulated details of the numbers/percentages of subjects out of each of these 48 groups who also reported *any* signs/symptoms possibly attributable to such falls in blood pressure, such as dizziness, syncope, falls or postural hypotension.

First round risk benefit balance by the clinical evaluator

The clinical evaluator was of the opinion that the risk-benefit balance was in favour of extending the indications of eplerenone to include the treatment of adult patients with NYHA Class II chronic heart failure (that is, eplerenone in addition to standard optimal heart failure therapy) subject to the resolution of issues raised in relation to the PI and to the receipt of satisfactory answers to the clinical questions posed by the clinical evaluator (see *List of Questions* above).

Clinical questions asked as part of the TGA's consolidated request for information

The clinical evaluator asked a number of questions of the sponsor, 4 to do with efficacy, 4 to do with safety and 2 to do with the proposed PI. Some of these questions and the sponsor's responses have already been referred to in the foregoing discussion. In the next section the Delegate will briefly canvass the issues raised in the questions.

Second round evaluation of clinical data submitted in response to questions

The first 2 efficacy questions concerned the position in the study of patients with moderately impaired renal function, that is, with an eGFR of 30 to 49 mL/min/1.73m². The inclusion of this sub-group of patients had been planned prospectively and the recommendation of a lower dose of 25 mg every second day had been based on a *post hoc* analysis of the results of a previous clinical trial in patients with post acute myocardial infarction (AMI) heart failure, the EPHESUS trial. There is a reference to this analysis by Banas et al in a footnote [9] under Clinical Findings. The sponsor was requested to supply a copy of the full article with its pre-ACPM response.

For *Efficacy Question* 3, the sponsor provided data which showed that the numbers of subjects within each category of protocol deviations were comparable between treatment groups.

For *Efficacy Question* 4, that relating to the outcomes of patients with and without LBBB at baseline, it would appear that there were only 688 subjects with baseline LBBB and not 888 as described in the first round evaluation report. Thus the sub-group was even smaller. Reassuringly, the results for the primary and main secondary endpoints stratified according to the presence or absence of baseline LBBB, shows directional consistency between the 2 columns of hazard ratios. However, the Delegate strongly endorsed the statement by the evaluator that the sponsor cannot claim that patients with LBBB at baseline experienced a significant benefit from treatment with eplerenone. The Delegate

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[12] That is, for the groups with 293, 250, 123 and 105 patients in the fifth row of results in Table 5 and for the groups of 125, 80, 47 and 29 patients in the fifth row of results in Table 6.

has already made some comments about this issue (see above) and has asked the sponsor to respond.

As noted previously by the Delegate, in answer to *Safety Question* 5 it would appear that the sponsor did not provide a direct summary of the incidences of treatment-related deaths and of the incidence of each cause of death but instead provided a summary of the incidences of all-cause SAEs and treatment-related SAEs occurring within 14 days of death and of deaths due to an unknown cause. There appear to be no worrying signals arising from this proxy or surrogate data. However, as requested by the Delegate, the sponsor was asked to explain why the direct data was not available. If the direct data is indeed available, then the sponsor was requested to provide a clarifying summary of the data. The Delegate was particularly anxious to know whether adverse events such as hyperkalemia, renal failure/impairment or hypotension can or cannot be shown to have been contributory factors to any of the deaths.

With regard to *Safety Question* 6, the additional data provided by the sponsor concerning the incidences of treatment-related SAEs did not raise any significant safety concerns.

With regard to *Safety Question* 7, the additional data addressing the incidences of adverse events in the sub-group of patients with LBBB at baseline did not appear to raise any additional concerns. According to the CER, the most commonly reported treatment-related AEs in the eplerenone group were hyperkalemia (eplerenone 8.3% versus placebo 2.6%), hypotension (eplerenone 1.8% versus placebo 0.0%) and renal impairment (eplerenone 1.5% versus 1.4%).

With regard to *Safety Question* 8, the sponsor did provide a *post hoc* analysis of the responder rates defined by reductions in SBP and DBP, stratified by age. These are the results shown in Tables 5 and 6. With regard to reductions >20 mmHg it was quite clear to the Delegate that eplerenone is a driver of a pronounced age-related effect, in that the percentages of those affected increase with age. The issue was canvassed in greater detail above. The Delegate requested an appropriately worded precaution in the PI and specifically requests the advice of the ACPM on this matter. Furthermore, the Delegate has requested the sponsor perform another *post hoc* analysis to characterise more clearly the actual extent of the maximum reductions in all the sub-groups who experienced maximum reductions of >20 mmHg and also an analysis of the rates of any adverse events possibly attributable to fall in blood pressure in each of the 48 sub-groups identified in Tables 5 and 6.

In PI and CMI Question 1 the sponsor was asked for a safety analysis of the sub-group of patients with an eGFR of 30-59 mL/min/1.73 m^2 to justify relaxation of the contra-indications from 'moderate to severe renal insufficiency' to 'severe renal insufficiency'. The incidences of AEs, SAEs and discontinuations were compared between the eplerenone and placebo groups in the sub-group of patients with baseline eGFR of 30-60 mL/min/1.73 m^2 and then between the sub-group of patients with baseline eGFR of 30-60 mL/min/1.73 m^2 and the subjects with baseline eGFR ≥60 mL/min/1.73 m^2. All comparisons were relatively comparable except that the incidence of SAEs was higher in the eplerenone group in the subgroup of subjects with baseline eGFR of 30-60 mL/min/1.73 m^2 (51.3%) than in the sub-group of subjects with baseline eGFR ≥60 mL/min/1.73 m^2 (38.9%). A similar difference in the incidence of SAEs was also observed for the corresponding comparison of placebo groups. However, these sorts of comparisons are fairy crude comparisons, involving as they do groups of adverse events. Mean changes from baseline in serum potassium, serum creatinine and eGFR in the sub-group of subjects with baseline eGFR of 30-60 mL/min/1.73 m^2, in the sub-group of subjects with baseline eGFR ≥60 mL/min/1.73 m^2 and the overall population, all three groups from the complete double-blind phase dataset, are shown in the CER. Comparisons between eplerenone and placebo across the various sub-groups were broadly comparable. Again the Delegate argued that comparison of mean changes, while providing some reassurance, is a fairly

crude tool. The Delegate has asked the sponsor to report on the numbers/percentages of subjects who moved from one grade of renal impairment to a more severe grade, eplerenone versus placebo and in the two major double-blind datasets, pCSR and sCSR. The Delegate now also requested that the sponsor, for each of the three parameters reported, provides also the median, interquartile range (showing lower and upper limits) and range (showing min and max) for each of the 6 sub-groups identified in each row of the table. As noted by the clinical evaluator, the incidence of hyperkalemia in the eplerenone group was also comparable between the subgroup of subjects with baseline eGFR of 30-60 ml/min/1.73 m^2 (potassium >5.5 mEq/L: 16.94%; potassium >6 mEq/L: 2.12%) and the subgroup of subjects with baseline eGFR of ≥60 ml/min/1.73 m^2 (potassium >5.5 mEq/L: 10.92%; potassium >6 mEq/L: 2.95%). For each of the 4 sub-groups referred to in the last sentence, the Delegate requested the sponsor to provide the following details of the serum potassium: mean, median, interquartile range (showing lower and upper limits) and range (showing min and max).

In PI and CMI Question 2, the sponsor was asked to justify the proposal that patients with mild to moderate renal impairment should be started at 25 mg daily. The Delegate was not entirely certain that the mean daily dose comparisons supplied by the sponsor can really serve to justify this proposal. In the single pivotal trial evaluated, patients with mild to moderate renal impairment were not commenced on 25 mg daily but on 25 mg every second day with increase in dose determined largely by serum potassium. The Delegate requested that the sponsor provide the numbers/percentages of subjects with mild to moderate renal impairment who remained on 25 mg every second day for at least the first 2, 4, 6 and 12 weeks, who remained on this dose for the entire study duration, the numbers/percentages of subjects who transitioned from 25 mg every second day to 25 mg every day without having to reduce the dose, the numbers/percentages of subjects who transitioned from 25 mg every second day to 25 mg every day and then had to return to the lower dose at least once during the study and finally the mean and median times during which subjects were on 25 mg every second day before transitioning to 25 mg every day. What percentage of subjects commenced on a dosage of 25 mg every second day were successfully transitioned to a dosage level of 50 mg per day? What percentage of subjects commenced on a dosage of 25 mg every day were successfully transitioned to a dosage level of 50 mg per day? At this stage, the Delegate was of the opinion that the dosage and administration instructions for subjects with mild to moderate impairment should reflect the conditions under which such subjects were prescribed eplerenone in the clinical trial. The ACPM was asked to express its views on the matter.

Risk management plan

It appeared that the sponsor had not yet responded [at the time of the Delegate's Overview] to the request for information arising from the RMP evaluation.[13]

The RMP evaluator is recommending 2 specific conditions of registration, the first relating to the implementation of the agreed RMP and the second relating to the provision of post-approval PSURs. The Delegate intended to recommend these as specific conditions of registration.

The most important of the outstanding issues relates to the serum potassium level at which eplerenone should be contra-indicated. The current wording of the contra-indication is "*Inspra should not be administered to patients with clinically significant hyperkalemia (serum potassium >5.5 mmol/L at initiation)*. OPR recommended contra-indication at a level >5.0 mmol/L, based on the fact that The Royal College of Pathologists of Australasia (RCPA) normal range is stated as 3.8-4.9 mmol/L. Also in the pivotal study

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[13]This may have been due to a misunderstanding in relation to the TGA's new streamlined submission process (TGA Assessment of sponsor's response to the RMP evaluation for Inspra).

subjects were required to have a serum potassium level of ≤5.0 mEq/L in the 24 hours prior to randomization. The Delegate was uncertain at this stage whether it would be reasonable to contra-indicate the use of eplerenone when the serum potassium exceeds the upper limit of normal by slightly more than 0.1 mmol/L. However, the Delegate requested the opinion of the ACPM on this matter. The ACPM was also requested to indicate whether the currently worded precaution with respect to hyperkalemia needs strengthening in any way. Is there any evidence from the data submitted that those patients whose serum potassium lay in the intermediate range of 5-5.5 mmol/L were at increased risk of adverse outcomes, particularly clinically significant or serious hyperkalemia? The sponsor was requested to address this issue. The RMP document refers to a recently published meta-analysis by Chatterjee et al., 2012[14] which found evidence of a statistically significant association of eplerenone with hyperkalemia. A copy of this meta-analysis was placed in the ACPM agenda papers.

The remainder of the RMP assessment was concerned with requesting amendments to the wording of the PI. The Delegate endorsed all of these requests.

Risk-benefit analysis

Delegate considerations

There was a statistically significant 37% relative risk reduction in the incidence of the primary composite endpoint of cardiovascular mortality or hospitalisation for heart failure in the eplerenone group compared to the placebo group. There was a statistically significant relative risk reduction of 23.9% in all-cause mortality for eplerenone compared to placebo, as well as statistically significant relative risk reductions of 42% in hospitalisation for heart failure and of 31% in cardiovascular hospitalisation for eplerenone compared to placebo. The Delegate was of the opinion that these represent clinically significant outcomes.

The main risks associated with the use of eplerenone are the following:

· Hyperkalemia

· Increase in serum creatinine and associated decrease in eGFR

· Falls in systolic and diastolic blood pressure

By and large the Delegate agreed with the clinical evaluator that the safety results from the study were consistent with the known adverse effects of eplerenone as outlined in the currently approved PI. However, the above specific adverse events, while well known, can be associated with very serious adverse outcomes. To this end the Delegate has asked the sponsor to characterise in greater detail the adverse event data relating to hyperkalemia, increased creatinine/decreased eGFR and falls in SBP/DBP.

For instance while there may have no statistically significant difference between treatment groups in the incidence of a serum potassium >6 mEq/L, the Delegate would like to know more about the comparative distribution of these actual excess potassium levels. For example, it is not known whether the bulk of patients experiencing such levels were experiencing levels just above 6 mEq/L or markedly above the latter. It tells us nothing of outliers. The ACPM has been asked to comment on whether the precaution in the PI relating to hyperkalemia needs to be strengthened and whether there needs to be a tightening of the contra-indication in relation to serum potassium.

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[14] Chatterjee S et al., Eplerenone is not superior to older and less expensive aldosterone antagonists, Am J Med 125(8): 817-825

Comparison of mean changes from baseline in serum creatinine and in eGFR is not a particularly refined instrument. Again, in relatively large groups, the effect of outliers may be masked. Yet it is outliers who would be of most concern.

For falls in SBP/DBP, the sponsor provided a *post hoc* analysis of responder rates, that is, the proportions of subjects who had falls of either type of blood pressure of up to 5 mmHg, of between 5 and 10 mmHg and so on. While the various tables of responder rates may have demonstrated comparability of those rates between treatment groups, they do not reveal information about the extent of the reductions above that maximum cut-off of 20 mmHg. In other words, there is no information about people who may have been outliers and the comparative rates of those outliers.

The sponsor submitted a comprehensive safety analysis stratified by age, that is, <75 years and ≥75 years. Overall safety analyses results in the subgroup of patients aged ≥75 years were consistent with those in the overall study population and did not indicate significantly greater safety concerns in this age group with the use of eplerenone. Although the incidences of all-causality AEs, treatment-related AEs, all-causality SAEs and treatment-related SAEs were higher in this subgroup of patients in the eplerenone group compared to those in the overall study population and to those aged <75 years, the incidences were also higher in the placebo group in the subgroup of patients aged ≥75 years compared with the respective placebo groups in the overall study population and in the subgroup of patients aged <75 years. This suggests that the higher incidences of these AEs and SAEs seen in the eplerenone groups in the subgroup of patients aged ≥75 years might be reflecting the generally higher incidence of AEs or SAEs in this more elderly age group, rather than an actual adverse effect of eplerenone in the subgroup of elderly patients. The ACPM was asked to comment on this issue. The profile of the most commonly reported AEs and SAEs, mean changes from baseline in serum potassium, serum creatinine and eGFR at the final follow-up assessment and incidence of serum potassium levels of >5.5 mEq/L in the eplerenone group in this subgroup of patients aged ≥75 years were all comparable with that in the overall study population and that in the subgroup of patients aged <75 years. Once again the Delegate has asked the sponsor to do a number of analyses aimed at determining whether there was a noticeable difference in outlier rates based on age. With regard to reductions >20 mmHg it is quite clear to the Delegate that eplerenone is a driver of a pronounced age-related effect, in that the percentages of those affected increase with age. The Delegate requested a strengthening of the precaution in the PI relating to falls in blood pressure on eplerenone.

Indication

The Delegate recommends adoption of the wording for the extension of indication proposed by the sponsor:

"Inspra is indicated:

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 <35%) in addition to standard optimal therapy (see Clinical Trials)."

Summary

On the strength of the evidence presented in the sponsor's current submission, it would appear that eplerenone does exhibit efficacy in those subjects with NYHA Class II (chronic) heart failure. The assessment of that efficacy was complicated by the fact that there were 3 different datasets presented for evaluation. The Delegate does have some concerns about the early stopping of the clinical trial, about the disparity between the predicted (18%) and the actual (12%) event rates and how these may have had an impact on the robustness or integrity of the trial. However, more importantly, the Delegate had a large number of questions about the safety results of the study, particularly concerning the

major (and well known) adverse events relating to hyperkalemia, renal insufficiency and reductions in blood pressure.

Until all of the issues flagged by these questions and requests for clarification are satisfactorily resolved, the Delegate did not have the confidence to recommend approval of the submission at this stage.

Recommendation

The Delegate proposed to reject this submission by Pfizer Australia Pty Limited to register Inspra tablets (containing eplerenone 25 mg or 50 mg) based on the safety and efficacy of the product not yet having been satisfactorily established for the indication below, for the reasons stated above in the Risk/Benefit Discussion and elsewhere in this document.

> *"Inspra is indicated:*
>
> *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 <35%) in addition to standard optimal therapy (see CLINICAL TRIALS)."*

Any future approval will be contingent upon the provision by the sponsor of satisfactory answers to all questions asked of the sponsor in this Overwew and also upon amendment of the proposed PI document to the satisfaction of the TGA.

The Delegate intended to impose the following specific conditions of registration, the first two recommended by the Office of Product Review and the third recommended by the Delegate:

1. The implementation of Risk Management Plans as follows:
   EU-RMP Version 1.0 (dated 18/03/2011, DLP 01/02/2011) and Australian specific annex (dated 06/03/2012)) and any future updates as may be agreed with the Office of Product Review.

2. Post marketing reports are to be provided in line with the current published list of European Union (EU) reference dates and frequency until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to meet the requirements in accordance with ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports[15] and Module VII of the EMA Guideline on Good Pharmacovigilance (GPV) Practices relating to PSURs[16]. Submission of the report must be within the 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may be made up of two periodic Safety Update Reports each covering six months.

3. The submission to the TGA, as soon as it is available, of the final clinical study report of the open-label extension phase of the pivotal study, the Eplerenone in Mild Patients Hospitalisation and Survival Study in Heart Failure, EMPHASIS-HF, Study A6141079. The data is to be submitted for formal evaluation as part of a Category 1 submission.

The sponsor should address the following issues in the Pre-ACPM response (see also discussions above):

   a. The sponsor was asked questions relating to the estimated and real event rates, the sample size and the early stopping of the pivotal trial.

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[15]<http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/12/WC500136402.pdf>

[16]<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129136.pdf>

b. The sponsor was asked to clarify and justify the actual process of testing for statistical significance amongst the secondary endpoints.

c. The sponsor was asked to discuss further the analysis of the primary efficacy endpoint for the sub-group of subjects with baseline LBBB.

d. The sponsor was requested to provide the actual rates, both as percentages and as numerator/denominator, of all-cause mortality, cardiovascular mortality and heart failure death the group aged less than 75 years and in the group aged at least 75 years in the pivotal study.

e. The sponsor was requested to account for the subjects apparently left out of the calculations for the complete double-blind phase dataset and the apparently low rates of completion of the double-blind phase. The sponsor was also requested to give a detailed overall accounting of the disposition and/or early transitioning of all subjects.

f. The sponsor was asked to comment on the lack of consistency in the results for the primary efficacy endpoint across the 3 populations, the pCSR, the post cut-off dataset and complete double-blind phase dataset, the post cut-off dataset being the odd one out.

g. The sponsor was asked to define precisely the term 'all causalities and treatment-related' as it relates to the reporting of AE rates anywhere in the dossier that the term was employed. The sponsor was also asked to provide tables showing the frequencies/incidences of actual treatment-related events for the OLE phase.

h. The Delegate requested the sponsor to clarify in detail the issue of the lack of 'direct data' in relation to patient deaths. The Delegate requested the most up-to-date and most accurate estimation possible of the numbers/rates of death attributable to study treatment, particularly eplerenone versus placebo. Along with this report, the sponsor was requested to identify clearly any limitations of that estimation.

i. The sponsor was requested to provide details of the frequencies, in descending order, of the ten most common treatment-related AEs leading to permanent discontinuation in the pCSR for eplerenone and for placebo.

j. The sponsor was requested to provide a number of further analyses regarding renal function/renal impairment in the pivotal study.

k. The sponsor was requested to provide a number of further analyses of the data relating to serum potassium levels >5.5 mEq/L and >6 mEq/L.

l. The sponsor was asked to do a number of further analyses regarding the extent of the blood pressure reductions above the maximum cut-off of 20 mmHg, with a focus on outliers. The sponsor was also asked to provide a further analysis of the rates of any adverse events possibly attributable to the falls in blood pressure corresponding to the results reported in Tables 5 and 6.

m. For each of the three parameters of change from baseline to final follow-up in each of serum potassium, serum creatinine and eGFR, the sponsor was requested to provide also the median, interquartile range (showing lower and upper limits) and range (showing min and max) for each of the 6 sub-groups identified in each row of the table.

n. As noted by the clinical evaluator, the incidence of hyperkalemia in the eplerenone group was also comparable between the subgroup of subjects with baseline eGFR of 30-60 ml/min/1.73 m2 (potassium >5.5 mEq/L: 16.94%; potassium >6 mEq/L: 2.12%) and the subgroup of subjects with baseline eGFR of ≥60 ml/min/1.73 m2 (potassium >5.5 mEq/L: 10.92%; potassium >6 mEq/L:

2.95%). For each of the 4 sub-groups referred to in the last sentence, the Delegate requested the sponsor to provide the following details of the serum potassium: mean, median, interquartile range (showing lower and upper limits) and range (showing min and max).

o. The sponsor was asked a number of questions which seek to clarify the rates of transitioning between various dosage levels in the pivotal study.

p. Is there any evidence from the dossier that those patients whose serum potassium lay in the intermediate range of 5-5.5 mmol/L were at increased risk of adverse outcomes, particularly clinically significant or serious hyperkalemia ?

ACPM's advice was requested regarding the following issues;

1. Having seen the data and also having had an opportunity to assess the pre-ACPM response of the sponsor, is the ACPM of the opinion that there is sufficient evidence to support the proposed extension of indications?

2. Does the ACPM have any concerns about the results of the analysis of the primary efficacy endpoint in the sub-group of subjects with baseline LBBB.

3. Does the ACPM have any concerns regarding the lack of consistency in the results for the primary efficacy endpoint across the 3 populations, that is, the pCSR, the post cut-off dataset and complete double-blind phase dataset, the post cut-off dataset being the odd one out?

4. Does the ACPM have any concerns about the issue of lack of 'direct data' in relation to causal attribution of patient deaths? Has the sponsor's pre-ACPM response been able to allay those concerns?

5. The ACPM was asked to express its opinion as to what extent the higher incidences of the AEs and SAEs seen in the eplerenone groups in the sub-group of patients aged ≥75 years might be reflecting the generally higher incidence of AEs or SAEs in the more elderly age group per se, rather than an actual adverse effect of eplerenone on the sub-group of elderly patients.

6. The ACPM was asked to express its opinion regarding the request of the clinical evaluator, strongly endorsed by the Delegate, for a precaution in the PI which draws attention to the increased sensitivity of the elderly to the blood pressure lowering adverse effects of eplerenone.

7. The ACPM was asked to express its views on the Delegate's opinion that the dosage and administration instructions for subjects with mild to moderate impairment should reflect the conditions under which such subjects were prescribed eplerenone in the clinical trial, in particular that such patients should be commenced on eplerenone 25 mg every second day.

8. Does the ACPM agree with the RMP evaluator that the use of eplerenone should be contraindicated at a serum potassium level exceeding 5.0 mmol/L?

This Overview was submitted for ACPM advice.

Response from Sponsor

Pfizer Australia Pty Ltd welcomed the opportunity to comment on the issues raised in the Delegate's Request for ACPM advice. The Delegate has proposed to reject the application to extend the Inspra indication "*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 ≤35%) in addition to standard optimal therapy (see CLINICAL TRIALS).*"

The sponsor was not in agreement with the Delegate's conclusion that the safety and efficacy of the product has not yet been satisfactorily established for the proposed indication and took this opportunity to address the issues raised in the Delegate's Overview.

Pfizer considers that the magnitude of benefit demonstrated by Inspra in reducing cardiovascular death and hospitalisation from heart failure, with an absolute risk reduction of 7.6% and a relative risk reduction of 37.0% (p<0.0001), to be a large and clinically important benefit for this population of patients. The sponsor welcomed the Delegate's statement that "*on the strength of the evidence presented in this submission, it would appear that eplerenone does exhibit efficacy in those subjects with NYHA Class II heart failure*".

When considering the safety profile of Inspra in this population, the Delegate has stated that "*the Delegate would agree with the clinical evaluator that the safety outcomes from the study were consistent with the known adverse effects of eplerenone as outlined in the currently approved PI. However, the above specific adverse events, whilst well known, can be associated with very serious adverse outcomes*". Pfizer acknowledged the potential for serious clinical outcomes in certain patient populations, and takes the opportunity to characterise in greater detail the adverse event data relating to impaired renal function, hyperkalemia, and reductions in blood pressure.

In the following comments the sponsor attempted to demonstrate with the responses to the multiple additional post-hoc analyses of these well known adverse effects, that the positive benefit/risk balance for the use of Inspra for the proposed indication, as presented in the original submission, is confirmed. In addition, the sponsor provided some critical appraisal of the severe limitations of the paper included by the Delegate in the ACPM meeting reading material (Chatterjee et al, 2012).[14]

1.   Impaired renal function: The Delegate requested a number of analyses of renal impairment to further characterise the profile of Inspra in patients with a range of baseline renal functions, including descriptive statistics of the change in renal function by eGFR and Cr, and categorical changes including from normal to mild, mild to moderate, and moderate to severe renal impairment.

For the clinically important subgroup of patients with moderate renal impairment with eGFR <60 ml/min/1.73m^2, comprising roughly 1 in 3 study participants, the rates of CV death and heart failure hospitalisation were 24.4% (107 / 439) for eplerenone, and 34.5% (163 / 473). The hazard ratio for this cohort of patients for the primary endpoint was 0.62 (0.486 – 0.792, p=0.0001), representing a 38% relative risk reduction in CV death and heart failure hospitalisation events.

Pfizer considers this a large and clinically meaningful benefit in reducing CV death and heart failure hospitalisation by an absolute 10.1%, and is in line with the results of the population with mild renal impairment or no renal impairment (eGFR ≥60 ml/min/1.73m^2), which demonstrates a hazard ratio for the primary endpoint of 0.691 (0.556 – 0.858, p=0.0008).

The Delegate has requested more detailed descriptive statistics for change from baseline in eGFR, with the cohort displayed in the following graph "Change in eGFR" being the same cohort of patients with moderate renal impairment (eGFR ≥60 ml/min/1.73m^2).

This demonstrates a comparable profile of change in renal function with eplerenone and placebo. The median change is centred round zero, with an almost complete overlap in the central interquartile range and the minimum and maximum. Pfizer noted that the outliers appear to be slightly skewed towards an increase in eGFR, reflecting outliers in the direction of improvement in renal function, with these being highly comparable between eplerenone and placebo.

Furthermore, the Delegate requested detail on categorical change in renal function, a 4x4 analysis, further divided into all subjects, <75 year and ≥75 year subgroups, a total of 24 patient cohorts analysed for each of eplerenone and placebo. For the 'all subjects' population, the sponsor finds comparable rates of change in renal function compared with placebo, with no new clinical information derived from the shift from normal to mild renal impairment, from mild to moderate renal impairment, or the shift from moderate to severe renal impairment.

Subgroup analyses are consistent with this finding, confirming the positive benefit risk balance in patients with moderate renal impairment at baseline, as well as the larger cohort of those with mild or no renal impairment at baseline. The response to issue k) provides further detail.

2.   *Hyperkalemia:* The Delegate indicated that *"The most important of the outstanding issues relates to the serum potassium level at which eplerenone should be contra-indicated".*

Inspra was first approved in Australia in 2005 with the current contraindication: "*Inspra should not be administered to patients with clinically significant hyperkalemia (serum potassium >5.5mmol/L at initiation)*". The RMP evaluator proposed to lower the cut-off for the contraindication from 5.5 mmol/L to 5.0 mmol/L, however the results of study A6141079 do not support this. For the subgroup with baseline serum potassium ≥5.0 mmol/L, the primary endpoint, CV death or heart failure hospitalisation was reported in 12 (21.4%) subjects in the eplerenone group (n=56) and 19 (31.7%) in the placebo group (n=60). This represents a large and clinically meaningful benefit, being a 10.3% absolute risk reduction of CV death or heart failure hospitalisation.

The Delegate requested a number of additional analyses of hyperkalemia, for which significant detail will be presented in response to issues l), o) and q). One request focused on the possibility of outliers in serum potassium values, requesting analyses of the robust statistics of median, interquartile range, minimum and maximum for patients with serum potassium readings of >5.5 mEq/L or >6.0 mEq/L. In the graph at right, "*Change of serum potassium –subjects with serum potassium >5.5 mEq/L*" there is almost complete overlap in the range of minimum to maximum and the interquartile ranges, when comparing eplerenone with placebo. The distribution is skewed towards outliers, as the analysis is based upon excluding all patients who might fit in the lower whisker with serum potassium of <5.5 mEq/L, which in this instance represents at least 2000 patients excluded from analysis.

Figure 1. Change in eGFR and shifts in eGFR impairment categories
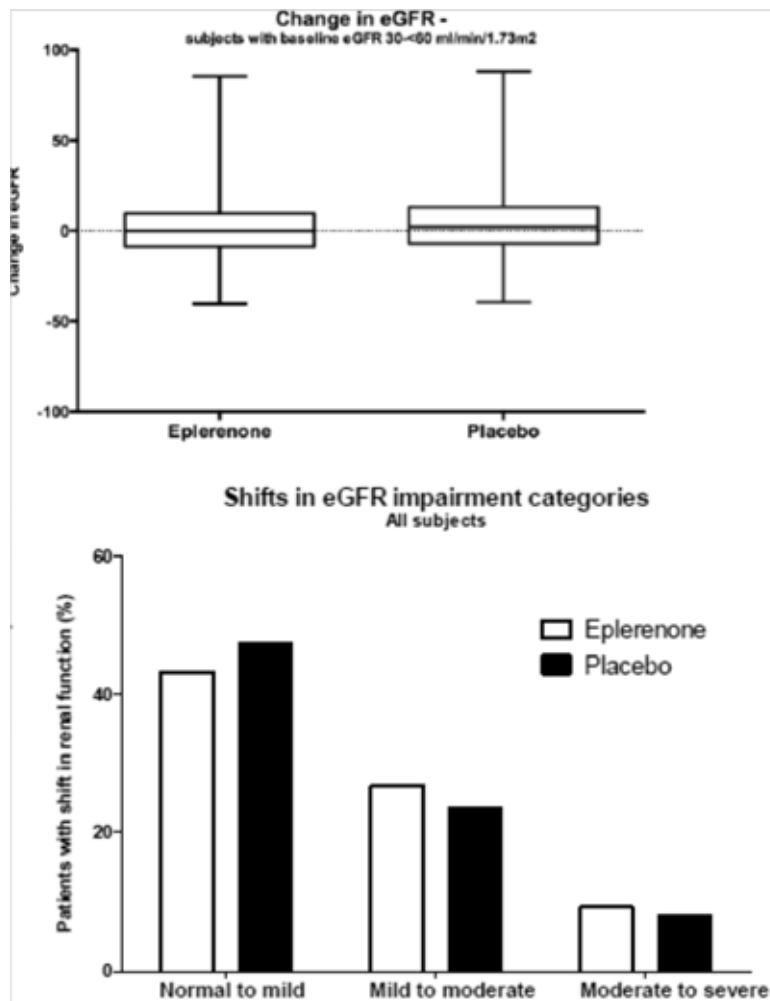
Figure 2. Subjects with serum potassium >5.5 mEQ/L
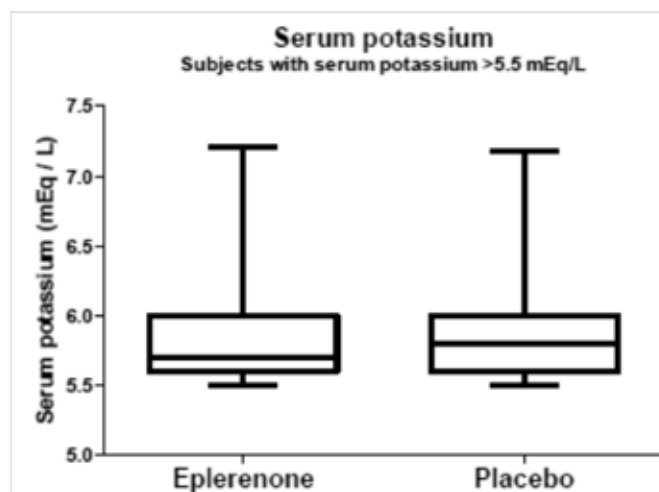
Another analysis requested was the change in serum potassium for all subjects, with descriptive statistics as above. As can be seen, the median change in serum potassium for both cohorts is centred round zero, with a tight grouping for both eplerenone and placebo for the interquartile range, an important measure of dispersion around the median central tendency. It is clear that there is substantial overlap in both the interquartile and complete range.

With a median follow-up time of 8 months, the 1343 eplerenone patients would be expected to have had 8 potassium measurements as per protocol. It is noted that this singular maximum value represents 1 data point out of approximately 10,000 measurements, and this one maximum value discards >99.99% of the available information for this patient cohort. Based on the prior analysis of patients with potassium >5.5 mEq/L, this singular maximum relative change in serum potassium from baseline does not appear to have resulted in a disproportionately high maximum absolute level of serum potassium, with the maximum value recorded in the eplerenone arm being 7.21 mEq/L, compared with 7.18 mEq/L in the placebo arm.

Hospitalisation for worsening renal failure was not reported in any subject while hospitalisation for hyperkalemia was reported in one subject in the eplerenone arm. The dosing guideline where doses are adjusted based on serum potassium appears to have contributed to the low rates of clinically important hyperkalemia in this population.

2.1 Chatterjee et al, 2012: The RMP evaluator has raised some concerns based upon a review of the data presented in Chatterjee et al, 2012[14], stating that: "*The sponsor should make appropriate changes to align the Australian PI with RCPA guidelines, that is, change the contraindication to a potassium level of >5.0 mmol/L, or provide a compelling justification why this is not necessary. This is particularly noteworthy as a recent meta-analysis has found a evidence of statistically significant association of eplerenone with hyperkalemia (Chatterjee et al., 2012)*."

The sponsor took exception with the analysis presented within Chatterjee et al., and strongly objects to the conclusions drawn by the authors. For the specific endpoint of hyperkalemia, the authors unfortunately mix definitions, with a number of studies using serious hyperkalemia with serum potassium >6 mmol/L, and some studies using a cut-off of 5.5 mmol/L to define hyperkalemia. In particular, the authors report a risk ratio of 2.19 for eplerenone versus placebo from the EMPHASIS-HF study, which is the subject of this application. Using the same definition from the other studies examined, the proportion of patients with serum potassium with eplerenone is 2.47% (33/1360) as compared to 1.87% (25/1369), for a risk ratio of 1.33 (0.79 – 2.22), with a non-significant p value of 0.29. This is expected to have lowered the Total risk ratio for eplerenone from 1.72 to 1.38 when compared to placebo, with significance level not determined. The calculations for spironolactone do not change, retaining a risk ratio of 1.80 for serious hyperkalemia compared to placebo. Further analysis of the multiple fundamental flaws of several important endpoint analyses in Chatterjee et al., were also presented by the sponsor [not in this AusPAR] and the sponsor considers that these numerous critical errors in the data as it is presented impact the statistical analysis and draw into question the integrity of the results and the credibility of the entire paper. The sponsor requests that the ACPM members consider both the Chatterjee et al publication provided as reading material, and the sponsor's analysis of the critical flaws of the data presented.

2.2 Hyperkalemia conclusion: The sponsor is reassured that the almost complete overlap in profile of interquartile range and minimum to maximum range in those patients with serum potassium >5.5 mEq/L, as well as the almost complete overlap in 'change in serum potassium' when compared with placebo. This is considered to be in line with the well known mechanism of action of eplerenone and is encouraged by the large and clinically meaningful benefit of a 10.3% absolute risk reduction for CV death or heart failure hospitalisation in patients with serum potassium of 5–5.5 mEq/L at baseline. Pfizer considers that the results of Study A6141079 do not support the proposal from the RMP evaluator to lower the cut-off for the contraindication from >5.5 mmol/L to >5.0 mmol/ L, when serum potassium is monitored on a regular basis.

Figure 3. Change of serum potassium. All subjects

Change of Serum Potassium -
all subjects
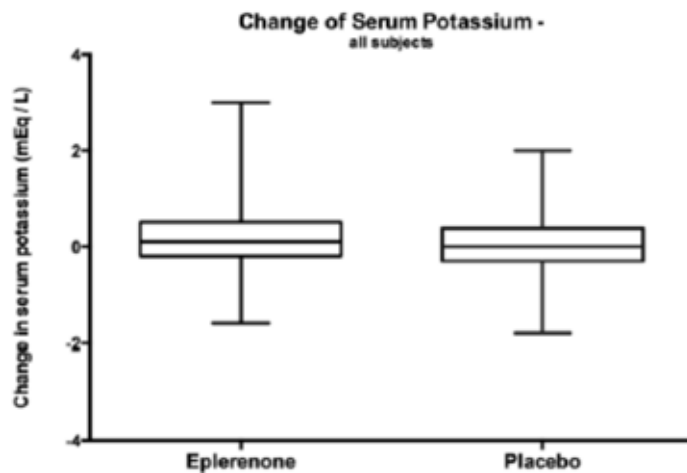
3. ***Blood pressure reductions (particularly in patients ≥75 years):*** With regards the safety of eplerenone in the ≥75 year cohort, the Delegate has stated: *"The sponsor submitted a comprehensive safety analysis stratified by age, that is, <75 years and ≥75 years. Overall safety analyses results in the subgroup of patients aged ≥75 years were consistent with those in the overall study population, and did not indicate significantly greater safety concerns in this age group with the use of eplerenone".*

Further descriptive statistics were requested for the cohort of patients with reductions in SBP and DBP of >20 mmHg, stratified further by age <75 and ≥75 years. There appeared to be no signals that differentiate the treatment effects for BP reductions: the changes noted between eplerenone and placebo did not show any clear differential effects for median, 25% interquartile and 75% interquartile range, nor did there appear to be any informative differences between the <75 and the ≥75 years old age groups, or between SBP and DBP measurements.

The sponsor offered the view that the originally submitted AE tabulations represent the most appropriate assessment of the potential adverse effects of BP reductions (a well established characteristic of a majority of heart failure medications).

As noted by the Delegate: "*Reassuringly, when the primary endpoint was analysed with respect to age, in particular comparing the group below the age of 75 years (n=2080) with that aged at least 75 years (n=657), the point estimates of the primary endpoint hazard ratio for each sub-group appear to be the same with the only difference being a modest widening of the confidence interval for the older age group. This slight widening is consistent with the smaller size of that more elderly sub-group. The upper limit of that slightly wider confidence interval is clearly less than 1.0*". This response to issue e) addresses the percentages of patients having all-cause mortality, cardiovascular mortality and heart failure mortality, stratified by age <75 and ≥75 years will be presented further down in this response.

Pfizer was reassured that the data presented for SBP and DBP reductions of >20 mmHg by age cohorts reinforces the positive benefit/risk balance in patients both <75 and ≥75 years evidenced by a significant reduction in CV mortality and heart failure hospitalisation together with the comprehensive safety analysis previously presented which demonstrates a profile in the ≥75 years age cohort that is consistent with the safety profile in the overall safety population.

Responses to issues raised in delegate's request: The following issues were raised by the delegate and are addressed below.

a. *The sponsor has been asked questions relating to the estimated and real event rates, the sample size and the early stopping of the pivotal trial. The study is endpoint driven and*

is sufficiently powered under the actual relative risk reduction of 37% (with DSMC's recommendation) when the study enrollment is stopped at the sample size of 2373.

Further clarification of the re-estimation of a sample size of 3100 based upon an event rate of 12% was provided.

b.   The sponsor was asked to clarify and justify the actual process of testing for statistical significance amongst the secondary endpoints.

In the SAP, there was no pre-defined hierarchy hypothesis testing process for efficacy endpoints. Results were considered statistically significant if a p value of less than 0.049 (adjusted for interim analyses) was obtained for primary endpoint and less than 0.01 for secondary endpoints (as an approximate adjustment for multiplicity).

c.   The sponsor was asked to discuss further the analysis of the primary efficacy endpoint for the sub-group of subjects with baseline LBBB.

The sponsor agreed with the Delegate that the sub-group with LBBB was not a well defined group and recommends that these data should be interpreted with recognition that this trial was not powered for this specific sub-group, which is a non-uniform population, as alluded to by the reviewer. The absence of a treatment interaction indicates that benefit was similar in this sub-group compared to the entire population (p value = 0.29). The Framingham study[17] showed that complete LBBB on the electrocardiogram (ECG) was usually associated with underlying diseases including hypertension, coronary artery disease, cardiomyopathy, heart failure and dilated cardiomyopathy. These diseases could also evolve during follow-up if not apparent on initial presentation. In essence, LBBB indicates the presence of one or more underlying diseases which may show variable response to treatment with a mineralocorticoid receptor antagonist.

The observation that the upper limit of the Confidence Interval appeared to be almost co-incident with 1 suggests that with the observed variability in response, this sub-group with only 688 subjects (25% of the total population) in the EMPHASIS-HF trial had inadequate power to detect the difference in treatment effect. This variability was also a reflection of the different underlying diseases in subjects with LBBB.

d.   The sponsor has been requested to provide the actual rates, both as percentages and as numerator/denominator, of all-cause mortality, cardiovascular mortality and heart failure death the group aged less than 75 years and in the group aged at least 75 years in the pivotal study.

The actual rates of all-cause mortality, cardiovascular mortality and heart failure death the group aged less than 75 years and in the group aged at least 75 years in the pivotal study are provided below, the complete table showing Survival Analysis of the Primary and Secondary Endpoints by Age (<75 and >= 75) was also provided [not shown in this AusPAR].

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[17]Schneider JF, Thomas Jr HE, Kreger BE, McNamara PM, Kannel WB. (1979). Newly acquired left bundle-branch block: Framingham study. Ann Intern Med 90:303-10

Table 12. Rates of all-cause mortality, cardiovascular mortality and heart failure mortality by age groups. Full analysis set. Cut-off database up to 25 May 2010.

	Age Subgroup	Eplerenone	Placebo
All-cause Mortality	<75	112/1034 (10.8%)	154/1046 (14.7%)
	>=75	59/330 (17.9%)	59/327 (18.0%)
CV Mortality	<75	96/1034 (9.3%)	134/1046 (12.8%)
	>=75	51/330 (15.5%)	51/327 (15.6%)
HF Mortality	<75	29/1034 (2.8%)	42/1046 (4.0%)
	>=75	16/330 (4.8%)	19/327 (5.8%)

e.   The sponsor was requested to account for the subjects apparently left out of the calculation for the complete double-blind phase dataset and the apparently low rates of completion of the double-blind phase. The sponsor was also requested to give a detailed overall accounting of the disposition and/or early transitioning of all subjects.

The disposition of the subjects who participated in this trial was demonstrated in a Consort diagram. These primary data, analysed according to the pre-specified statistical analysis plan, were presented in the Amended Primary CSR (Amended pCSR).
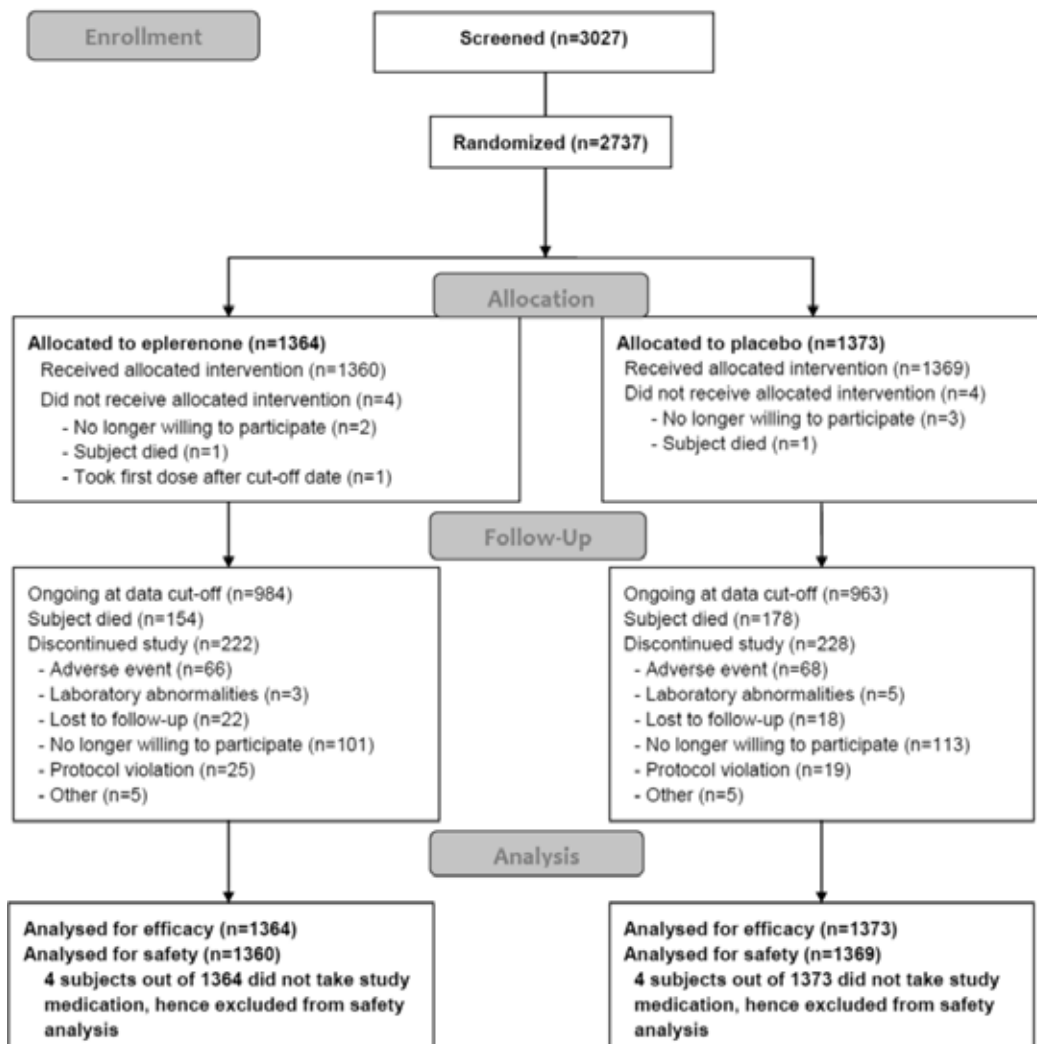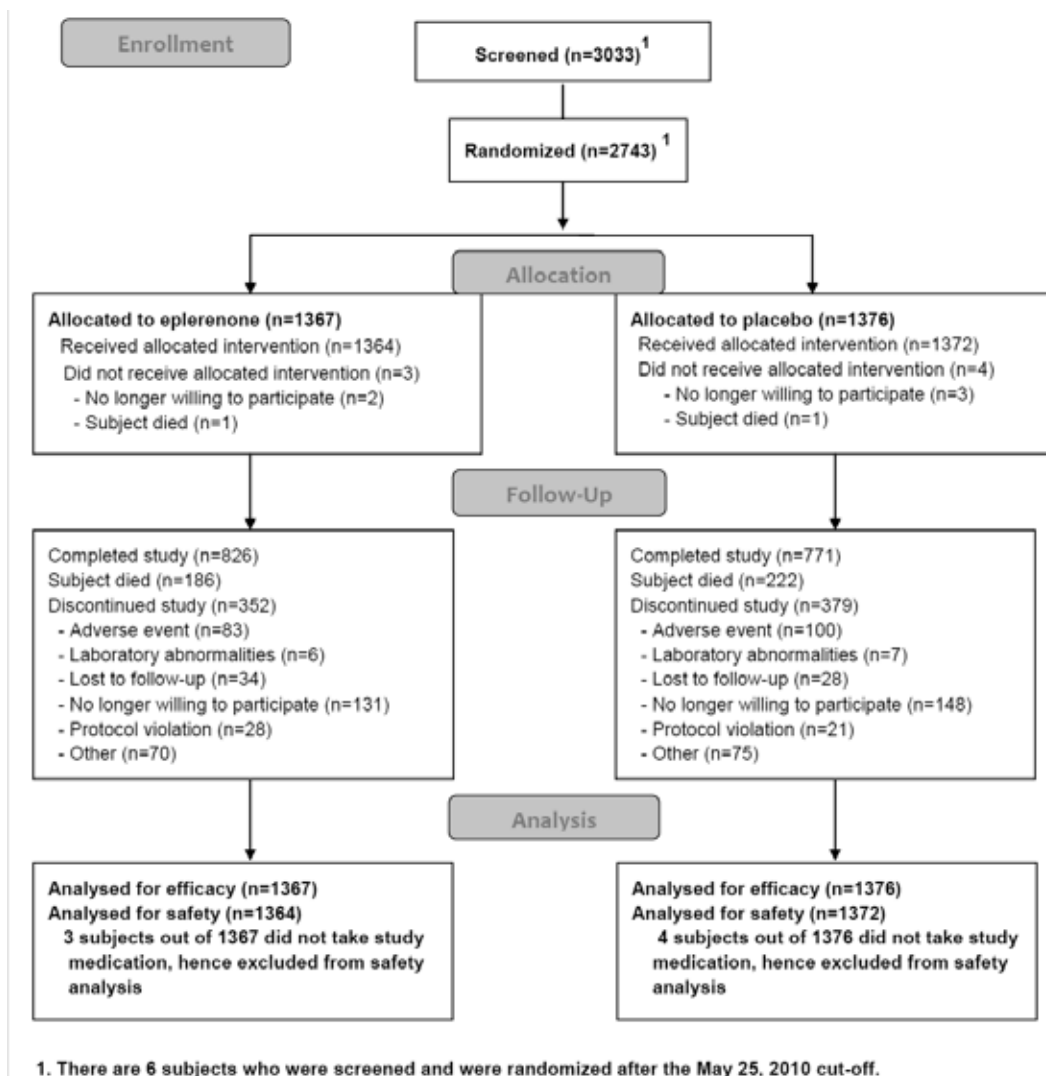
Figure 4. Subject disposition flow diagram. Study A6141079. Cut-off database 25 May 2010.

Figure 5. Subject disposition flow diagram. Study A6141079. Complete double-blind phase.


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   Enrollment              Screened (n=3033)¹


                           Randomized (n=2743)¹


                              Allocation

Allocated to eplerenone (n=1367)          Allocated to placebo (n=1376)
  Received allocated intervention (n=1364)   Received allocated intervention (n=1372)
  Did not receive allocated intervention (n=3)  Did not receive allocated intervention (n=4)
  - No longer willing to participate (n=2)      - No longer willing to participate (n=3)
  - Subject died (n=1)                          - Subject died (n=1)


                              Follow-Up

Completed study (n=826)                   Completed study (n=771)
Subject died (n=186)                      Subject died (n=222)
Discontinued study (n=352)                Discontinued study (n=379)
  - Adverse event (n=83)                    - Adverse event (n=100)
  - Laboratory abnormalities (n=6)          - Laboratory abnormalities (n=7)
  - Lost to follow-up (n=34)                - Lost to follow-up (n=28)
  - No longer willing to participate (n=131)  - No longer willing to participate (n=148)
  - Protocol violation (n=28)               - Protocol violation (n=21)
  - Other (n=70)                            - Other (n=75)


                              Analysis

Analysed for efficacy (n=1367)            Analysed for efficacy (n=1376)
Analysed for safety (n=1364)              Analysed for safety (n=1372)
  3 subjects out of 1367 did not take study    4 subjects out of 1376 did not take study
  medication, hence excluded from safety       medication, hence excluded from safety
  analysis                                      analysis
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1. There are 6 subjects who were screened and were randomized after the May 25, 2010 cut-off.

Subjects already enrolled were maintained in the double blind phase, (past the primary CSR data cut off date), while preparing transition into an OLE phase. Thus, additional double blind phase data (after the enrolment termination) were collected. The Supplemental Clinical Study (sCSR) presents these data (that is, the full double blind data set). This dataset included the 6 subjects who were randomised on the day enrollment was terminated.

Interim CSR Open Label Extension (OLE) (dated 25 August 2011): data included in the analyses for the OL until 14 June 2011. Note, this was the data that had being submitted to date with the application. Finally, the Open Label Extension (OLE) phase presents all data from the end of the double blind phase to the end of the OLE phase. The OLE dataset included data from subjects who completed the double-blind phase, with the exception of subjects from countries that withdrew participation in the OLE, sites that withdrew participation in the OLE and subjects who did not meet the renal entry criterion for the OLE.

f.   The sponsor was asked to comment on the lack of consistency in the results of the primary efficacy endpoint across the 3 populations, the pCSR, the post cut-off dataset and complete double-blind phase dataset, the post cut-off dataset being the odd one out.

The inconsistencies mentioned above refer to data collected from May 26, 2010 to the start of the Open Label Extension phase. The results referred to were submitted with this

response as frequency listings of events that were adjudicated but not subjected to statistical analysis and were not part of the efficacy analyses reported in the pCSR. These data were reported in the Supplemental CSR, sCSR.

During the process of cleaning the database for the complete double-blind data, the sponsor became aware of 4 events (2 in the placebo group and 2 in the eplerenone group) that occurred before the May 25, 2010 cut-off date, but which had been omitted in error in the pCSR. These data do not change the outcome of the previous analyses in the pCSR. This number of subjects who completed the double-blind phase is different from the number of subjects who transitioned into the OLE because some countries opted out of the OLE upon completion of the double-blind phase, and in the US, two VA hospitals opted out because they already receive free drug.

Consequently, the number of subjects who transitioned into the OLE is less than the number of subjects who completed the double-blind phase of the trial. In essence, the reports are all consistent with the phase of trial to which they refer.

The sponsor has clarified the contents of each of the study reports submitted:

1. The primary CSR, pCSR contains data that accrued before the 25th of May. 2010. Based on the SAP, all reported efficacy analyses are part of this report

2. The Supplemental study report, sCSR contains data that accrued up to the end of the double-blind phase (beginning of the Open Label Extension phase) as well as the individual level data. Based on the SAP, the data in the sCSR were reported as frequency listings. The denominators reflect the numbers of subjects in each arm at the end of the double-blind trial.

3. The synopsis report for the Open Label Extension phase contains safety frequency listings up until 14 June 2011, as the OLE phase of the study was not completed at the time of submission. The final Open Label Extension (OLE) report is now available and will be submitted for evaluation in due course.

This post cut-off dataset is small, collected over a short interval compared to the data in the pCSR and underpowered but general conclusions that can be drawn from a broad range of mortality and hospitalisation end points, show that the events appear numerically lower for eplerenone than for placebo.

Pfizer considers these results to be consistent in direction with the results presented in the complete double-blind phase as reported in the pCSR.

g. *The sponsor has been asked to define precisely the term 'all causalities and treatment-related' as it relates to the reporting of AE rates anywhere in the submission that the term was employed. The sponsor was also asked to provide tables showing the frequencies/incidences of actual treatment-related events for the OLE phase.*

'*All causalities*' were for all AEs reported from the clinical trial '*Treatment related*' AEs were defined as AEs reported as possibly related to the study medication by the investigator from either of the study arms. No new safety signals have emerged from the clinical analysis.

h. *The Delegate requested the sponsor to clarify in detail the issue of the lack of 'direct data' in relation to patient deaths. The Delegate requested the most up-to-date and most accurate estimation possible of the numbers/rates of death attributable to study treatment, particularly eplerenone versus placebo. Along with this report, the sponsor was to identify clearly any limitations of that estimation.*

A review of all death Narratives (CIOMS) from the entire EMPHASIS-HF OLE segment study show that all but one of the cases listed were reported by the Principal Investigator, and agreed by Sponsor Safety Review, to be NOT related to study drug. The one case, a

death from "Unknown Causes" in Greece was reported by the Investigator as '*…reasonable possibility… (of relatedness)…*' with which the Sponsor Safety Review did not agree.

i.   *The sponsor was requested to provide details of the frequencies, in descending order, of the ten most common treatment-related AEs leading to permanent discontuation in the pCSR for eplerenone and placebo.*

The analysis of these data has indicated no meaningful differences between the two treatment arms. Tables 13 and 14 represent the ten most common treatment-related AE's leading to study discontinuation for eplerenone and placebo, respectively.

Table 13. The ten most common treatment-related AE's leading to study discontinuation

Events leading to treatment discontinuation	Eplerenone					Placebo				
	N	%	mild	mod	sev	N	%	mild	mod	sev
Hyperkalaemia	12	0.90%	6	3	3	11	0.80%	7	3	1
Renal impairment	5	0.40%	0	4	1	5	0.40%	0	2	3
Cardiac failure	3	0.20%	0	2	1	1	0.10%	0	0	1
Pruritus	3	0.20%	2	1	0	1	0.10%	1	0	0
Nausea	2	0.10%	1	1	0	1	0.10%	0	1	0
Gynaecomastia	2	0.10%	1	1	0	1	0.10%	0	1	0
Acute myocardial infarction	1	0.10%	0	0	1	0	0.00%	0	0	0
Atrial fibrillation	1	0.10%	0	0	1	0	0.00%	0	0	0
Bradycardia	1	0.10%	0	0	1	0	0.00%	0	0	0
Conduction disorder	1	0.10%	0	1	0	0	0.00%	0	0	0

Table 14. The ten most common treatment-related AE's leading to study discontinuation

Events leading to treatment discontinuation	Placebo					Eplerenone				
	n	%	mild	mod	sev	N	%	mild	mod	sev
Hyperkalaemia	11	0.80%	7	3	1	12	0.90%	6	3	3
Renal impairment	5	0.40%	0	2	3	5	0.40%	0	4	1
Renal failure	3	0.20%	0	1	2	0	0.00%	0	0	0
Blood creatinine increased	2	0.10%	1	0	1	0	0.00%	0	0	0
Cardiac failure	1	0.10%	0	0	1	3	0.20%	0	2	1
Pruritus	1	0.10%	1	0	0	3	0.20%	2	1	0
Nausea	1	0.10%	0	1	0	2	0.10%	1	1	0
Gynaecomastia	1	0.10%	0	1	0	2	0.10%	1	1	0
Abdominal pain	1	0.10%	0	1	0	1	0.10%	1	0	0
Diarrhoea	1	0.10%	0	1	0	1	0.10%	0	0	1

j.   *The sponsor was requested to provide a number of further analyses regarding renal function/renal impairment in the pivotal study.*

The sponsor provided a shift table for the eGFR as requested. The data are consistent with the interpretation that there is no clinically meaningful differentiation between eplerenone treated and placebo treated subjects. That is to say, the renal function appeared to be mirrored between the two treatments with no asymmetry in shifts noted for the duration of the study. The comparison of treatment groups, eplerenone and placebo, in the elderly sub-population was consistent with the overall cohort.

The sponsor took the position that the eGFR is the parameter of choice and that serum creatinine is not useful. Firstly, there are no established classifications for Mild, Moderate, Severe for creatinine (Cr), whereas we have used the National Kidney Foundation eGFR criteria. Although doubling of serum creatinine has been used historically as a surrogate

for endpoints of end stage renal disease in clinical nephropathy registrational programs (for example, irbesartan and losartan diabetic nephropathy indications) recent regulatory guidance in EU[18] strongly dictates use of eGFR and related measures while discouraging the use of Cr.

k. *The sponsor was requested to provide a number of further analyses of the data relating to serum potassium levels >5.5 mEq/L and >6 mEq/L.*

The requested analyses were provided. There appear to be no signals that differentiate the treatment effects for maximum serum potassium: the changes noted between eplerenone and placebo do not show any clear differential effects, nor do there appear to be any informative differences between the <75 and the ≥75 years old age groups.

l. *The sponsor was asked to do a number of further analyses regarding the extent of the blood pressure reductions above the maximum cut-off of 20 mmHg, with a focus on outliers. The sponsor was also asked to provide a further analysis of the rates of any adverse events possibly attributable to the falls in blood pressure corresponding to the results reported in Tables 5 and 6.*

The requested additional 8 sub-population cells blood pressure (BP) analyses from the sub-population of 'greater than 20 mmHg reductions in blood pressure' from the same dataset as the originally submitted Tables 5 and 6 were submitted. Please note that the 'minimum' and 'maximum' data actually represent the range of the reductions: so, the 'Minimum' of "-74" represents for that cell a drop of 74 mmHg from Baseline, and the 'Maximum' of "-20.5" represents a reduction of 20.5 mmHg from Baseline.

There appear to be no signals that differentiate the treatment effects for BP reductions: the changes noted between eplerenone and placebo do not show any clear differential effects, nor do there appear to be any informative differences between the <75 and the >= 75 years old age groups. The row of 'Minimum' appears to possibly suggest that in eplerenone treated subjects there may be outliers contributing to the result but the dataset is too small to be definitive.

As these BP values were taken at the regularly scheduled office visits and adverse event (AE) incidents were overwhelmingly not at the same time as these visits, there is no way to address the request to '.. *provide a further analysis of the rates of any AEs possibly attributable to the falls in BP corresponding to the results reported in Tables 5 and 6…*'.

Another important limitation to the Question posed is the study's exclusion criteria allowed a potentially broad range of Baselines (study excluded "Subjects with uncontrolled hypertension, defined as having a systolic blood pressure (SBP) >180 mmHg and/or a diastolic blood pressure (DBP) >110 mmHg.").

Clearly an observed reduction of 30 mmHg (systolic) from a Baseline of 180 mmHg is a different case than a drop of 30 mmHg from a Baseline of 100 mmHg.

The sponsor respectfully offered that the originally submitted AE tabulations represent the most appropriate assessment of the potential adverse effects of BP reductions (a well established characteristic of a majority of heart failure medications).

m. *For each of the three parameters; change from baseline to follow-up in each of serum potassium, serum creatinine and eGFR, the sponsor was requested to provide also the median, interquartile range (showing lower and upper limits) and range (showing min and max) for each of the 6 sub-groups identified in each row of the table.*

New tables displaying the requested additional 6 subgroups were submitted. The sponsor took no new clinically meaningful insights from these data.

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[18] Predictors of outcome and renal clearance UB AMA 23.3.2012

n. As noted by the clinical evaluator, the incidence of hyperkalemia in the eplerenone group was also comparable between the subgroup of subjects with baseline eGFR of 30-60 ml/min/1.73m² (potassium >5.5 mEq/L: 16.94%; potassium >6 mEq/L: 2.12%) and the subgroup of subjects with baseline eGFR of 60 ml/min/1.73m² (potassium >5.5 mEq/L: 10.92%; potassium >6 mEq/L: 2.95%). For each of the 4 sub-groups referred to in the last sentence, the Delegate requested the sponsor to provide the following details of the serum potassium: mean, median, interquartile range (showing lower and upper limits) and range (showing min and max).

The requested analyses were provided.

In these subjects, the requested variables are numerically similar between the eplerenone and the placebo group, with the exception that the maximum values of serum potassium were measured in the placebo group (7.18 mmol/L versus 6.8 mmol/L) in subjects with eGFR 30-<60 ml/min/1.73 m². In the subgroup of subjects with eGFR >60 ml/min/1.73 m², the values of the variables were similar in the two treatment arms except for the maximum value which was higher in the eplerenone group (7.21 mmol/L versus 6.69 mmol/L). These data support our earlier conclusion that the range of changes in serum potassium was generally similar in the placebo and eplerenone groups and supports the sponsor's application.

o. The sponsor was asked a number of questions which seek to clarify the rates of transitioning between various dosage levels in the pivotal study.

The dosing schedules requested were submitted. These data suggest that a majority of these subjects (82%) remained on 25 mg every other day for up to 4 weeks, while about 25% of subjects remained on this dose for the rest of the trial. More than one half of the subjects (53%) were successfully up-titrated to the maximum dose of 25 mg daily for the rest of the trial. While subjects with moderate renal impairment may not tolerate 50 mg daily because of hyperkalemia, a majority of these subjects will tolerate 25 mg daily, with appropriate serum potassium monitoring.

p. Is there any evidence from the dossier that those patients who serum potassium lay in the intermediate range of 5-5.5 mmol/L were at increased risk of adverse outcomes, particularly clinically significant or serious hyperkalemia?

The sponsor analysed outcomes data in subjects with baseline serum potassium of 5.0>≤5.5 mmol/L from the complete double-blind database. The number of subjects who met these criteria was 55 in the eplerenone arm and 57 in the placebo arm. The primary endpoint (CV death or heart failure hospitalisation) was reported in 12 (21.8%) in the eplerenone arm and 18 (31.6%) in the placebo arm. Hospitalisation for hyperkalemia was reported in 1 (1.8%) in the eplerenone arm and zero in the placebo arm. None of the subjects was hospitalised for worsening of renal function.

The frequency of a majority of the secondary endpoint events was lower in the eplerenone arm compared to the placebo arm Data for subjects with baseline serum potassium >5.0 mmol/L were also submitted.

The adverse events reported in subjects with baseline serum potassium 5.0-≤5.5 mmol/L were submitted. Overall, there is no obviously discernible difference in the pattern or frequency of the reported events between the eplerenone and placebo groups except for cardiac failure which was reported less frequently in the eplerenone group.

In subjects with baseline serum potassium of >5.0 mmol/L, the frequency and pattern of adverse events are similar in the eplerenone and placebo treated groups except for cardiac failure which was reported less frequently in the eplerenone group.

A review of the adverse events in subjects with serum potassium >5.0 mmol/L and ≤5.5 mmol/L shows similar profiles. It appeared from these data that with the careful monitoring of serum potassium employed in this trial the adverse event profiles were

similar in these groups and hyperkalemia resulting in hospitalisation was not significantly more frequent in any one group.

Other issues raised in Delegate's overview

Banas et al: the full article is not available, a copy of the Banas abstract was provided.

RMP recommendations: all changes relating to the PI have been addressed.

Changes have been made to the PI in response to requests from various TGA evaluators and the Delegate.

A corresponding CMI document was also provided.

Specific conditions of registration

The sponsor agreed to adopt the three specific conditions of registration proposed by the Delegate.

Conclusion

Pfizer believed that the issues raised by the Delegate have been positively addressed and that the benefit/risk profile for Inspra remains favourable.

The treatment of chronic heart failure is considered an unmet medical need with significant mortality, morbidity and health economic consequences. Age-related prevalence of CHF is increasing with a concomitant increase in the number of hospitalisations for worsening HF. The results from the EMPHASIS-HF study provide the first evidence from a placebo-controlled, outcomes trial that treatment with eplerenone results in significant cardiovascular benefit in patients with NYHA Class II (chronic) heart failure. This has resulted in the Australian National Heart Foundation, the Heart Failure Society of America and the European Society of Cardiology making updates to their clinical practice guidelines, incorporating recommendations to use mineralocorticoid antagonists, including eplerenone, in patients with NYHA Class II Heart Failure.

Inspra is generally well-tolerated, with a safety profile for the NYHA Class II study cohort consistent with that seen in previously studied populations.

The submitted data and the positive recommendation by the clinical evaluator support the application to extend the Inspra indication as follows: "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 ≤35%) in addition to standard optimal therapy (see Clinical Trials).*"

Advisory Committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality and the provision of satisfactory information by the sponsor to the majority of the issues raised by the Delegate, considered these products to have an overall positive benefit-risk profile for the proposed indication**;**

> *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 ≤30%, confirmed with echocardiogram) in addition to standard optimal therapy.*

The ACPM noted that the NYHA scale was a qualitative rather than a quantitative assessment, thus there was potential for bias in patient selection.

The ACPM agreed with the Delegate that safety issues were of most concern. The pre-ACPM clarifications were reassuring.

Proposed PI/CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

· Renal impairment has not been adequately addressed in the PI. The reader is directed to several sections but no clear statement is made. It should be referred to by one name, preferably "chronic kidney disease (CKD)"[19]. This requires a heading and some prominence. The section should include the following statements:

   – Doses of eplerenone above 25 mg daily have not been studied in Stage 3 CKD (eGFR 30-59 ml/min/1.73m2) and an increased dose is not recommended.

   – Periodic monitoring of serum potassium will be particularly important in this population to avoid serum potassium levels greater than 5.5 mmol/L.

   – Eplerenone has not been evaluated in more severe Stage 4 and 5 CKD (eGFR less than 30 ml/min/1.73m2).

   – Eplerenone is not dialysable.

   – In the trials, the exclusion of patients with a potassium level above 5 mmol/L provided very limited data on those between 5 mmol/L and the 5.5 mmol/L level proposed by the sponsor. This should be stated in Contraindications section.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

· Amendment of the Product Information to the satisfaction of the TGA.

· The implementation of the most recent Risk Management Plans and Australian specific annex as agreed by the Office of Product Review.

· Post marketing reports to be provided in line with the current published list of European Union (EU) reference dates.

· The submission of the final clinical study report of the open-label extension phase of the pivotal study to the TGA, as soon as it is available.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

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[19]Stage of Chronic Kidney Disease eGFR ml/min/1.73 m2

Stage 1: the eGFR shows normal kidney function but you are already known to have some kidney damage or disease. For example, you may have some protein or blood in your urine, an abnormality of your kidney, kidney inflammation, etc. 90 or more ml/min/1.73 m2

Stage 2: mildly reduced kidney function AND you are already known to have some kidney damage or disease. People with an eGFR of 60-89 without any known kidney damage or disease are not considered to have chronic kidney disease (CKD). 60 to 89 ml/min/1.73 m2

Stage 3: moderately reduced kidney function. (With or without a known kidney disease. For example, an elderly person with ageing kidneys may have reduced kidney function without a specific known kidney disease.) 45 to 59 ml/min/1.73 m2 (3A) 30 to 44 ml/min/1.73 m2 (3B)

Stage 4: severely reduced kidney function. (With or without known kidney disease.) 15 to 29

Stage 5: very severely reduced kidney function. This is sometimes called end-stage kidney failure or established renal failure. Less than 15 ml/min/1.73 m2

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Inspra (eplerenone) tablets for oral administration, for the additional indication:

> *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 ≤30% or LVEF ≤35% in addition to QRS duration of >130 msec) in addition to standard optimal therapy (see Clinical Trials).*

Specific conditions relating to these therapeutic goods:

1. The implementation of Risk Management Plans as follows:

2. EU-RMP Version 1.0 (dated 18/03/2011, DLP 01/02/2011) and Australian specific annex (dated 06/03/2012) and any future updates as may be agreed with the Office of Product Review.

3. The submission to the TGA, as soon as it is available, of the final clinical study report of the open-label extension phase of the pivotal study, the Eplerenone in Mild Patients Hospitalisation and Survival Study in Heart Failure, EMPHASIS-HF, Study A6141079. The data is to be submitted for formal evaluation as part of a Category 1 submission.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration