CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Inspra 25 and 50, film-coated tablets 25 mg and 50 mg Pfizer bv, the Netherlands

eplerenone

This assessment report is published by the Medicines Evaluation Board (MEB) pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow-organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0506/001-002/MR
Registration number in the Netherlands: RVG 29963-29964

15 November 2012

Pharmacotherapeutic group:	aldosterone antagonists
ATC code:	C03DA04
Route of administration:	oral
Therapeutic indication:	to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction and clinical evidence of heart failure after recent myocardial infarction
Prescription status:	prescription only
Date of first authorisation in NL:	16 March 2004
Concerned Member States:	Mutual recognition procedure with AT, BE, DE, DK, EL, ES, FI, FR, IE, IS, IT, LU, NO, PT, SE, UK, repeat-use procedure with CY, CZ, EE, HU, LT, LV, MT, PL, SI and SK
Application type/legal basis:	national application based on Directive 2001/83/EC, Article 8(3), full application, followed by a mutual recognition and repeat-use procedure

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

List of abbreviations

ACE	Angiotensin-converting-enzyme
AE	Adverse Event
AF/flutter	Atrial Fibrillation/flutter
Al	Aluminium
AMI	Acute Myocardial Infarction
AR	Assessment Report
AR	Androgen Receptor
ARB	Angiotensin receptor blocker
ARR	Absolute Risk Reduction
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BNP	B-type Natriuretic Peptide
BP	British Pharmacopoeia
BUN	Blood Urea Nitrogen
CAD	Coronary Artery Disease
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
Cl/F	Apparent Plasma Clearance
C_{max}	Maximum plasma concentration
CrCl	Creatinine Clearance
CRT	Cardiac Resynchronisation Therapy
CV	Cardiovascular
DB	Double Blinded
DDPS	Detailed Description of the Pharmacovigilance System
DM	Diabetes Mellitus
DME	Designated Medical Event
DSMC	Data Safety Monitoring Committee
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EF	Ejection Fraction
eGFR	Estimated Glomerular Filtration Rate
EOD	Every Other Day
ERA	Environmental Risk Assessment
ESC	Executive Steering Committee
EU	European Union
FAS	Full Analysis Set
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GR	Glucocorticoid Receptor
hERG	Human Ether-à-go-go-Related Gene
HF	Heart Failure
HPLC	High-performance liquid chromatography
HR	Heart Rate
ICD	Implantation of Cardiac Defibrillator
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
ITT	Intention-to-treat
LBBB	Left Bundle Branch Block
IV	Intravenous

LV	Left Ventricle
LVEF	Left Ventricle Ejection Failure
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
MI	Myocardial Infarction
MR	Mineralocorticoid Receptor
MRA	Magnetic Resonance Angiography
MRP	Mutual Recognition Procedure
NfG	Note for Guidance
NOAEL	No-observed-adverse-effect level
NYHA	New York Heart Association
OD	Once Daily
OECD	Organisation for Economic Co-operation and Development
OLE	Open-label Extension
OTC	Over The Counter (to be supplied without prescription)
PAC	Post Approval Commitment
PAR	Public Assessment Report
PD	Pharmacodynamic
PEC	Predicted Environmental Concentration
PH	Proportional Hazards
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PL	Package Leaflet
PNEC	Predicted No Effect Concentration
PP	Pulsus Paradoxus
PR	Progesterone Receptor
PSUR	Periodic Safety Update Report
PVC	Polyvinylchloride
QT/QTc	QT interval represents electrical depolarization and repolarization of the left and right ventricles
RAAS	Renin-angiotensin-aldosterone-system
RALES	Randomised Aldactone Evaluation Study
RH	Room Humidity
RMC	Risk Management Committee
RRR	Relative Risk Reduction
SBP	Systolic Blood Pressure
SD	Standard Deviation
SAE	Serious Adverse Event
SGOT	Serum glutamic oxaloacetic transaminase
SMQ	Standardised MedDRA Query
SPC	Summary of Product Characteristics
SOC	System Organ Classes
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TME	Targeted Medical Event
TSE	Transmissible Spongiform Encephalopathy
ULN	Upper Limit of Normal
USP	Pharmacopoeia in the United States
UV	Ultraviolet
Vc/F	Apparent volume of distribution after non IV administration

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board of the Netherlands (MEB) has granted a marketing authorisation for Inspra 25 and 50, film-coated tablets 25 mg and 50 mg, from Pfizer bv. The date of authorisation was on 16 March 2004 in the Netherlands.

The product is indicated to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction and clinical evidence of heart failure after recent myocardial infarction.

A comprehensive description of the indications and posology is given in the SPC.

Heart failure (HF) is a clinical syndrome with a variety of causes. The abnormality of the heart may be related to primary impairment of myocardial function or to (chronic) pressure and/or volume overload. HF usually worsens progressively and the prognosis of HF is poor. For patients with chronic HF in NYHA functional class IV (= symptomatic at rest), the 1-year mortality rate is at least 50%. The rate of the progression is dependent on both the primary pathology and the activity of the compensatory processes. These compensatory processes are predominantly neural, endocrine, renal and morphological. Although some of these processes are beneficial in short-term, most chronic compensatory processes (e.g. renin-angiotensin-aldosterone-system) are detrimental in the long term.

The goals of treatment of HF include improvement in symptoms and cardiovascular morbidity and reduction in mortality. The treatment of chronic HF may include diuretics, ACE inhibitors, β-blockers, angiotensin II receptor blockers, nitrates, digoxine and the aldosterone antagonist spironolactone.

Spironolactone [registered in the Netherlands as (Aldactone®)] is a competitive and non-selective aldosterone blocker. Notably, the efficacy of spironolactone in patients with chronic HF has been investigated in a large clinical trial. In the *Randomised ALdactone Evaluation Study* (RALES), placebo or spironolactone was administered at doses of 25-50 mg QD (once daily) to patients with severe HF (> 99% NYHA class III or IV) and a LVEF of no more than 35 per cent, and who were also receiving an ACE-I and a loop diuretic. The rates of all cause mortality (46% placebo and 35% spironolactone, respectively) represented a 30% reduction in risk of death. Significant improvements compared to placebo were also observed for CV mortality, CV mortality/hospitalisation and all cause mortality/hospitalisation. The mechanism behind the reduction in the risk of death associated with the use of spironolactone is not known. The currently approved therapeutic indications for spironolactone in the Netherlands include the treatment of cardiac oedema with secondary hyperaldosteronism and as an adjuvant in the treatment of hypertension. Spironolactone is not registered in the Netherlands for the reduction of the risk of death in patients with (chronic, advanced) HF, as it was never applied for.

Inspra contains the new active substance eplerenone, a steroid nucleus-based anti-mineralocorticoid that acts as a competitive and selective blocker of aldosterone at mineralocorticoid receptor sites in various tissues throughout the body. Eplerenone has relative selectivity in binding to recombinant human mineralocorticoid receptors compared to its binding to recombinant human glucocorticoid, progesterone and androgen receptors. Eplerenone prevents the binding of aldosterone, a key hormone in the renin-angiotensin-aldosterone-system (RAAS), which is involved in the regulation of blood pressure and the pathophysiology of cardiovascular disease.

The national procedure to obtain a marketing authorisation for Inspra concerned a so-called full dossier application according to Article 8(3) of Directive 2001/83/EC, a dossier with administrative, chemical-pharmaceutical, pre-clinical and clinical data.

The MAH consulted the MEB for Scientific Advice before national application, to obtain input and agreement on the single trial strategy, the acceptability of the target patient population and the overall study design and statistical rationale for the phase III heart failure post myocardial infarction study. No paediatric development programme has been submitted, as this was not a requirement at the time of registration.

The national procedure was immediately followed by a mutual recognition procedure (MRP), which started on 7 May 2004 and ended on 5 August 2004. At day 90 (5 August 2004) the marketing authorisation for Inspra was mutually recognised by AT, BE, DE, DK, EL, ES, FI, FR, IE, IS, IT, LU, NO, PT, SE and UK. The dossier has been updated with data and changes from both the first round MRP as well as post-approval variations. Upon finalisation of the MRP, a repeat-use procedure was initiated during which marketing authorisations were acquired for the following 10 new European member states: CY, CZ, EE, HU, LT, LV, MT, PL, SI and SK. Day 90 was 22 December 2005 and all member states recognised the Dutch marketing authorisation.

On page 17 the post-approval variations are summarised. The steps taken after finalisation of the initial procedure (variations) are included in a list on pages 18-19.

In addition, one annex is included concerning the discussion of type II variation NL/H/0506/001-002/II/028. Through this variation an additional indication was approved: “Reduction of the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤ 30%) in addition to standard optimal therapy”. Procedure NL/H/0506/001-002/II/028 was finalised on 15 February 2012.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1. Quality aspects

Compliance with Good Manufacturing Practice
The MEB was assured that acceptable standards of GMP (see Directive 2003/94/EC) were in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
Eplerenone is a new active substance. The drug substance is a white to off-white solid. Eplerenone is optically active as expected for a single enantiomer and contains eight chiral atoms. The absolute configuration is fixed by the optically active starting material. Two polymorphs (Form I and II) exist; Form II is the principal crystal form in the eplerenone drug substance.

Manufacturing process
There are two synthetic routes for eplerenone. Process A involves two steps and Process B involves four steps. The synthesis steps are described in sufficient detail. Also the particle size reduction process — either an impact mill or a fluid energy mill — has been described in detail. Representative lot data are presented along with a comparison of assay, impurities, and polymorph data on the drug substance prior to and after the particle size reduction process. For 14 batches, batch results are given regarding assay (on dried basis), heavy metals, individual impurities, unspecified impurities, total impurities, % polymorph Form I, and residue on ignition, all prior to and after the milling.

Quality control of drug substance
Specifications for eplerenone include testing on identity (IR spectrometry), assay by HPLC, related substances by HPLC (including 5 specified impurities), polymorph (Form I) content, specific rotation, loss on drying, residue on ignition, heavy metals, residual solvents and particle size. The monograph is adequate to guarantee a satisfactory quality of the drug substance. About 17 possible structures related to the drug substance (synthesis related or degradation products) have been identified, and are controlled by HPLC to assure acceptable low levels of these impurities in the drug substance. The specification is acceptable in view of the route of synthesis and the various European guidelines. Analytical data demonstrating compliance with the drug substance specification have been provided for several (commercially scaled) batches.

Stability of drug substance
The MAH claimed a re-test period of 2 years in specified storage material without specific storage conditions. Test parameters are appearance, assay by HPLC, and total degradation products by HPLC. The drug substance specification and methods are applied. The stability results met specification at all storage conditions and testing intervals. No trends have been observed in description, assay or degradation products during the performed tests. Herewith the claimed re-test period without specific storage conditions can be accepted. The MAH committed to place the first three commercial batches of drug substance at stability.

Medicinal Product

Composition
The dosage form is an arc-diamond shape, debossed, yellow, film-coated, immediate release tablet at dosage strengths of 25 and 50 mg. The tablet strengths are distinguished by identifying markings as follows:

- 25 mg tablet "Pfizer" on one side of tablet, "NSR" over "25" on other side of tablet
- 50 mg tablet "Pfizer" on one side of tablet, "NSR" over "50" on other side of tablet.

The excipients are:

- *Tablet core* - lactose monohydrate, microcrystalline cellulose (E460), croscarmellose sodium (E468), hypromellose (E464), sodium laurilsulfate, talc (E553b), magnesium stearate (E470b).
- *Tablet coating* – opadry yellow: hypromellose (E464), titanium dioxide (E171), macrogol 400, polysorbate 80 (E433), iron oxide yellow (E172), iron oxide red (E172).

The tablets are packed in opaque PVC/aluminium foil blisters. This type of packaging is acceptable for film-coated tablets.

The compositions of the cores of both strengths are fully dose-proportional. The content of the active ingredient is 28% for both strengths.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product was initially formulated as a capsule for early-phase clinical studies and, subsequently, as an immediate release film-coated tablet for late-phase clinical studies and the commercial dosage form. Formulation tablets of the early phase tablet formulation consisted of the same two diluents, disintegrant, wetting agent and lubricant as the early clinical phase capsule formulation. The components, percent compositions and the manufacturing process of the commercial tablet formulations are similar to those of the late clinical phase tablets, except for a minor change in the film-coat composition regarding colourants. It was decided to modify the product image to a single colour with the arc-diamond shape. Dissolution testing for the batches used in the bioequivalence study as well as representative batches of late clinical phase (white, round) and commercial image (yellow, arc diamond) 25 mg film-coated tablets manufactured at the commercial site, have been compared in dissolution studies. The dissolution profiles were similar.

The pharmaceutical development of the product has been adequately performed in accordance with the relevant European guidelines.

Manufacturing process

Process validation is completed for all manufacturing steps. The number of validation data on the three validation batches for the mutual blend, and the resulting 25 mg and 50 mg core batches are considered as being sufficient. The (final lubricated) blend uniformity results were satisfactory, content uniformity of the core tablets was satisfactory, and test results on individual tablet weight, thickness, hardness, friability, disintegration time, and dissolution were satisfactory. The manufacturing process was adequately validated according to relevant European guidelines.

Excipients

The used excipients are well known and safe in the proposed concentrations. The excipients comply with the Ph.Eur. or in-house specifications. These specifications are acceptable.

Microbiological attributes

The microbiological attributes of the drug product are controlled through excipient testing. Excipients in eplerenone tablets are tested according to and conform to Ph.Eur. microbial limits. Water is tested to Ph.Eur. limits for purified water.

Quality control of drug product

The main release specifications of the drug product comprise testing on identity of the drug substance (HPLC, IR), assay (HPLC), related substances (HPLC), dissolution (UV detection), colourant identification, uniformity of mass, and microbiological purity (results of validation batches are present). The release specifications are sufficiently adequate. The two strengths can be sufficiently distinguished by different inscriptions on the tablet, and by differences in size and weight. The resulting validation batches of the film-coated tablets have been tested according to the drug product specifications, and results met the specifications. In conclusion, the provided validation data demonstrates satisfactory homogeneity within a

batch and satisfactory reproducibility between batches, and sufficient control of the manufacturing process.

Stability of drug product
Satisfactory stability evaluation for eplerenone round tablets packaged in commercial equivalent opaque PVC/aluminium foil blisters is completed up to 6 months at 40 °C/75% RH, up to 1 year at 30°C/70% RH, and up to 3 years at 25°C/60% RH for 3 lots at each dosage strength. In addition, satisfactory stability results for one lot each of 25 mg and 50 mg eplerenone arc-diamond tablets packaged in both clear and opaque PVC/aluminium foil blister stored up to 18 months at 25°C/60% RH, up to 18 months at 30°C/60% RH, and up to 9 months at 40°C/75% RH have been provided. Finally, data from stability studies were provided for 2 lots of 25 mg and one lot of 50 mg eplerenone arc-diamond tablets packaged in clear PVC/aluminium foil blister stored through 1 year at 25°C/60% RH and through 6 months at 40°C/75% RH.

The stability samples were evaluated using a validated, stability-indicating HPLC method for the drug substance and for degradation products. The drug product was also evaluated for dissolution. The appearance, assay, degradation products and dissolution of the stability studies met specification at all storage conditions and testing intervals. No trends are observed in appearance, assay, degradation or dissolution results over time.

The results from the stability studies above indicate that the shape, colour, and package have no effect on stability of the tablets. Photostability data for assay, degradation and appearance met the specification after exposure to intense light conditions, as prescribed by ICH Q1B. Stability testing demonstrated no observed changes for eplerenone. The data above justify the claimed shelf life of 3 years in PVC/Al blister, without specific storage condition.

II.2. Non clinical aspects

Pharmacology
The data submitted by the MAH indicate that eplerenone binds to and inactivates the mineralocorticoid receptor and that plasma proteins do not substantially affect the mineralocorticoid receptor binding affinity of eplerenone. Eplerenone is a more selective aldosterone blocker than spironolactone, with significantly improved MR selectivity relative to glucocorticoid, androgen and progesterone receptor (GR, AR and PR). The conclusion that eplerenone metabolites do not contribute to the pharmacological activity of eplerenone is reasonable.

In several experimental heart failure models including different species (mice, rat and dog), eplerenone demonstrated cardio-protective effects in general, independent from a significant reduction in blood pressure or major changes in water or electrolyte homeostasis. The beneficial effects occurred both when eplerenone was administered prior to or during the heart failure development. The cardio-protective effects were accompanied by a reduced expression of pro-inflammatory cytokines and hypertrophy genes and observed at plasma concentrations similar to those obtained in heart failure patients given eplerenone 50 mg once a day for 5 days. It can be concluded that the results from studies in heart failure models support the indicated clinical use of eplerenone.

Almost all studies mentioned in the section “Secondary pharmacodynamics” were conducted in (genetically) hypertensive animals combined with salt administration. These studies demonstrated anti-hypertensive effects of eplerenone. This supports the potential use of this agent in patients with salt-sensitive hypertension. In several animal models, eplerenone also demonstrated protective effects on brain, kidney, vascular and myocardial tissues, however, mostly in combination with salt administration. In some studies, eplerenone has shown end-organ protective effects without the use of exogenous salt. Eplerenone’s end-organ protection is not strictly dependent on salt excess, which supports the clinical potential of eplerenone’s end-organ protection in heart failure patients. However, the protection is not independent of dietary salt restriction.

In the safety pharmacology studies including those on the cardiovascular, respiratory, gastrointestinal, urinary and endocrine system, eplerenone displayed no effects of clinical concern. In the

pharmacodynamic drug interactions studies, the combination of eplerenone with ACE inhibitors or losartan was found to be safe.

Pharmacokinetics

The pharmacokinetics of eplerenone were studied sufficiently and described well in mice, rats, rabbits and dogs after single and repeat doses, with greater emphasis on the primary toxicology species, rats and dogs, and on oral administration.

Eplerenone was rapidly absorbed after oral administration with peak plasma concentrations generally occurring within three hours of dosing. The bioavailability of eplerenone varied across species, being approximately 26% in male rats, 66% in female rats, 32% in pregnant female rabbits, and 85% in dogs. After single or repeat oral dose administration to mice rats or dogs, the percent of the dose excreted as eplerenone in faeces increased as the dose increased. Absorption does not appear to be modulated by P-glycoprotein, since eplerenone was shown not to be a substrate for this transporter *in vitro*. Although absolute oral bioavailability in man is not available at this time, 67% of an oral dose of [^{14}C]eplerenone was shown to be absorbed and excreted in urine. Following intravenous administration, eplerenone was eliminated rapidly in all species studied, with elimination half-lives of 0.8 to 2.3 hours.

[^{14}C]Eplerenone exhibited relatively low (< 60%) plasma protein binding in all species, including human. There was no preferential partitioning into red blood cells. The volume of distribution of eplerenone ranged from approximately 0.6 to 2 L/kg across species. These values were greater than the volume of total body water, suggesting that eplerenone was available to tissues, as confirmed in tissue distribution studies with [^{14}C]eplerenone in male and female non-pigmented, and male pigmented rats. Highest concentrations of radioactivity were found in the organs of absorption and elimination, and there was no retention of radioactivity in body tissues for extended times. Eplerenone was present in the milk of lactating rats dosed with eplerenone, and was systemically available to rat and rabbit foetuses and to suckling rat pups.

Eplerenone was extensively metabolized in all species, including human. Cytochrome P450 3A isoforms are primarily responsible for metabolism of eplerenone, specifically CYP3A4 in human. The major route of metabolism of eplerenone was hydroxylation to form the inactive metabolite, 6β-OH eplerenone (SC-71597), which was mediated by CYP3A4. Other metabolic steps included hydroxylation at the 21-position and reduction of the 3-ketone. Metabolic profiles in nonclinical species were qualitatively similar to those in man. All of the human metabolites were identified in rat excreta, and some were detected in the excreta of mice and dogs. Human plasma primarily contained eplerenone with much lower concentrations of the metabolites SC-70303 free acid and 6β-OH eplerenone. The metabolic profiles of mouse and rat plasma and in vitro rat liver S9 incubates also included these metabolites.

Upon repeat-dose administration in mouse and rat, there was evidence that eplerenone induced CYP3A and hence its own metabolism. In dogs induction was only measurable at higher doses and in rabbit there was no evidence of induction. Additionally, eplerenone induced hepatic UDPGT-2B1 in the rat, which is responsible for the conjugation of the thyroid hormone, thyroxin (T4).

The primary route of elimination after IV and oral administration to mice and rats was faecal, whereas, in the rabbit (and human), the major route of elimination was urinary. In dogs, a slightly greater amount was excreted in faeces than urine after oral dosing; however, after IV dosing, a larger fraction of the dose was excreted in the urine. The percentage of the dose eliminated in faeces as eplerenone increased as the dose increased, probably due to dissolution-limited absorption. Little eplerenone was excreted in the urine, indicating that renal clearance of eplerenone was a minor elimination pathway, and that eplerenone was mainly eliminated by metabolism.

A study of the ability of eplerenone to inhibit the activity of the major human cytochrome P450 isoforms indicated that it is unlikely that eplerenone will inhibit the metabolism of other compounds due to its high Ki (> 300 µM) for inhibition of these CYP isoforms. Very potent CYP3A4 inhibitors (such as erythromycin, fluconazole, ketoconazole, cyclosporine and saquinavir) were likely to reduce the metabolism of eplerenone. Clinical studies confirmed that co-administration of potent CYP3A4 inhibitors significantly increased total plasma exposure of eplerenone. Eplerenone exposure was also shown to be increased in

an *in vivo* study in the dog, when co-administered with ketoconazole. Drug-drug interactions mediated via P-glycoprotein are unlikely since eplerenone is neither a substrate for, nor inhibitor of, this transporter.

Toxicology
Eplerenone has a low level of acute toxicity in mice, rats and dogs.

Mice have been dosed 2 and 13 weeks (up to 1000 mg/kg/day). Findings were predominantly at the highest dose level: an increased liver weight (accompanied by hypertrophy of hepatocytes) and increased thyroid weight. Also, a decrease of prostate (in one study) and kidney weight was observed. NOAEL (no observed adverse effect level) for mice was 100 mg/kg/day, a dose resulting in AUC values similar to human therapeutic levels.

Rats have been dosed up to 1000 mg/kg/day during 8 days, up to 500 mg/kg/day until 26 weeks, and up to 250 mg/kg/day until a period of 1 year. Predominant histopathologic effects were observed in the liver, thyroid, kidney, adrenals and prostate, while organ weight changes were observed in the epididymides and the ovaries. The thyroid effects were considered not clinically relevant, since these effects have shown to be related to the liver effects: thyroxin glucuronidation increased, leading to an increase in thyroid stimulating hormone. NOAEL for rats was 100 mg/kg/day for females, 200 mg/kg/day for males until 26 weeks, *i.e.* approximately 3 times clinical exposure. Longer exposure (1 year) resulted in a NOAEL of 20 mg/kg/day (AUC values similar to therapeutic exposure). Rats treated with eplerenone sub-chronically or chronically had a dose-related increase in chronic progressive nephropathy, which was prominent at the highest dose (5 to 15 times human exposure), and related effects. Chronic progressive nephropathy is a common spontaneous rat disease that does not have a human counterpart.

Dog studies showed overt signs of toxicity at 300 mg/kg/day. The toxicity was associated with serum electrolyte disturbances and was considered to be mediated by the pharmacological action of eplerenone. In addition, effects were observed in the adrenals. Male dogs treated orally with eplerenone sub-chronically or chronically had prostate atrophy due to competitive binding with androgen receptors at high, but relevant exposure levels. The prostatic atrophy occurred at AUC multiples of free eplerenone that were possibly clinically relevant, *i.e.* the safety margin was low. A warning has been included in section 5.3. Furthermore, effects on the epididymides (decreased weight) and liver (increased weight) were observed.

Eplerenone did not adversely affect fertility in female rats up to the highest tested level of 1000 mg/kg/day. Male rats treated at the highest dosage of 1000 mg/kg/day had decreased seminal vesicle size and the untreated females impregnated by these males had slightly increased pre-implantation loss. The NOAEL for this effect was 300 mg/kg/day, providing a sufficient safety margin. The findings in rat epididymides in the repeated dose studies did not lead to functional disturbances in male fertility.

Eplerenone did not cause foetal anomalies or other developmental abnormalities in embryo-foetal development studies in rats and rabbits at dosages that either achieved maternal toxicity (rabbits at 300 mg/kg/day) or complied with ICH guidelines for an upper limit dosage (rats at 1000 mg/kg/day). At the NOAEL the exposure in the rabbits was 12.5 times the human exposure.

Eplerenone did not result in any pre- or postnatal development concerns in F1 rats that were exposed *in utero* and via the mothers' milk.

Eplerenone was negative in all *in vitro* and *in vivo* genotoxicity studies. In a 6-month carcinogenicity bioassay in heterozygous p53 knock-out mice, there were no treatment-related neoplasms or other proliferative lesions attributable to the administration of eplerenone. In a 2-year rat carcinogenicity bioassay, there was an increased incidence of benign thyroid follicular cell adenomas at 250 mg/kg/day in both sexes (6 to 10 times human exposure) and at 75 mg/kg/day in males (2 times human exposure) and an increased incidence of kidney tubular cell adenomas in females at 250 mg/kg/day. The rat thyroid and kidney effects were related to mechanisms irrelevant to human health, as described above. The weight of evidence indicates that eplerenone does not represent a carcinogenic risk to humans.

Studies in rabbits showed that eplerenone is a slight irritant for the eyes and is not a dermal irritant. Eplerenone is a mild intramuscular- and a slight intravascular irritant. In guinea pigs, it was shown that eplerenone was not a dermal sensitizer, nor was it antigenic in mice, rats and guinea pigs.

There are 5 impurities present in amounts higher than 0.1%, which have been sufficiently qualified.

III.3. Clinical aspects

Pharmacokinetics
Thirty-two pharmacokinetic studies, including 5 studies in Japanese subjects were submitted.

Three formulations were used in the various clinical studies supporting this application, all showed bioequivalence. Absolute bioavailability was not defined for eplerenone. The amount of eplerenone absorbed was estimated at > 66%. Eplerenone administered with food showed in one study a reduced rate of absorption, 19% reduction in C_{max} and an increase of t_{max} with 2.4 hours executed with early-phase clinical trial capsules, a difference that was not observed in a second study using the tablet formulation. The changes observed in the first study normally do not indicate clinically relevant changes and dose-adjustments need not be made assuming that the drug does not have a narrow therapeutic index. The therapeutic index was estimated from the dose-ranging study. Urinary aldosterone levels were used as biomarker for efficacy and serum potassium as a marker for safety.

After multiple dosing, steady-state is reached after 2 days. The volume of distribution at steady state of eplerenone is approximately 50 L. Circa 50% of eplerenone is bound to human plasma protein. Eplerenone is extensively metabolised by CYP3A4, but there is no major first-pass effect. The metabolites do not have any appreciable anti-aldosterone activity. In a ^{14}C study with eplerenone 67% of radioactivity was excreted in the urine and 32% in faeces. Only 1% of the radioactive drug dose was recovered in faeces and 2% in urine in the form of unchanged drug. The major route of eplerenone elimination is by metabolism and not renal excretion of unchanged drug. Single dose administration reveals a dose-linearity over the clinically relevant dose range from 10 to 100 mg, higher (non-clinical) doses, up to 1000 mg do not show dose linear absorption. With a 1000 mg dose the observed $t_{1/2}$ is longer than that in therapeutic dose ranges, nevertheless AUC is lower. This is caused by a saturation of drug dissolution. In the therapeutic range, 25 mg to 100 mg, $t_{1/2}$ ranges from 3.3 hours to 4.9 h (in two separate studies).

The comparison of the pharmacokinetic profile of eplerenone in HF patients relative to healthy volunteers is inconclusive, as large variations in PK parameters were observed, especially for AUC. Possible pharmacokinetic differences, an increase of AUC of 15% - 40% for HF patients proved not clinically relevant as the large pivotal EPHESUS trial (n=3307) showed the overall efficacy and safety of eplerenone in patients with heart failure.

Pharmacokinetics were not influenced to a large extent in patients with impaired renal function. Patients with mild to moderate renal impairment (CrCl > 30ml/min) need no dose adjustments. On pharmacokinetic grounds this is agreed to. AUC and C_{max} of the inactive metabolites, SC-70303 and SC-71597 were increased with increasing (moderate or severe) renal dysfunction. For haemodialysis patients AUC and C_{max} were increased too, therefore haemodialysis is not an effective method to remove eplerenone from the systemic circulation in case of overdosage.

Moderate hepatic impairment led to a 29% reduced clearance of eplerenone and a 42% increased AUC at steady state. Despite the increased exposure to eplerenone the MAH suggested no initial dose adjustments as the observed differences are of such magnitude that this is not necessary. Child-Pugh scores are not explicitly summarised for the investigated patients. Severely hepatic impaired patients (Child-Pugh class C) have not been investigated; eplerenone is therefore contra-indicated in patients with severe hepatic impairment.

Gender differences in PK parameters were not observed. Negroid subjects had a significantly 26% lower AUC then Caucasian subjects and C_{max} was 19% lower in steady state, but this poses no safety nor

efficacy concerns. Globally pharmacokinetics seemed similar in Japanese subjects, though studies were not assessed in detail. Impact of weight was found to be relevant in a population pharmacokinetic model investigating hypertensive children and adults. The Vc/F (the apparent volume of distribution after non IV administration) was 38 L for a 50 kg patient. With a doubling of weight Vc/F increased with 45% resulting in a C_{max} reduction of 28%. The importance of this finding is unclear, as children are not a relevant target group in the current application. Weight adjustments are not necessary in adult patients. Drug clearance was decreased with 26-31% in elderly patients (65-77 years), AUC increased with 45%. The MAH nevertheless does not recommend dose-adjustments. Dose adjustments with respect to different age, gender, body weight or race are not necessary. However, in the elderly where there is the risk of declining renal function and an increased risk of hyperkalaemia, serum potassium levels should be periodically monitored in this patient group as is also mentioned in the SPC.

The main conclusions from the population pharmacokinetic studies are the impact of weight in the study with hypertensive children and adults. A critical remark regarding the submitted studies is that rather small sample sizes were used for estimation of the population pharmacokinetic model, which should be considered when drawing conclusions from these studies. The data for children is not relevant for the current application. Cl/F was ranging from 4.91 L/hr in patients with CHF, and in hypertensive patients from 7.33 L/hr to 8.19 L/hr. Weight and SGOT were the only covariates contributing to statistically significant differences in eplerenone pharmacokinetics. The impact of SGOT is clinically not relevant.

Based on in-vitro findings the MAH concludes that eplerenone does not inhibit CYP1A2, CYP2C19, CYP2C9 and CYP2D6. Eplerenone is also not a substrate or inhibitor for P-glycoprotein. The lack of inhibition of the P-GP-system was confirmed in a drug-drug interaction study with cyclosporin. CYP3A4 appears the main iso-enzyme in eplerenone metabolism. It is agreed that strong inhibitors of CYP3A4, like ketoconazole and itraconazole, should not be co-administered with eplerenone. Weaker CYP3A4 inhibitors fluconazole, verapamil, saquinavir and erythromycin led to two- to threefold increases of eplerenone AUC. A dosing advice of 25mg once daily is proposed in the SPC for concurrent treatment of eplerenone with these and other weak or intermediate CYP3A4 inhibitors. The impact of eplerenone on verapamil, saquinavir, and erythromycin plasma concentrations resulted in a 15%-30% reduction of plasma levels. These findings were however not clinically relevant. No clinically relevant effects of eplerenone interacting with other drugs were observed on pharmacokinetic profiles of CYP3A4 substrates, glyburide, midazolam, cisapride, norethisterone acetate and simvastatin. This was also unlikely based on *in vitro* found high inhibitor concentration to produce 50% inhibition (IC_{50}) (>300 µM) against the major human CYP isoforms.

AUC of digoxin increased 16% when co-administered with eplerenone. The effects of eplerenone on PT values when co-administered with warfarin were negligible.

Pharmacokinetics for type 2 diabetes patients on glyburide treatment are not affected by concurrent treatment with eplerenone. Small changes in pharmacodynamic profile were observed: insulin concentrations were increased in subjects taking glyburide; these changes did however not result in consistent changes in glucose levels. The findings seem therefore not clinically relevant.

In conclusion, the pharmacokinetic study parameters of eplerenone are well investigated and pose no specific problems in the therapeutic range. Sufficient safeguards have been built into the SPC to control for hyperkalaemia in especially the vulnerable elderly patient with HF.

Pharmacodynamics
Three pharmacodynamic studies were considered most relevant. Besides measurements of aldosterone and plasma renin levels, the PD studies evaluated the urinary $\log_{10}$ (Na+/K+) ratio in healthy subjects as an indicator of mineralocorticoid agonist activity. The administration of the synthetic mineralocorticoid fludrocortisone decreases urinary Na+ excretion and increases urinary K+ excretion, resulting in a decrease of the urine Na+/K+ ratio. In this manner, fludrocortisone mimics the activity of aldosterone. Aldosterone antagonists reverse the fludrocortisone-induced urinary electrolyte changes. Therefore, the anti-aldosterone activity of eplerenone or spironolactone can be determined by the degree to which it reverses fludrocortisone-induced changes of the urinary excretion of Na+ and K+.

The studies in healthy volunteers consistently confirmed the pharmacodynamic effects expected from a competitive blocker of aldosterone at the mineralocorticoid receptor, with an apparent minimal effective dose of eplerenone 25 mg QD (daily). A dose dependent response was present, although not consistently up to 1000 mg. The duration of the effect on urinary $\log_{10}$ (Na+/K+) ratio was also dose related. With respect to this urinary $\log_{10}$ (Na+/K+) ratio, both spironolactone and eplerenone showed rather comparable responses at a dose-range of 50-100 mg QD, although serum aldosterone levels with spironolactone 100 mg QD were more comparable to eplerenone 300 mg QD than to eplerenone 100 mg QD. This suggests that eplerenone is equally or slightly less potent compared to spironolactone in blocking the aldosterone receptor at similar dosages. Notably, the underlying mechanism between these anti-mineralocorticoid properties of spironolactone and the beneficial effects in patients with heart failure has never been elucidated. Serum sodium levels remained stable during administration of eplerenone and spironolactone, while serum potassium levels tended to increase in a dose dependent manner with eplerenone at dosages ≥ 100 mg. No events of hyperkalaemia were seen in eplerenone and spironolactone treatment groups, but only healthy subjects participated in these studies. Based on these studies, it is considered acceptable that the major dose response studies were carried out with a dose range between 25 and 100 mg, in particular because higher dosages will increase the risk of hyperkalaemia in patients with LV dysfunction.

No effect of eplerenone on cardiac repolarisation was observed. However, patient groups, e.g. congestive heart failure patients, females and elderly that are at increased risk of QT/QT_c interval prolongation and torsade de pointes were not studied. No clinical relevant problems are however expected.

Clinical efficacy

Dose Selection. A total daily dose of 50 mg eplerenone led to an effect comparable with 25 mg spironolactone, which was used in RALES. Increasing the eplerenone dose did not lead to higher aldosterone trough levels. Hyperkalaemia was associated with withdrawal in two patients who were on 100 mg eplerenone daily, no withdrawals in patients on lower eplerenone doses for hyperkalaemia were recorded, although hyperkalaemia by itself was not significantly differently associated with any dose of eplerenone. Using the experience from the EPHESUS trial it seems reasonable to accept PK-results as long as they stay within patient-exposures of eplerenone that fall within the typical dose-range used in that trial.

Clinical efficacy data were based on two dose-ranging studies (study 011 and 402) and one pivotal clinical outcome study (study 035). Eplerenone was extensively investigated in patients with hypertension, but no overview of efficacy data relating to this indication was submitted.

Table 1: Overview clinical studies

Study	Eplerenone Doses	Patient population	Primary efficacy endpoint	Concomitant medication	Treatment duration
011	25 mg QD 25 mg BID 50 mg QD 100 mg QD	Symptomatic chronic HF; LVEF<40%; NYHA Class II-IV; patients with AMI within 6 months were excluded	Neurohormone levels; NYHA functional classification; sodium retention score	ACE-I and loop diuretic with or without digoxin Active control spironolactone	16 weeks
402	25 mg QD 50 mg QD 100 mg QD	Japanese patients with symptomatic chronic HF; LVEF<40%; NYHA Class II-IV; patients with AMI within 6 months were excluded	RAAS and other cardio-renal hormone levels; NYHA function classification	ACE-I and/or loop diuretic with or without digoxin No active control	12 weeks
035 EPHESUS	25 mg QD increased to 50 mg QD at 4 weeks	AMI documented by ECG and enzyme changes, or history and enzyme changes in the presence of pace ventricular rhythm or LBBB; LVEF<40%; symptomatic HF	All cause mortality CV mortality or hospitalisation	Standard of care could have included ACE-I, diuretics, nitrates, P-blockers, aspirin, anticoagulants, antiplatelets, or revascularisation with thrombolytics, PTCR, or CABG. No active control	Mean duration of 16 months

The two short term (12-16 weeks) dose-ranging studies showed consistent evidence of blockade at the mineralocorticoid receptor at doses of at least 50 mg eplerenone per day in both Caucasian and Asian patients with symptomatic HF, LVEF < 40% and stable NYHA classification II-IV.

Study 035 (EPHESUS) was the pivotal phase 3 study comparing eplerenone (50 mg QD) to placebo on top of standard therapy in patients with a recent diagnosis of AMI with symptomatic HF and LV dysfunction. This large multicenter, double-blind, placebo-controlled, randomised study had acceptable in/exclusion criteria, dosing adjustment schedule and clinical endpoints. The absolute and relative numbers of patients receiving study medication and exposure to the study medication in each treatment group were sufficient. Baseline characteristics in both treatment groups were comparable. The investigated population using concomitant medication is considered to be sufficiently representative for the target patient population.

In EPHESUS, the rates of both co-primary endpoints were statistically significantly lower in the eplerenone treatment group compared to placebo, with substantial risk reductions relative to placebo of 15% for all cause mortality and 13% for CV mortality/hospitalisation, both with acceptable 95% confidence intervals for the risk ratio. The absolute risk reductions for the endpoints all cause mortality and CV mortality/hospitalisation were 2.3 and 3.3%, respectively. Accordingly, the number needed to treat was 50 and 33 patients, respectively. Both Kaplan-Meier curves showed a sustained difference in cumulative incidence in favour of eplerenone treated patients. Therefore, both co-primary endpoints showed a statistically significant and clinically relevant beneficial effect in favour of eplerenone in the whole population. In accordance with the primary endpoints, the rates of all secondary endpoints were also statistically significant lower in the eplerenone group compared to the placebo group. The precise mechanism behind the association of the use of eplerenone on top of standard therapy and reductions in all cause mortality and CV mortality/hospitalisation in patients with HF post-MI with LV dysfunction remains unknown, despite several sub-studies in EPHESUS conducted by the applicant. Subgroup analyses with respect to important factors such as region, serum creatinine, gender, diabetic status and concomitant medication appeared to confirm efficacy of eplerenone in these patients, except for those patients aged ≥75 years old in whom no beneficial effects could be demonstrated: the rate of all cause mortality was 26.8% with eplerenone and 26.3% with placebo, and the rate of CV mortality/hospitalisation was 45.5% with eplerenone and 40.8% with placebo.

No substantial difference in change from baseline in urinary aldosterone level in the 24-hour urine collections between eplerenone 25 mg BID and 50 mg QD was observed in study 011, and changes of aldosterone levels in both dose-ranging studies indicated that a maintenance dose of 50 mg per day

would be appropriate for EPHESUS. Eplerenone has a relatively short elimination half-life (4-6 hours), but -unlike spironolactone-no active metabolites with a long elimination half-life have been identified in human plasma. Therefore, eplerenone 25 mg BID is expected to exert pharmacodynamic activity during a larger part of the dosing interval than 50 mg QD, which might positively influence the efficacy of the drug. The MAH provided an adequate clarification for selecting the once daily dosing regimen in the EPHESUS study. The once daily dosing regimen was selected for the pivotal EPHESUS trial based on the nature of the mechanism of action, the dose-finding data comparing pharmacodynamic effects of 25 mg BID with 50 mg QD in BID in hypertension and heart failure patients, and the aldosterone-blocking performance of these doses relative to the RALES dose of spironolactone.

In summary, these data showed a clinically relevant beneficial effect of treatment with eplerenone plus standard therapy compared to placebo plus standard therapy on all cause mortality and CV mortality or hospitalisation in patients with symptomatic HF post-AMI and LV dysfunction. Efficacy appeared to be consistent among regions and subgroups; however, there were doubts for patients above 75 years of age. The rate of all cause mortality was 26.8% with eplerenone and 26.3% with placebo, and the rate of CV mortality/hospitalisation was 45.5% with eplerenone and 40.8% with placebo.

Clinical safety
Clinical safety of eplerenone was adequately documented. The number of patients exposed and the duration of exposure to eplerenone at dosages from 25 to 50 mg per day is sufficient. It is acknowledged that the target dose of eplerenone 50 mg QD was reached by the majority of patients without subsequent dose change due to increased serum potassium, and a large majority of eplerenone treated patients received 50 mg QD as their final dose. Nevertheless, the fact that 9% remained on eplerenone 25 mg QD underlines the importance of monitoring potassium levels in these patients.

In all 3 clinical studies, the overall incidence of treatment-emergent AEs was comparable among treatment groups. Statistically significantly higher percentages of eplerenone-treated patients experienced increased BUN, increased creatinine and hyperkalaemia compared to placebo, of which only hyperkalaemia was observed in ≥ 1.0% excess in EPHESUS. The absolute increases in BUN and creatinine were small and are considered of minor clinical importance.

The principal safety issue with eplerenone is hyperkalaemia in these HF post-AMI patients, often using ACE inhibitors (90%). In both dose ranging-studies, a dose dependent incidence of hyperkalaemia was present. In EPHESUS, a higher incidence of hyperkalaemia was observed with both decreasing baseline creatinine clearance and increasing age. Four independent risk factors were associated with serum potassium > 6.0 mmol/l: eplerenone treatment, baseline serum potassium, a history of diabetes and baseline creatinine clearance. This is in line with the knowledge on the use of spironolactone. The proportion of patients in EPHESUS with a creatinine clearance < 50 ml/min increased with age, evolving into a majority in patients aged ≥ 75 years. Hyperkalaemia is common in this age group since 12.7% of patients in the placebo group experienced serum potassium > 5.5 mmol/l. Hyperkalaemia was even more common in patients aged ≥ 75 years treated with eplerenone (21.5%), but age ≥ 75 was not an independent risk factor for serum potassium > 6.0 mmol/l. In these very elderly patients, the risk of hyperkalaemia was primarily due to an age-related decline in renal function. The MAH submitted second phase additional information. Although the incidence of hyperkalaemia was increased in the > 75 years age group, this did not warrant a contra-indication for this group of patients. Potassium elevations in EPHESUS were predictable, manageable and non-fatal. It is important however that the prescriber is aware of the occurrence of hyperkalaemia and the need for monitoring. Therefore in the revised SPC recommendations were included about dosing and monitoring in the elderly.
A small beneficial effect was present in terms of a decreased incidence of the infrequent adverse event hypokalaemia with eplerenone compared to placebo (0.5% vs. 1.5%, respectively).

In contrast to the use of spironolactone in the RALES study, the long-term administration of eplerenone was not associated with an increased incidence of sex-hormone related adverse events compared to placebo. Notably, the incidence of gynaecomastia in men was very low (eplerenone 0.5%; placebo 0.6%). The low incidence of sex-hormone related adverse events with eplerenone is likely due to a lower binding affinity for the progesterone and androgen receptors compared to spironolactone.

Overall, a statistically significantly greater percentage of patients in the placebo group experienced treatment-emergent SAEs (serious adverse events) compared to the eplerenone group and the majority of SAEs was of cardiovascular origin. The incidence of the treatment-emergent SAEs hypotension and syncope were comparable between treatment groups and incidences were low (≤ 1.4%). For the majority of SAEs with statistically significant differences between treatment groups, the incidence was significantly higher in the placebo group. For the events that were significantly more frequent in the eplerenone treatment group, the incidences were very low (≤ 0.5%). Although a substantial number of patients died in the 3 clinical trials, it is acknowledged that the population investigated suffered a large disease burden and that the prognosis of HF is poor. Deaths in two studies and non-endpoint deaths in EPHESUS showed no excess in any treatment group or dose dependency. As expected, most deaths were attributed to cardiovascular causes. Across the 3 clinical trials, no significant differences were observed between treatment groups in the overall percentage of patients experiencing treatment-emergent adverse events causing permanent discontinuation of study medication. In EPHESUS, cardiac failure and hyperkalaemia were relatively frequent causes for discontinuation of the study medication, but absolute incidences were very low (≤ 0.8%). Notably, hypotension rarely caused permanent discontinuation of study medication.

In summary, the safety profile of eplerenone is considered acceptable. Hyperkalaemia is the principal risk during treatment with eplerenone, especially in patients with impaired renal function (often elderly patients). However, during treatment with eplerenone no deaths due to hyperkalaemia occurred and the rate of discontinuation due to hyperkalaemia was very low (0.7%). Thus, as the SPC adequately reflects the potassium monitoring policy used in EPHESUS, hyperkalaemia is considered to be a manageable safety issue, except for patients excluded in the pivotal trial due to an initial serum potassium level > 5.0 mmol/l, moderate to severe renal insufficiency and severe hepatic insufficiency. These patients have been contra-indicated in section 4.3 of the SPC.

Overall benefit/risk assessment

The benefit/risk ratio of eplerenone was assessed to be positive as a consistent and clinically relevant reduction in all cause mortality and CV mortality/hospitalisation has been demonstrated in stable patients with LV dysfunction and heart failure after recent myocardial infarction, with an acceptable safety profile.

As expected, hyperkalaemia is the major safety issue, but the incidence of discontinuation of eplerenone due to hyperkalaemia was very low and no deaths occurred due to hyperkalaemia. The incidence of sex-hormone related adverse events, in particular gynaecomastia, was low. In general, the results on clinical efficacy are in line with those obtained with spironolactone in another patient group with more severe chronic heart failure as a result of LV systolic dysfunction (RALES study), but both studies should be compared with caution, mainly because substantial differences exist in patient characteristics (eg. severity of HF), concomitant medications used and the timing of initiation of therapeutic intervention.

Product information

During the assessment in the MRP, common product information texts were determined. The MAH updated the national translations for the Netherlands accordingly. The SPC has been adapted according to recent CPMP recommendations (see EMEA/CPMP/3538/03), to contain a more general wording on the prevention indication in Section 4.1 and a balanced description of the pivotal trial relevant to the prescriber in Section 5.1. The MAH also agreed to include more specific notifications concerning the risk of hyperkalaemia, recommendations for the monitoring of serum potassium and possible subsequent dose adjustments in Section 4.2 ‘Posology’ of the SPC. Also, Section 4.3 ‘Contra-indications’ and Section 4.4 ‘Special warnings’ have been brought in line with the policy and results of the EPHESUS trial, to ensure safe eplerenone administration in patients at risk for hyperkalaemia, such as (elderly) patients with impaired renal function.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The MEB considered during the national procedure, on the basis of the data submitted, that Inspra 25 and 50, film-coated tablets 25 mg and 50 mg demonstrate adequate evidence of efficacy for the approved indications as well as a satisfactory benefit-risk profile, and therefore granted a marketing authorisation. During the mutual recognition and repeat-use procedure that proceeded immediately after national registration in the Netherlands, the other member states mutually recognised the Dutch marketing authorisation.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates.

During the national procedure, discussion of the application in the Board meeting of 30 October 2003 focussed on the clinical pharmacological part of the dossier. Mainly, it was noted that the description of the indication should clearly state that the product is indicated directly after an acute myocardial infarction. The Board followed the advice of the assessors. The MEB, on the basis of the data submitted, considered that quality, efficacy and safety were demonstrated. Therefore, the Board granted a marketing authorisation. Inspra 25 and 50, film-coated tablets 25 mg and 50 mg were authorised in the Netherlands on 16 March 2004.

The mutual recognition procedure, followed by a repeat-use procedure, was initiated directly upon registration in the Netherlands. Agreement between member states was reached during a written procedure. The mutual recognition procedure was finished on 5 August 2004. The repeat-use procedure was finalised on 22 December 2005.

Post-approval commitments (PACs)
During the repeat use procedure, several commitments made during the first MRP have been solved. The following post-approval commitments have been made during the repeat use procedure or are still outstanding:

Chemical-pharmaceutical part: The applicant committed to submit a variation updating the Certificate of Suitability for magnesium stearate and a notification to update the application form to include a specific manufacturing site.
Patient information leaflet and labelling: The applicant committed initiating the PIL and packaging harmonisation process within 6 months after completion of the MRP.
Environmental toxicity: The applicant committed to submit an Environmental Risk Assessment report.
Clinical part: As part of a pre-planned Phase 3b (placebo controlled) study, the applicant will collect data in the elderly population to further investigate the incidence of stroke.

Renewal
The first renewal was positively concluded on 27 April 2009. Renewal was granted for an unlimited period. During the renewal procedure the MAH made the commitment to submit a cumulative overview of all hepatic events together with a thorough discussion in the next PSUR and to closely monitor:

- Breast-related disorders
- Hyperkalaemia
- Hepatic Events
- Renal Events
- Skin Events
- Vasculitis
- Cases involving patients with medical histories indicative of renal disorders, particularly the elderly with severe outcomes

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
PSUR (16.03.04 - 15.09.04)						
Post approval commitment: collection of data in the elderly population to further investigate the incidence of stroke as part of a pre-planned Phase 3b (placebo controlled) study		PAC	20-12-2004	01-03-2005	Approval	N
Post approval commitment: conduction of an hERG study (data to be provided within 6 months after the end of the procedure)		PAC	20-12-2004	14-04-2005	Approval	N
Addition of a secondary packaging site of the finished product.	NL/H/0506/001-002/IA/002	IA	10-02-2005	24-02-2005	Approval	N
Addition of a secondary packaging site of the finished product.	NL/H/0506/001-002/IA/003	IA	10-02-2005	24-02-2005	Approval	N
Addition of a secondary packaging site of the finished product.	NL/H/0506/001-002/IA/004	IA	10-02-2005	24-02-2005	Approval	N
Change of the name of the manufacturer of the finished product	NL/H/0506/001-002/IA/005	IA	15-02-2005	01-03-2005	Approval	N
PSUR (16.09.04-15.03.05)					Approval	N
Change in the pack size of the finished product (change in the number of tablets in a pack within the currently approved range).	NL/H/0506/001-002/IA/006	IA	15-02-2005	29-07-2005	Non-Approval	N
Repeat use MRP	NL/H/0506/001-002/E/01		08-09-2005	22-12-2005	Approval	N
Change in the pack size of the finished product (change in the number of tablets in a pack within the currently approved range).	NL/H/0506/001-002/IA/007	IA	28-04-2006	12-05-2006	Approval	N
PSUR (16.03.05 – 15.09.05)						
Post approval commitment: responses to environmental toxicity queries (ERA)		PAC	04-05-2007	17-10-2007	Approval	N
Change address MAH in IE	NL/H/0506/001-002/IA/008	IA	28-04-2005	12-05-2006	Approval	N
Change address MAH in EE	NL/H/0506/001-002/IA/009	IA	28-04-2005	12-05-2006	Approval	N
Change address MAH in AT	NL/H/0506/001-002/IA/010	IA	28-04-2005	12-05-2006	Approval	N
Change address MAH in SE	NL/H/0506/001-002/IA/011	IA	28-04-2005	12-05-2006	Approval	N
PSUR (19.09.05-15.03.06)						
Harmonisation of the PIL and labelling within the member states	NL/H/0506/001-002/II/012	II (PAC)	29-09-2006	20-04-2007	Approval	N
Addition of a statement regarding two adverse events (gynecomastia and angioneurotic oedema) in section 4.8 of the SPC	NL/H/0506/001-002/II/013	II	25-09-2006	20-04-2007	Approval	N
Addition of a primary packaging site for the finished product	NL/H/0506/001-002/IA/014	IA	25-09-2006	09-10-2006	Approval	N
Addition of a manufacturer responsible for batch release including batch control/testing	NL/H/0506/001-002/IA/015	IA	25-09-2006	09-10-2006	Approval	N
Post approval commitment chemical-pharmaceutical part: notification to update the application form to include a specific manufacturing site		PAC	26-10-2006	1-11-2006	Approval	N
Submission of an updated TSE Ph. Eur. Certificate of Suitability for an excipient, namely magnesium stearate.	NL/H/0506/001-002/AI/016	IA (PAC)	06-11-2006	20-11-2006	Approval	N

Change address MAH in SI	NL/H/0506/001-002/IA/017	IA	06-11-2006	20-11-2006	Approval	N
Change of the name of the manufacturer of the finished product	NL/H/0506/001-002/IA/018	IA	22-02-2007	08-03-2007	Approval	N
Change in the address of the MAH in DE	NL/H/0506/001-002/IA/019	IA	15-10-2008	29-10-2008	Approval	N
Renewal	NL/H/0506/001-002/R/001		3-12-2008	27-4-2009	Approval	N
Change in the address of the MAH in IT	NL/H/0506/001-002/IA/020	IA	30-01-2009	13-02-2009	Approval	N
Addition of alternate manufacturing process for the active substance including addition of supplier for the last step	NL/H/0506/001-002/II/021	II	02-07-2009	18-02-2010	Approval	N
Change in the name of active substance manufacturer	NL/H/0506/001-002/IA/022	IA	08-06-2009	22-06-2009	Approval	N
Deletion of a testing site	NL/H/0506/001-002/IA/023	IA	08-06-2009	22-06-2009	Approval	N
Deletion of a batch release site and packaging site	NL/H/0506/001-002/IA/024	IA	08-06-2009	22-06-2009	Approval	N
Change in the name of the packaging site	NL/H/0506/001-002/IA/025	IA	08-06-2009	22-06-2009	Approval	N
Change to a test procedure of the immediate packaging of the finished product	NL/H/0506/001-002/IB/026	IB	06-10-2009	05-11-2009	Approval	N
Change of the name of the MAH in ES	NL/H/0506/001-002/IA/027	IA	01-03-2011	31-03-2011	Approval	N
Addition indication: reduction of the risk of mortality and morbidity in patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (EF < 35%) in addition to standard optimal therapy.	NL/H/0506/001-002/II/028	II	28-04-2011	15-02-2012	Approval	Y
Change of the pack size outside the currently approved range	NL/H/0506/001-002/IB/029	IB	24-06-2011	24-07-2011	Approval	N
Change in source of an excipient or reagent: from TSE risk material to vegetable or synthetic origin	NL/H/0506/001-002/IA/030	IA	04-08-2011	01-09-2011	Approval	N

ANNEX I – Addition of the indication: "Reduction of the risk of cardiovascular mortality and morbidity in adult patients with NYHA class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤ 30%) in addition to standard optimal therapy'' (Type II variation NL/H/0506/001-002/II/028).

I RECOMMENDATION

Based on the review of the data on safety and efficacy, the Medicines Evaluation Board of the Netherlands (MEB) has accepted to extend the indication to:

"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 ≤30%) (see Section 5.1)".

A comprehensive description of the indications and posology is given in the SPC.

II EXECUTIVE SUMMARY

II.1 Scope of the variation

The product was initially indicated to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction and clinical evidence of heart failure after recent myocardial infarction. In this type II variation, the MAH is seeking an extension of the 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%) in addition to standard optimal therapy.

In support of this application, the MAH submitted one study, the 'Eplerenone in Mild Patients Hospitalisation And Survival Study in Heart Failure (EMPHASIS-HF) trial. EMPHASIS-HF was a double-blind, placebo-controlled, parallel group trial comparing the effect of eplerenone versus placebo on top of standard heart failure therapy on mortality and morbidity outcomes in patients with mild chronic systolic heart failure (NYHA functional Class II) and left ventricular systolic dysfunction.
EMPHASIS-HF was designed to enrol approximately 3100 subjects and to run until 813 primary endpoint events had been reported. During the second protocol-specified interim analysis on 6 May 2010, the Data Safety Monitoring Committee (DSMC) confirmed that the study had reached its primary efficacy endpoint early, that the pre-specified stopping rules for efficacy had been met, and advised the Executive Steering Committee (ESC) to recommend terminating the trial for efficacy. Consequently, the ESC recommended that the sponsor should terminate further enrolment of subjects into the double-blind phase of the trial and provide a mechanism to make eplerenone available to all participating subjects. Enrolment into the study was accordingly halted on 26 May 2010, and the MAH initiated the regulatory and ethics board processes to add an open-label extension phase to the study. All active subjects who were participating in the double-blind phase of EMPHASIS-HF were given the opportunity to receive open-label eplerenone for a period of 12 months.

The MAH consulted the MEB on 21 December 2010 for Scientific Advice before submission of the variation. The MEB circulated the preliminary report on 21 June, 2011. The main concerns were related to SPC changes. During the assessment of the responses, the RMS requested on 10 November 2011 further supplementary data which were considered important for adequate assessment of the responses, in particular the exact incidence of cardiovascular (CV) hospitalisations in the recruited patients, analysis of deaths reported in the long term extension study, and specific data for patients above 75 years. The MAH sent their supplementary response on 23 November, together with an adaptation of the proposed indication, more in line with the submitted data. Following the assessment of the responses and the adaptation of the SPC, the benefit risk assessment of eplerenone in this new indication is considered positive.

III SCIENTIFIC DISCUSSION

III.1 Quality aspects

N/A.

III.2 Non-clinical aspects

No new data have been submitted.

Environmental Risk Assessment

Since the use of the product is expected to increase after authorisation of the additional indication, the company provided an updated ERA (first submitted ERA in 2007). It is concluded that the environmental risk is still acceptable and unchanged by the current variation.

III.3 Clinical aspects

The extension of the indication is supported by data from a single study (EMPHASIS-HF). This was a multinational (29 countries), randomised, double-blind, placebo-controlled, parallel-group trial. **EMPHASIS-HF** is the first study investigating a mineralocorticoid antagonist (MRA) in patients with mild symptoms of heart failure. Spironolactone is recommended in current guidelines for patients with moderate to severe heart failure in addition to standard optimal therapy, but this has not been assessed for regulatory purposes.

III.3.1 CLINICAL EFFICACY

Objectives

The primary objective of this trial was to evaluate the efficacy and safety of eplerenone versus placebo on top of standard HF therapy on the cumulative incidence of CV mortality or hospitalisation for heart failure (a composite primary endpoint). A separate objective of this study was to collect data to further investigate the incidence of stroke in very elderly patients (≥75 years) with chronic systolic heart failure with mild symptoms. This was part of a post-approval commitment (PAC) agreed to by the sponsor as part of the approval of Inspra in Europe in 2004.

Methods

Main inclusion criteria

Subjects in the double-blind phase must have been ≥ 55 years of age with chronic systolic HF of either ischemic or non-ischemic aetiology (duration of at least 4 weeks; left ventricular ejection fraction (LVEF) ≤30% or LVEF ≤ 35% in addition to QRS duration ≥130 ms; NYHA II; treated with ACE inhibitors and/or ARBs, beta-blockers, diuretics), serum potassium level ≤ 5.0 mmol/l within 24 hours prior to randomisation, estimated glomerular filtration rate (eGFR) ≥ 30 ml/min/1.73 m^2 within 24 hours prior to randomisation, and randomisation must have occurred no later than 6 months from the date of admission to a hospital for a CV reason (or, in the absence of a recent admission to hospital for a CV reason, documentation of a plasma concentration of B-type natriuretic peptide [BNP] of at least 250 pg/mL or amino-terminal proB-type natriuretic peptide [NT-proBNP] of at least 500 pg/mL for males and 750 pg/mL for females, within 15 days of randomisation).

According to the MAH, patients in NYHA functional class II chronic systolic heart failure may be stable and prone to few or infrequent events, making any study in this population a substantial challenge. To avoid recruitment problems, the MAH included entry criteria of patients with increased risk profile, see discussion.

Analysis showed that there were only 96 subjects randomised on the basis of LVEF 31-≤35% and QRS > 130 ms, the majority of the patients were recruited on the basis of a LVEF ≤ 30%.

Study treatment

For the first 4 weeks of treatment, subjects received eplerenone 25 mg or matching placebo (1 tablet) once daily [once every other day (EOD) for subjects with an eGFR between 30 and 49 mL/min/1.73m^2}. The first dose of study drug was to be taken at randomisation. At week 1 following randomisation, the dose of study drug could be adjusted (according to serum potassium level) as shown in the following table (Table E1).

Table E1. Dose adjustment or maintenance of study drug at 1 week after randomisation

Serum Potassium (K^+) (mmol/L)	eGFR 30-49 mL/min/1.73 m^2	eGFR ≥50 mL/min/1.73 m^2
<5.5	Continued 25 mg (1 tablet) EOD	Continued 25 mg (1 tablet) OD
5.5 – 5.9	Withheld dose – rechecked K^+ within 72 hours: If K^+ <5.0, restarted 25 mg (1 tablet) EOD; If K^+ ≥5.0, continued to monitor K^+, restarted study drug/eplerenone ONLY when K^+ was <5.0.	Decreased dose to 25 mg (1 tablet) EOD
≥6.0	Withheld dose – rechecked K^+ within 72 hours: If K^+ <5.0, restarted at 25 mg (1 tablet) EOD; If K^+ ≥5.0, continued to monitor K^+, restarted study drug/eplerenone ONLY when K^+ was <5.0.	Withheld dose – rechecked K^+ within 72 hours: If K^+ <5.0, restarted at new dose of 25 mg (1 tablet) EOD; If K^+ ≥5.0, continued to monitor K^+, restarted study drug/eplerenone ONLY when K^+ was <5.0.

At 4 weeks and at each subsequent clinic visit, the serum potassium level was checked and the study drug/eplerenone dose was adjusted as shown in table E2. Additionally, the serum potassium level was checked 1 week after any dose adjustment. For subjects with an eGFR from 30 to 49 ml/min/1.73 m^2, the maximum daily dose of eplerenone was not to exceed 25 mg.

Table E2: Dose adjustment or maintenance of study drug at week 4 and at subsequent visits

Serum Potassium (K^+) (mmol/L)	eGFR 30-49 mL/min/1.73 m^2	eGFR ≥50 mL/min/1.73 m^2
<5.0	Increased dose as follows: 25 mg (1 tablet) EOD to 25 mg (1 tablet) OD.	Increased dose as follows: 25 mg (1 tablet) EOD to 25 mg (1 tablet) OD; 25 mg (1 tablet) OD to 50 mg (2 tablets) OD[a].
5.0 – 5.4	Continued current dose (no adjustment).	Continued current dose (no adjustment).
5.5 – 5.9	Decreased as follows: 25 mg (1 tablet) OD to 25 mg (1 tablet) EOD. If current dose was 25 mg (1 tablet) EOD, withheld dose and rechecked K^+ within 72 hours: If K^+ <5.0, restarted at 25 mg (1 tablet) EOD; If K^+ was ≥5.0, continued to monitor K^+ and restarted study drug/eplerenone at 25 mg (1 tablet) EOD ONLY when K^+ was <5.0.	Decreased as follows: 50 mg (2 tablets) OD to 25 mg (1 tablet) OD; 25 mg (1 tablet) OD to 25 mg (1 tablet) EOD. If current dose was 25 mg (1 tablet) EOD, withheld dose and rechecked K^+ within 72 hours: If K^+ <5.0, restarted at 25 mg (1 tablet) EOD; If K^+ was ≥5.0, continued to monitor K^+ and restarted study drug/eplerenone at 25 mg (1 tablet) EOD ONLY when K^+ was <5.0.
≥6.0	Withheld dose – rechecked K^+ within 72 hours and restarted study drug/eplerenone at 25 mg (1 tablet) EOD ONLY when K^+ was <5.0.	Withheld dose – rechecked K^+ within 72 hours and restarted study drug/eplerenone at 25 mg (1 tablet) EOD ONLY when K^+ was <5.0.

Efficacy evaluations

The primary efficacy endpoint was the first occurrence of CV mortality or hospitalisation for heart failure. The secondary efficacy endpoint was the first occurrence of all-cause mortality or HF hospitalisation. Other secondary endpoints included: all-cause mortality; CV mortality; all-cause hospitalisation; HF hospitalisation; all-cause mortality or all-cause hospitalisation; HF mortality or HF hospitalisation; CV hospitalisation; fatal/nonfatal myocardial infarction (MI); fatal/nonfatal stroke; implantation of cardiac defibrillator (ICD); implantation of resynchronisation device (cardiac resynchronisation therapy (CRT)); new-onset atrial fibrillation(AF)/flutter; new-onset diabetes mellitus (DM); worsening renal function (if it results in hospitalisation); and hospitalisation for hyperkalaemia.

Statistical methods

The data cut-off date was 25 May 2010. The Full Analysis Set (FAS) was composed of all randomised subjects. For all efficacy analyses during the double-blind phase, available data from the FAS were analysed according to the intention-to-treat (ITT) principle based on the subjects' randomised treatment assignment, and all subjects were followed for mortality and other major endpoints for the duration of the double-blind treatment period, regardless of compliance with the study drug and the protocol.

The primary statistical analysis model for the double-blind phase was determined as the Cox proportional hazards regression model adjusting for baseline prognostic factors based on the FAS. All pre-specified primary and secondary efficacy endpoints for the double-blind phase listed were analysed using this adjusted Cox PH (proportional hazards) model. All hypothesis tests for efficacy endpoints were 2-sided. Results were considered statistically significant if a p-value of <0.049 (adjusted for interim analyses) was obtained for the primary hypotheses and <0.01 for the secondary hypotheses.

An independent Data Safety Monitoring Committee (DSMC) reviewed un-blinded data and provided recommendations to the Executive Steering Committee (ESC) on early termination and conduct of the trial. Interim analyses examining the primary efficacy endpoint were performed after a total of approximately 271 and 542 primary endpoint events had occurred. Final analysis was planned when 813 events had occurred.

Study termination
At the time of the protocol-specified second interim analysis by the DSMC, a total of 501 adjudicated primary endpoint events were reviewed and analysed. This analysis showed benefit in the eplerenone-treated group compared to the placebo arm, according to the pre-specified stopping rules. As a result, the DSMC informed the ESC, and both committees subsequently recommended that further recruitment be stopped. Hence, the protocol was amended to incorporate a 12-month open-label extension, eplerenone-only phase to permit the continued administration of eplerenone to these subjects once appropriate regulatory and ethics committee approvals were obtained. Recruitment was stopped as of 26 May 2010, by the recommendation of the DSMC and ESC, and a 12-month open-label phase was added

Results

Patient disposition
A total of 3027 subjects were screened for participation in this study, and 1364 and 1373 subjects were assigned to the eplerenone and placebo groups, respectively. Of these patients 1360 and 1369 subjects in the eplerenone and placebo groups were treated respectively. Eight subjects (4 in each treatment group) were randomised but not treated in this study.

Demographics
Out of the 2737 randomised subjects, the majority were Caucasian (1141 subjects (83.1%) in the placebo group, and 1127 subjects (82.6%) in the eplerenone group). Of these, 78.1% and 77.3% were male in the placebo and eplerenone groups respectively. The mean age was 68.6 years in the placebo group and 68.7 years in eplerenone group. The two treatment groups were comparable with respect to the baseline characteristics and the use of various cardiac medications at enrolment. Patient's demographics are in line with the expected target population. The mean follow-up time was 21.1 months, which is an adequate study duration. The majority of the patients had a history of ischemic heart failure which is in line with heart failure studies (table E3). The disease duration (around 5.3 years) and the fact that more than half of the patients (around 52%) were already previously hospitalised for heart failure confirm that this is not the typical NYHA II population. In the current study, there is adequate representation of patients with moderate renal impairment (eGFR: 30 to 60 ml/min/1.73m2) (n=912 in total); contrary to the EPHESUS study, where such patients were excluded. The dose selection in patients with mild and moderate renal impairment is addressed under Safety.

Table E3: Important concomitant diseases and medical history

	Eplerenone	Placebo
Ischemic heart failure, n (%)	951 (69.7)	935 (68.1)
Disease duration, years		
Number of subjects	950	935
Mean (SD)	5.36 (6.27)	5.34 (5.87)
Nonischemic heart failure, n (%)	410 (30.1)	436 (31.8)
Disease duration, years		
Number of subjects	410	435
Mean (SD)	3.43 (4.82)	3.17 (4.42)
Previous myocardial infarction, n (%)	686 (50.3)	695 (50.6)
Diabetes mellitus at screening, n (%)	459 (33.7)	400 (29.1)
Atrial fibrillation/flutter at screening, n (%)	409 (30.0)	435 (31.7)
Previous hospitalization for congestive heart failure	714 (52.3)	726 (52.9)
Prior hospitalization admitting diagnosis		
Heart failure	740 (54.3)	756 (55.1)
Acute coronary syndromes	202 (14.8)	188 (13.7)
Arrhythmia	94 (6.9)	103 (7.5)
Cerebrovascular disease	2 (0.1)	11 (0.8)
Peripheral vascular disease	2 (0.1)	1 (0.1)
Other cardiovascular reasons	72 (5.3)	80 (5.8)
Elective hospitalization for ICD/CRT placement	46 (3.4)	40 (2.9)
Days between hospital admission and the start of randomization, mean (SD)	57.7 (56.3)	56.1 (61.9)

Concomitant medications

Table E4 summarises the most important medications co-administered with the study medication. It can be concluded that patients received state of the art treatment, with most of the patients administered beta-blockers (~90%), ACE.I (~80%), diuretics (~89%). As ACE.I were administered in the majority of the patients, it is reassuring to observe that ARBs were only administered in ~24%, considering that the triple combination of ACE.I, ARBs and eplerenone should not be administered according to the ESC guideline for heart failure (2008). In line with these recommendations, the triple combination is contraindicated in the agreed SmPC.

Table E4: Summary of selected concomitant drug treatments (Full Analysis Set)

	Number (%) of Subjects	
	Eplerenone	Placebo
Total number of subjects	1364	1373
Concomitant drug treatments		
ACE inhibitors, combinations	7 (0.51)	10 (0.73)
ACE inhibitors, plain	1095 (80.28)	1091 (79.46)
Angiotensin II antagonists, combinations	8 (0.59)	9 (0.66)
Angiotensin II antagonists, plain	333 (24.41)	341 (24.84)
Other agents acting on the renin-angiotensin system	3 (0.22)	2 (0.15)
Beta-blockers	1233 (90.40)	1248 (90.90)
Diuretics	1203 (88.20)	1231 (89.66)

Administered dose

The percentage of subjects who were up-titrated to 50 mg OD at month 5 was 61.3% in the eplerenone group and 66.3% in the placebo group. At Month 5, the mean dose of eplerenone was 39.5 mg and of placebo was 41.1 mg. At study cut-off, the mean final dose was 37.4 mg in the eplerenone group and 39.2 mg in the placebo group.

Discontinuations from treatment.
Discontinuations were generally balanced between the treatment groups: a total of 376 (27.6%) and 406 (29.7%) subjects from the eplerenone and placebo groups, respectively, discontinued the study. The most common reasons for treatment discontinuation were death, reported more in the placebo group (11.3% and 13.0% subjects in the eplerenone and placebo group respectively) and subject no longer willing to participate in the study (7.4% and 8.3% in the eplerenone group and placebo groups respectively).

Efficacy Results
The primary endpoint was time to the first occurrence of either CV death or hospitalisation for HF. A total of 249 (18.3%) subjects in the eplerenone group and 356 (25.9%) subjects in the placebo group reported having CV mortality or hospitalisation for HF (Fig 1; Table E5). This represents a statistically significant 37.0% relative risk reduction for the eplerenone group compared to the placebo group (p <0.0001). Importantly each of the components of the primary endpoint showed significant results as well. Hospitalisation for HF occurred in 164 (12.0%) subjects in the eplerenone group and 253 (18.4%) subjects in the placebo group. This represents a 42.4% relative risk reduction for the eplerenone group compared to the placebo group (p <0.0001). CV mortality occurred in 147 (10.8%) subjects in the eplerenone group and 185 (13.5%) subjects in the placebo group. This represents a 24.3% relative risk reduction for the eplerenone group compared to the placebo group (p = 0.0120).
The results indicate a clinically relevant benefit for eplerenone as also shown by absolute risk reduction of the primary endpoint (7.6%) and hospitalisations due to heart failure (6.4%) followed by overall mortality (3%) and CV mortality (2.7%).

Table E5. Survival analysis of heart failure hospitalisation or cardiovascular death (Full Analysis Set)

	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

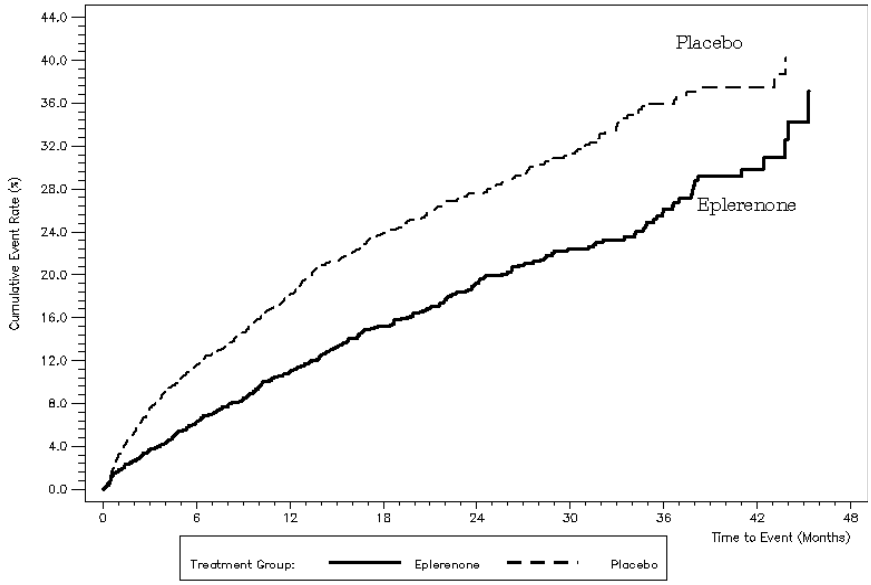

Figure 1: Incidence of CV death or hospitalisation for HF in eplerenone and placebo treated subjects (primary endpoint: FAS)

Secondary endpoints

There was a statistically significant relative risk reduction for the eplerenone group compared to the placebo group for the secondary endpoints of all-cause mortality (RRR: 24%; p = 0.0081), all-cause mortality or HF hospitalisation, all-cause hospitalisation, HF hospitalisation, all-cause death or all-cause hospitalisation, HF death or HF hospitalisation, CV hospitalisation (Table E6), and new-onset AF/flutter. Fatal/nonfatal MIs occurred in 45 (3.3%) eplerenone-treated subjects and in 33 (2.4%) placebo group subjects; this difference was not significant (p = 0.2321). Further analysis of this issue based on the incidence of adjudicated fatal/non-fatal MI observed in the full analysis dataset between the eplerenone group (49 events, 3.6%) and the placebo group (40 events, 2.9%) supports that this may be a chance finding. Patients medical history revealed that around 50% of these patients already had CAD (coronary artery disease), but the respective frequency in placebo patients was not given, precluding a conclusion on this point. However, the presented data does not support that administration of eplerenone per se could have played a role in the incidence of fatal/non fatal MI.

Table E6: Survival analysis of the secondary endpoints (Full Analysis Set)

	Number (%) of Subjects		Hazard Ratio	P-value	95% CI for Hazard Ratio
	Eplerenone (N = 1364)	Placebo (N = 1373)			
All-cause mortality or HF hospitalization	270 (19.8)	376 (27.4)	0.647	<0.0001	0.552, 0.757
All-cause mortality	171 (12.5)	213 (15.5)	0.761	0.0081	0.622, 0.932
CV mortality	147 (10.8)	185 (13.5)	0.757	0.0120	0.609, 0.941
All-cause hospitalization	408 (29.9)	491 (35.8)	0.768	<0.0001	0.673, 0.876
HF hospitalization	164 (12.0)	253 (18.4)	0.576	<0.0001	0.473, 0.702
All-cause death or all-cause hospitalization	462 (33.9)	569 (41.4)	0.751	<0.0001	0.664, 0.849
HF death or HF hospitalization	170 (12.5)	262 (19.1)	0.577	<0.0001	0.475, 0.701
CV hospitalization	304 (22.3)	399 (29.1)	0.694	<0.0001	0.598, 0.806
Fatal/nonfatal MI	45 (3.3)	33 (2.4)	1.316	0.2321	0.839, 2.064
Fatal/nonfatal stroke	21 (1.5)	26 (1.9)	0.789	0.4213	0.443, 1.406
ICD	61 (4.5)	59 (4.3)	0.994	0.9754	0.694, 1.424
Implantation of resynchronization device (CRT)	33 (2.4)	41 (3.0)	0.770	0.2652	0.485, 1.220
Hospitalization for worsening renal function	9 (0.7)	8 (0.6)	0.971	0.9537	0.366, 2.578
Hospitalization for hyperkalemia	4 (0.3)	3 (0.2)	1.154	0.8539	0.251, 5.312

Table E7 summarises the causes of CV death and CV hospitalisation.

Table E7: Summary of causes for cardiovascular death and cardiovascular hospitalisation (Full Analysis Set)

	Eplerenone	Placebo
Total number of subjects	1364	1373
Total number of adjudicated endpoints	921	1174
Number (%) of subjects with HF hospitalization or CV death	249 (18.3)	356 (25.9)
Number (%) of subjects with HF hospitalization	164 (12.0)	253 (18.4)
Number (%) of subjects with CV death	147 (10.8)	185 (13.5)
Sudden cardiac death	60 (4.4)	76 (5.5)
Worsening heart failure	45 (3.3)	61 (4.4)
Myocardial infarction	13 (1.0)	8 (0.6)
Arrhythmia	7 (0.5)	7 (0.5)
Stroke	6 (0.4)	7 (0.5)
Emergency CV procedure/operation	0	0
Other CV event	3 (0.2)	1 (0.1)
Unknown	13 (1.0)	25 (1.8)
Number (%) subjects with CV hospitalization	304 (22.3)	399 (29.1)
Heart failure	164 (12.0)	253 (18.4)
Arrhythmia	49 (3.6)	74 (5.4)
Myocardial infarction, unstable angina, other chest pain	68 (5.0)	61 (4.4)
Stroke, TIA	25 (1.8)	32 (2.3)
Syncope/near syncope, hypotension	19 (1.4)	18 (1.3)
Cardiac tamponade, endocarditis, hypertension, valvular heart disease, other CV event, other	25 (1.8)	40 (2.9)
Pulmonary embolism	1 (0.1)	2 (0.1)
Other peripheral arterial problem	13 (1.0)	11 (0.8)
Ruptured aneurysm	1 (0.1)	0

Subgroup analysis

The effect of eplerenone in reducing the risk of CV death or hospitalisation for HF was consistent across subgroups, and the significant risk reductions were present in a majority of the subgroups (Fig 2 and Tables E8-E10). The difference between eplerenone and placebo did not achieve statistical significance in subgroups of subjects who had no prior beta-blocker use, subjects who had no prior ACE.I or ARB use, subjects with prior hospitalisation >180 days, and subjects with LBBB present, and the numbers of the subjects in those subgroups are relatively small.

Importantly, for patients from west Europe/Australia (n=1100) the results are in line with the main study. Of special interest are patients vulnerable to potassium retention. Efficacy data of the subgroup of patients with mild or moderate renal impairment or patients with diabetes are in line with the general cohort. Patients ≥ 75 years were well represented in the study (n=657 in total) and showed comparable results to the main cohort (Table E8). Incidence of fatal and non fatal stroke was comparable in patients ≥ 75 years administered eplerenone (2.7%) and placebo (2.4%). Therefore the post authorisation commitment PAC to address the issue of safety of eplerenone in this patient population is considered fulfilled.

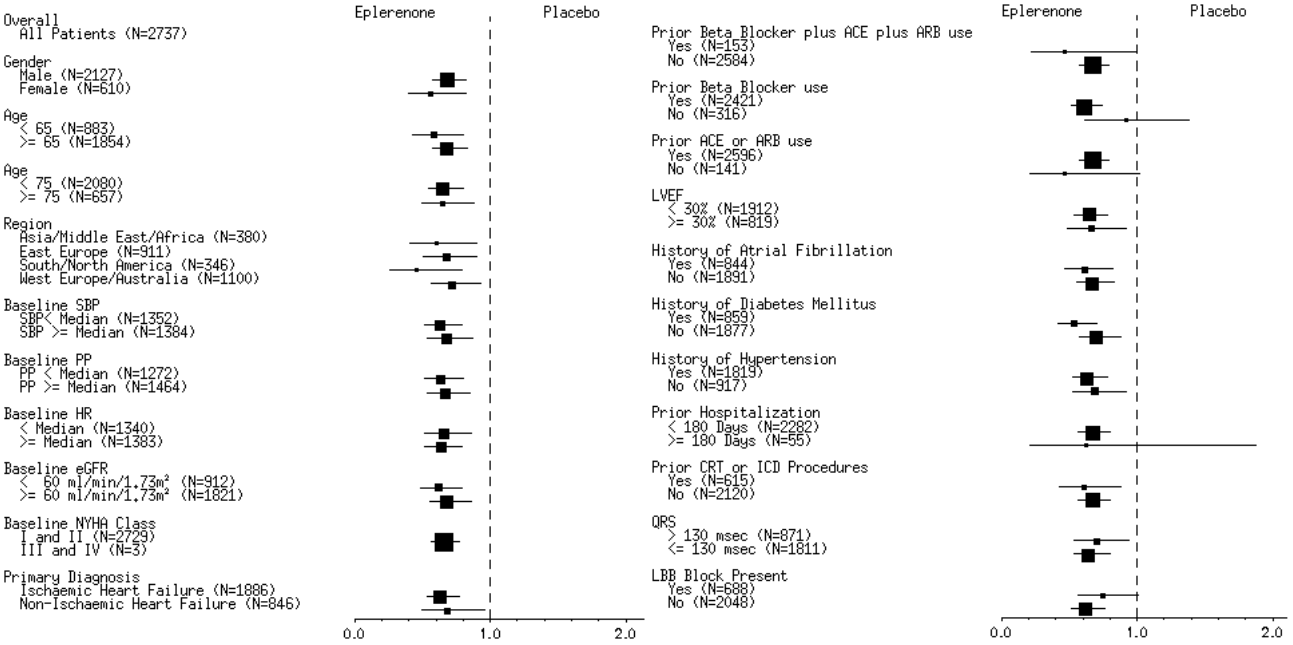

Figure 2: Selected subgroup analyses of the primary endpoint (CV death or hospitalisation for HF) in eplerenone and placebo treated subjects (FAS subgroups)

Table E8: Survival analysis of the primary and secondary endpoints (age ≥ 75)

	Eplerenone	Placebo	Hazard Ratio (a)	P-value (a)	95% CI for Hazard Ratio (a)
Total number of Subjects	330	327			
HF Hospitalization/CV Death	78 (23.6%)	107 (32.7%)	0.657	0.0048	(0.490, 0.879)
All-cause mortality or heart failure (HF) hospitalization	85 (25.8%)	114 (34.9%)	0.671	0.0053	(0.506, 0.888)
All-cause mortality	59 (17.9%)	59 (18.0%)	0.981	0.9168	(0.684, 1.407)
Cardiovascular (CV) mortality	51 (15.5%)	51 (15.6%)	0.981	0.9245	(0.666, 1.447)
All-cause hospitalization	112 (33.9%)	147 (45.0%)	0.686	0.0027	(0.537, 0.878)
Heart failure (HF) hospitalization	50 (15.2%)	83 (25.4%)	0.545	0.0007	(0.383, 0.773)
All cause death or all cause hospitalization	128 (38.8%)	163 (49.8%)	0.709	0.0035	(0.562, 0.893)
HF death or HF hospitalization	52 (15.8%)	84 (25.7%)	0.559	0.0010	(0.396, 0.791)
CV hospitalization	85 (25.8%)	123 (37.6%)	0.621	0.0007	(0.471, 0.819)
Fatal/non-fatal MI	16 (4.8%)	11 (3.4%)	1.441	0.3514	(0.668, 3.105)
Fatal/non-fatal stroke	9 (2.7%)	8 (2.4%)	1.094	0.8537	(0.422, 2.837)
Implantation of cardiac defibrillator (ICD)	10 (3.0%)	13 (4.0%)	0.744	0.4816	(0.326, 1.696)
Implantation of resynchronization device (CRT)	6 (1.8%)	10 (3.1%)	0.572	0.2794	(0.208, 1.574)
Hospitalization for worsening renal function	5 (1.5%)	3 (0.9%)	1.609	0.5150	(0.384, 6.732)
Hospitalization for hyperkalemia	1 (0.3%)	1 (0.3%)	0.965	0.9802	(0.060, 15.439)

Table E9: Survival analysis of the primary and secondary endpoints - by baseline eGFR (Full Analysis Set) baseline 30 <= eGFR < 60 (ml/min/1.73m^2)

	Eplerenone	Placebo	Hazard Ratio (a)	P-value (a)	95% CI for Hazard Ratio (a)
Total number of Subjects	437	471			
HF Hospitalization/CV Death	107 (24.5%)	163 (34.6%)	0.621	0.0001	(0.486, 0.793)
All-cause mortality or heart failure (HF) hospitalization	117 (26.8%)	178 (37.8%)	0.619	<.0001	(0.490, 0.782)
All-cause mortality	70 (16.0%)	99 (21.0%)	0.681	0.0143	(0.501, 0.926)
Cardiovascular (CV) mortality	58 (13.3%)	81 (17.2%)	0.693	0.0332	(0.494, 0.971)
All-cause hospitalization	157 (35.9%)	218 (46.3%)	0.691	0.0004	(0.562, 0.848)
Heart failure (HF) hospitalization	77 (17.6%)	123 (26.1%)	0.598	0.0004	(0.450, 0.796)
All cause death or all cause hospitalization	178 (40.7%)	247 (52.4%)	0.686	0.0001	(0.565, 0.832)
HF death or HF hospitalization	80 (18.3%)	127 (27.0%)	0.602	0.0004	(0.455, 0.797)
CV hospitalization	120 (27.5%)	179 (38.0%)	0.635	0.0001	(0.504, 0.801)
Fatal/non-fatal MI	17 (3.9%)	12 (2.5%)	1.447	0.3278	(0.691, 3.030)
Fatal/non-fatal stroke	6 (1.4%)	8 (1.7%)	0.679	0.4749	(0.234, 1.966)
Implantation of cardiac defibrillator (ICD)	20 (4.6%)	17 (3.6%)	1.197	0.5861	(0.627, 2.287)
Implantation of resynchronization device (CRT)	14 (3.2%)	12 (2.5%)	1.184	0.6678	(0.547, 2.561)
Hospitalization for worsening renal function	5 (1.1%)	8 (1.7%)	0.568	0.3236	(0.185, 1.747)
Hospitalization for hyperkalemia	1 (0.2%)	2 (0.4%)	0.500	0.5710	(0.045, 5.513)

Table E10: Survival analysis of the primary and secondary endpoints - by history of Diabetes Mellitus (Full Analysis Set)

	Eplerenone	Placebo	Hazard Ratio (a)	P-value (a)	95% CI for Hazard Ratio (a)
Total number of Subjects	459	400			
HF Hospitalization/CV Death	99 (21.6%)	141 (35.3%)	0.541	<.0001	(0.418, 0.699)
All-cause mortality or heart failure (HF) hospitalization	107 (23.3%)	146 (36.5%)	0.563	<.0001	(0.439, 0.723)
All-cause mortality	72 (15.7%)	79 (19.8%)	0.745	0.0717	(0.542, 1.026)
Cardiovascular (CV) mortality	61 (13.3%)	69 (17.3%)	0.724	0.0664	(0.513, 1.022)
All-cause hospitalization	160 (34.9%)	168 (42.0%)	0.743	0.0071	(0.598, 0.922)
Heart failure (HF) hospitalization	70 (15.3%)	104 (26.0%)	0.523	<.0001	(0.386, 0.709)
All cause death or all cause hospitalization	175 (38.1%)	196 (49.0%)	0.694	0.0005	(0.566, 0.852)
HF death or HF hospitalization	71 (15.5%)	108 (27.0%)	0.510	<.0001	(0.378, 0.688)
CV hospitalization	122 (26.6%)	143 (35.8%)	0.659	0.0007	(0.517, 0.839)
Fatal/non-fatal MI	24 (5.2%)	14 (3.5%)	1.426	0.2919	(0.737, 2.757)
Fatal/non-fatal stroke	6 (1.3%)	9 (2.3%)	0.538	0.2405	(0.191, 1.514)
Implantation of cardiac defibrillator (ICD)	21 (4.6%)	28 (7.0%)	0.608	0.0852	(0.345, 1.071)
Implantation of resynchronization device (CRT)	14 (3.1%)	15 (3.8%)	0.760	0.4599	(0.367, 1.575)
Hospitalization for worsening renal function	5 (1.1%)	7 (1.8%)	0.601	0.3854	(0.191, 1.896)
Hospitalization for hyperkalemia	4 (0.9%)	2 (0.5%)	1.693	0.5479	(0.308, 9.191)

Clinical studies in special populations
N/A

Analysis performed across trials (pooled analyses and meta-analysis)
The submitted study represents the first study of eplerenone in this population, thus no integrated analysis of efficacy across other studies in this population is available.

Efficacy Discussion and Conclusions.
In EMPHASIS-HF, eplerenone on top of standard therapy was shown to significantly decrease the incidence of CV mortality and HF hospitalisation in heart failure NYHA II patients compared to placebo. These primary endpoints are generally in line with the relevant NfG on the clinical investigation of medicinal products for the treatment of heart failure CPMP/EWP/235/95, Rev1. In the CHMP guideline all cause mortality is the preferred component of the primary endpoint, however, considering that the mechanism of action and the safety profile of eplerenone are already established, the choice of cardiovascular mortality appears justifiable. In any case, all cause mortality is investigated as a secondary endpoint. The recruited patients were a veteran NYHA II population, with multiple co-morbidities questioning the generalisability of the results. Further analysis of the data showed that 85.4% of the patients reported a prior hospitalisation for a cardiovascular reason. However comparing other characteristics of these patients with those recruited in previous HF studies, it is observed that patients recruited in EMPHASIS were essentially NYHA II patients, regarding their LVEF (around 26%) or their mortality rate. Data also indicate that the EMPHASIS population showed better mortality results than recruited patients in NYHA III in other trials.

The MAH considers that recruiting patients with prior cardiovascular hospitalisation did not otherwise modify the study population beyond characteristics of the NYHA Class II category. For example, analysis of the CHARM study did not indicate that prior CV hospitalisation was among the three most powerful prognostic variables. This argument is not fully supported. Prior CV hospitalisation was an inclusion criterion, more than 85.4% of recruited patients in EMPHASIS were hospitalised for CV reasons within 3 months of randomisation. Of these patients around 50% were hospitalised for heart failure, indicating that EMPHASIS patients are recovering patients and not “new” NYHA II HF patients. Several published studies emphasize the burden of an acute heart event resulting in hospitalisation on myocardial function. If the majority of the recruited patients in EMPHASIS suffered from such an acute episode compromising their cardiac function, it is difficult to generalise this benefit to truly mild heart failure patients classified as NYHA II, especially when this benefit comes at a cost of an increased risk of hyperkalaemia. It is also noted that although the inclusion criteria included CV hospitalisation within 180 days from randomisation, the mean duration was actually around 57 days. In addition, the number of patients who were not previously hospitalised (eplerenone=25; placebo=30) and their events rates (5 and 9 respectively) are too few precluding any robust assessment of a benefit for eplerenone in this group. On the other hand, considering the global nature of the study, it is difficult to conclude on the actual need for the reported CV hospitalisations which largely depends on national health policies. This questions the advisability of the explicit mention of this criterion in the indication.

It is questioned whether the same impressive effect size would have been shown if these patients were treated with implantable defibrillators or cardiac resynchronisation therapy (used in only 20%). At this point in time, it is difficult to estimate the actual effect size of eplerenone, if the study had included really mild NYHA II heart failure. It is also not clear which risk factors/characteristics contributed the most, and which are relevant enough. Acknowledging the need to identify these NYHA II patients who benefited the most to allow extrapolation, it is important to include their main characteristics in section 5.1 with a cross reference in section 4.1.

Subgroups: Benefit is shown to be consistent among the subgroups analysed.

III.3.2 CLINICAL SAFETY

Patient exposure
The Safety Analysis Set for the double-blind phase included all randomised subjects who received at least 1 dose of the randomised study drug during the double-blind phase. Similar to the FAS for efficacy analyses, the subject safety data were also analysed according to the ITT principle based on the subjects' randomised treatment assignment (as randomised) regardless of their actual treatment received.

Adverse events
A similar number of patients reported AEs in the eplerenone and placebo treatment groups: 72.0% versus 73.6% respectively (all causality), and 20.6% versus 15.9% respectively (treatment related) (table S1).
The majority of AEs was considered to be unrelated to study treatment and mild or moderate in severity.

Table S1. Overview of treatment-emergent adverse events (all causalities and treatment-related) - safety population

Number (%) of Subjects	Eplerenone	Placebo
	All Causalities	
Subjects evaluable for AEs	1360	1369
Number of AEs	3431	3530
Subjects with AEs	979 (72.0)	1007 (73.6)
Subjects with SAEs	509 (37.4)	614 (44.9)
Subjects with severe AEs	368 (27.1)	444 (32.4)
Subjects discontinued due to AEs	188 (13.8)	222 (16.2)
Subjects with dose reduced or temporary discontinuation of study drug due to AEs	229 (16.8)	185 (13.5)
	Treatment-Related	
Subjects evaluable for AEs	1360	1369
Number of AEs	436	322
Subjects with AEs	280 (20.6)	218 (15.9)
Subjects with SAEs	37 (2.7)	30 (2.2)
Subjects with severe AEs	30 (2.2)	18 (1.3)
Subjects discontinued due to AEs	46 (3.4)	42 (3.1)
Subjects with dose reduced or temporary discontinuation of study drug due to AEs	121 (8.9)	65 (4.7)

The most common AEs reported included cardiac failure, hyperkalaemia, dyspnoea, dizziness, atrial fibrillation, chest pain, and peripheral oedema.
The most populated system organ classes (SOC) for treatment-related AEs included metabolism and nutrition disorders (107 [7.9%] and 59 [4.3%] subjects in the eplerenone and placebo groups, respectively), investigations (40 [2.9%] and 24 [1.8%] subjects in the eplerenone and placebo groups, respectively), and gastrointestinal disorders (38 [2.8%] and 39 [2.8%] subjects in the eplerenone and placebo groups, respectively). The only treatment-related AE that occurred in >2% of subjects in either treatment group was hyperkalaemia. Treatment-related events of hyperkalaemia occurred in 90 (6.6%) subjects in the eplerenone group and 38 (2.8%) subjects in the placebo group.

Serious adverse events and deaths
Deaths. The number of deaths reported and adjudicated was 171 (12.5%) in eplerenone-treated subjects and 213 (15.5%) in placebo subjects. All adjudicated deaths were included in the final analyses. The eplerenone group experienced a significant reduction in relative risk of all-cause mortality compared to the placebo group. These results were analysed as a pre-specified secondary endpoint (see efficacy).
Serious adverse events. A total of 509 (37.4%) subjects in the eplerenone and 614 (44.9%) in the placebo group reported 1105 and 1349 SAEs, respectively. Thirty-seven (2.7%) eplerenone-treated subjects had 50 SAEs and 30 (2.2%) placebo subjects had 38 SAEs that were considered treatment related (table S1). Events encoded to preferred terms PTs in the SOC cardiac disorders were the most frequently recorded SAEs, with 22.5% of eplerenone group and 28.7% of placebo subjects reporting at least 1 SAE in this class. In both groups, the majority of SAEs were severe in intensity (642/1105 SAEs in eplerenone group; 753/1349 placebo group). A higher incidence of treatment-related SAEs were reported

in the eplerenone group (n=14; 1% and n=13; 1%) compared to placebo (n=6; 0.4% and n=4; 0.3%) in metabolism and nutrition disorders and cardiac disorders (table S2). Under metabolism and nutrition disorders, 12 serious cases of hyperkalaemia (0.9%) were reported in the eplerenone group versus 3 cases in the placebo group (0.2%).

Table S2: Incidence of treatment-emergent serious adverse events (treatment related) - safety population

	Eplerenone		Placebo	
	n	(%)	n	(%)
Cardiac disorders	13	(1.0)	4	(0.3)
Gastrointestinal disorders	1	(0.1)	2	(0.1)
General disorders and administration site conditions	2	(0.1)	2	(0.1)
Infections and infestations	0		2	(0.1)
Injury, poisoning and procedural complications	0		1	(0.1)
Investigations	1	(0.1)	1	(0.1)
Metabolism and nutrition disorders	14	(1.0)	6	(0.4)
Musculoskeletal and connective tissue disorders	0		1	(0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4	(0.3)	0	
Nervous system disorders	3	(0.2)	4	(0.3)
Renal and urinary disorders	6	(0.4)	11	(0.8)
Respiratory, thoracic and mediastinal disorders	1	(0.1)	0	
Vascular disorders	1	(0.1)	0	

Table S3 shows the analysis of the reported serious cardiac disorders considered to be treatment related. The most frequently reported SAE is cardiac failure (0.4% and 0.2% in the eplerenone and placebo groups respectively).

Table S3: Analysis of reported serious cardiac disorders (treatment related) - safety population.

Number of Subjects evaluable for adverse events	Eplerenone (n=1360)		Placebo (n=1369)	
	N	(%)	N	(%)
CARDIAC DISORDERS	13	(1.0)	4	(0.3)
Acute myocardial infarction	1	(0.1)	0	
Atrial fibrillation	1	(0.1)	0	
Bradycardia	1	(0.1)	0	
Cardiac arrest	1	(0.1)	0	
Cardiac failure	5	(0.4)	3	(0.2)
Cardiac failure acute	1	(0.1)	0	
Cardiac failure congestive	1	(0.1)	0	
Cardiogenic shock	0		1	(0.1)
Conduction disorder	1	(0.1)	0	
Ventricular fibrillation	2	(0.1)	0	
Ventricular tachycardia	1	(0.1)	1	(0.1)

Discontinuations due to adverse events

Discontinuations were similar in the eplerenone group compared to the placebo group. A total of 188 (13.8%) and 222 (16.2%) subjects in the eplerenone and placebo groups, respectively, discontinued the study due to AEs. A total of 229 (16.8%) and 185 (13.5%) subjects in the eplerenone and placebo groups, respectively, had temporary discontinuations or dose reductions of study drug due to AEs.

Laboratory findings and vital signs

Median changes from baseline in laboratory parameters and eGFR were minimal and similar between treatment groups. A total of 522 (39%) subjects in the eplerenone group and 457 (34%) subjects in the

placebo group had laboratory abnormalities. The most common abnormalities were blood urea nitrogen (BUN) >1.3x upper limit of normal (ULN), creatinine >1.3x ULN, and potassium >1.1x ULN.
There were differences between treatment groups in the change from baseline in serum creatinine and potassium at the final follow-up assessment. Mean change from baseline in serum creatinine was 0.09±0.37 mg/dL for the eplerenone group and 0.04±0.40 mg/dL in the placebo group (p = 0.0157). The mean change from baseline in serum potassium was significant between treatment groups: 0.16 ±0.56 mEq/L for the eplerenone group and 0.05±0.53 mEq/L for the placebo group (p <0.0001).

Vital signs
There were no clinically significant median changes from baseline to last observation in vital signs or physical examination findings. There were significant differences between treatment groups in mean change from baseline in systolic blood pressure: (-2.47 mm Hg in the eplerenone group and -0.25 mm Hg in the placebo group [p = 0.0005; and diastolic blood pressure: -1.83 mm Hg in the eplerenone group and -0.71 mm Hg in the placebo group [p = 0.0014].

Events of special interest
Hyperkalaemia and hypokalaemia. The mean change from baseline in serum potassium was 0.16±0.56 mEq/L for the eplerenone group and 0.05 ±0.53 mEq/L for the placebo group (p <0.0001). A summary of the incidence of hyperkalaemia and hypokalaemia in the laboratory tests is provided in Table S4.

Table S4. Incidence of Hyperkalaemia and Hypokalaemia – Safety Population

		Eplerenone		Placebo		Fisher's Exact Test
Parameter	Criteria	N	n (%)	N	n (%)	(P-value)
Potassium	>6 mEq/L	1336	33 (2.47)	1340	25 (1.87)	0.2917
	>5.5 mEq/L	1336	158 (11.83)	1340	96 (7.16)	<0.0001
	<4 mEq/L	1336	519 (38.85)	1340	648 (48.36)	<0.0001
	<3.5 mEq/L	1336	100 (7.49)	1340	148 (11.04)	0.0017

There were significant differences between the treatment groups for the 3 categories of potassium levels: >5.5 mEq/L (p <0.0001), <4 mEq/L (p <0.0001), and <3.5 mEq/L (p = 0.0017). As summarised in the SPC, continued periodic monitoring of serum potassium and appropriate dose adjustments are indicated during eplerenone treatment.
Hypokalaemia (potassium <3.5 to 4.0 mmol/l) was significantly decreased in subjects randomised to eplerenone treatment. This is important because a serum potassium <4.0 mmol/l is associated with increased arrhythmias and has been associated with an increased risk of all-cause mortality in subjects with systolic heart failure.

Both angiotensin receptor blockers (ARBs) and angiotensin converting enzyme (ACE) inhibitors are standard care treatments for HF, and each alone has the potential to cause hyperkalaemia. As such, an additional contraindication for the triple co-administration has been proposed in section 4.3.

Safety in special populations
***Patients* >75 years:**
Table S5 presents a summary of the serum **potassium**, **sodium** and water levels (**eGFR**) in this subgroup. The mean change from baseline in serum potassium in the eplerenone group was 0.20±0.59 mmol/l (n=279) and 0.04±0.56 mmol/l in the placebo group (n=272). For the overall study population, baseline mean serum potassium was 4.32±0.42 mmol/l in the eplerenone group (n=1362) and 4.30±0.43 mmol/l in the placebo group (n=1368), while the corresponding values at the end of the double-blind phase were 4.47±0.51 mmol/l and 4.36±0.50 mmol/l in the eplerenone and placebo groups, respectively. The mean change in serum potassium at the end of the double-blind phase of this trial was 0.16 (0.57) mmol/l in the eplerenone group compared to 0.05 (0.54) mmol/l in the placebo group, respectively. The mean baseline, and mean change from baseline values for serum potassium are therefore similar for subjects aged >75 years compared to the overall study population. The mean change from baseline in **eGFR** at the end of the double-blind phase for subjects aged >75 years was -5.22 (18.54) ml/min/1.73 m2 in the eplerenone group and -2.78 (17.35) ml/min/1.73 m2 in the placebo group. For the overall population, the mean change from baseline was - 3.94 (19.58) ml/min/1.73 m2 in the eplerenone group and -1.81 (18.97) ml/min/1.73 m2 in the placebo group (n=1232).

Table S5: Serum potassium, sodium and water levels (eGFR) in patients >75 years

			Eplerenone		Placebo
		N	Mean (SD)	N	Mean (SD)
Serum Potassium (mmol/L)	Baseline	284	4.31 (0.43)	278	4.29 (0.45)
	Final Follow-up Assessment	280	4.51 (0.51)	273	4.33 (0.48)
	Change from Baseline	279	0.20 (0.59)	272	0.04 (0.56)
Sodium (mmol/L)	Baseline	276	140.62 (3.62)	271	140.13 (3.72)
	Final Follow-up Assessment	25	138.97 (3.15)	19	138.53 (2.57)
	Change from Baseline	25	-1.66 (2.93)	19	-1.37 (3.86)
eGFR (ml/min/1.73 m^2)	Baseline	284	64.28 (20.45)	280	61.63 (19.73)
	Final Follow-up Assessment	260	59.72 (20.50)	251	59.74 (19.76)
	Change from Baseline	260	-5.22 (18.54)	251	-2.78 (17.35)

The incidences of **hyperkalaemia** and **hypokalaemia** in patients aged > 75 years are shown in Table S6, and those of the whole study in Table S7. As depicted in Table S6, hospitalisation for worsening renal function was reported in 5 (1.8%) subjects in the eplerenone arm and 4 (1.4%) subjects in the placebo group. For the entire population, 10 (0.7%) subjects in the eplerenone group (n=1367), and 10 (0.7%) subjects in the placebo group were hospitalised for worsening renal function.

Table S6: Incidence of hyperkalaemia and hypokalaemia in patients aged >75 years

			Eplerenone			Placebo			
Age Group	Parameter	Criteria	N	n	(%)	N	n	(%)	P Value
>75	Potassium^	>6 MEQ/L	280	9	3.21	273	4	1.47	0.2616
		>5.5 MEQ/L	280	38	13.57	273	21	7.69	0.0276
		<4 MEQ/L	280	113	40.36	273	149	54.58	0.0009
		<3.5 MEQ/L	280	21	7.50	273	35	12.82	0.0478
	Hospitalization for hyperkalemia^^		285	1	0.4	280	1	0.4	0,9841
	Hospitalization for worsening renal function^^		285	5	1.8	280	4	1.1	0.5145

Table S7 Incidence of hyperkalaemia and hypokalaemia – safety population

		Eplerenone		Placebo		Fisher's Exact Test
Parameter	Criteria	N	n (%)	N	n (%)	(P-value)
Potassium	>6 mEq/L	1336	33 (2.47)	1340	25 (1.87)	0.2917
	>5.5 mEq/L	1336	158 (11.83)	1340	96 (7.16)	<0.0001
	<4 mEq/L	1336	519 (38.85)	1340	648 (48.36)	<0.0001
	<3.5 mEq/L	1336	100 (7.49)	1340	148 (11.04)	0.0017

Patients with Diabetes Mellitus

In patients with diabetes mellitus, baseline serum **potassium** was 4.34 mmol/l in the eplerenone group (n=457) and 4.32 mmol/l in the placebo group (n=399) (Table S8). At the end of the double-blind phase,

the corresponding values of serum potassium were 4.53 mmol/l and 4.38 mmol/l in the eplerenone and placebo arms, respectively. In patients who did not have a history of diabetes mellitus, baseline serum potassium was 4.30 mmol/l in the eplerenone group (n=905) and 4.32 in the placebo group (n=969). At the end of the double-blind phase, the corresponding values were 4.49 mmol/l in the eplerenone group and 4.36 mmol/l in the placebo group. The change from baseline was 0.19 mmol in the eplerenone arm compared to 0.07 mmol/l in the placebo arm. In patients with no history of diabetes mellitus, the change from baseline in serum potassium was 0.18 mmol/l in the eplerenone group compared to 0.04 mmol/l in the placebo group.

Table S8: Serum potassium levels in patients with diabetes and patients with no diabetes.

	Baseline		**End of double-blind phase**		**Difference**
	Eplerenone	Placebo	Eplerenone	Placebo	
Diabetes	N=457 4.34 mmol/l	N= 399 4.32 mmol/l	4.53 mmol/l	4.38 mmol/l	Eplerenone = 0.19 mmol Placebo = 0.07 mmol
No Diabetes	N= 905 4.30 mmol/l	N= 969 4.32 mmol/l	4.49 mmol/l	4.36 mmol/l	Eplerenone = 0.18 mmol Placebo = 0.04 mmol

In addition, there were no significant differences in the AE profiles subjects with a history of diabetes compared with the overall study population. The incidence of severe **hyperkalaemia** in the eplerenone-treated subjects with diabetes mellitus was 4.0% compared to 2.8% in the placebo arm and 2.5% in the overall eplerenone-treated population.

Mean **eGFR** in patients with history of DM at baseline was 69.29 ml/min/1.73 m2 in the eplerenone arm and 69.01 ml/min/1.73 m2 in the placebo arm. The mean change from baseline at the end of the double-blind phase was -5.56 ml/min/1.73 m2 in the eplerenone arm and -4.77 ml/min/1.73 m2 in the placebo arm in this patient population.

Patients with Renal Impairment

In ***mild renal impairment*** (eGFR 60-90 ml/min/1.73 m2), mean eGFR at baseline in the eplerenone treatment arm was 73.85 ml/min/1.73 m2 (n=692) compared to 73.58 ml/min/1.73 m2 (n=666) in the placebo arm. The mean change from baseline to the end of the double-blind phase was -2.87 ml/min/1.73 m2 in the eplerenone arm and -1.68 ml/min/1.73 m2 in the placebo arm.
In ***moderate renal impairment*** (eGFR 30-<60 ml/min/1.73 m2), mean eGFR at baseline was 48.69 ml/min/1.73m2 in the eplerenone arm and 48.74 ml/min/1.73 m2 in the placebo arm. At the end of the double-blind phase, the corresponding values were 51.76 ml/min/1.73 m2 in the eplerenone arm and 52.77 ml/min/1.73 m2 in the placebo arm. The mean change from baseline at the end of the double-blind phase was 1.77 ml/min/1.73m2 in the eplerenone arm and 3.81 ml/min/1.73 m2 in the placebo arm. There were no significant differences in the AE profiles for subjects with baseline mild or moderate renal impairments compared to the overall study population.

The frequency of ***hyperkalaemia*** and ***hypokalaemia*** was examined in subjects using different cut-off eGFR values. Serum potassium and incidence of severe hyperkalaemia (>6 mEq/L) appeared comparable among these groups. The incidence of hypokalaemia was higher in the placebo arms. Overall, the profiles for both hyperkalaemia and hypokalaemia were similar between subjects with eGFR 30-<50 ml/min/1.73 m2 and eGFR 50-<60 ml/min/1.73 m2, and between eGFR 30-<60 ml/min/1.73 m2 and eGFR 60-90 ml/min/1.73 m2 and across the whole study population.

Table S9: Summary of hyperkalaemia and hypokalaemia with different eGFR cut-offs

eGFR 30 – < 50 ml/min/1.73m2		Eplerenone			Placebo			Fischer's Exact Test (P value)
CRITERIA		N	n	(%)	N	n	(%)	
		222			233			
	>6 mEq/L	216	4	1.85	227	8	3.52	0.3829
	>5.5 mEq/L	216	38	17.59	227	25	11.01	0.0566
	<4 mEq/L	216	99	45.83	227	109	48.02	0.7033
	<3.5 mEq/L	216	21	9.72	227	32	14.10	0.1876

eGFR 50 – < 60 ml/min/1.73m2		Eplerenone			Placebo			Fischer's Exact Test (P value)
CRITERIA		N	n	(%)	N	n	(%)	
Total number of Subjects		213			236			
Potassium	>6 mEq/L	209	5	2.39	233	8	3.42	0.5829
	>5.5 mEq/L	209	34	16.27	233	27	11.59	0.1687
	<4 mEq/L	209	83	39.71	233	118	50.64	0.0221
	<3.5 mEq/L	209	10	4.78	233	19	8.15	0.1801

eGFR 30 – < 60 ml/min/1.73m2		Eplerenone			Placebo			Fischer's Exact Test (P value)
CRITERIA		N	n	(%)	N	n	(%)	
Total number of Subjects		435			469			
Potassium	>6 mEq/L	425	9	2.12	460	16	3.48	0.3100
	>5.5 mEq/L	425	72	16.94	460	52	11.30	0.0197
	<4 mEq/L	425	182	42.82	460	227	49.35	0.0588
	<3.5 mEq/L	425	31	7.29	460	51	11.09	0.0630

eGFR 60-90 ml/min/1.73m2

		Eplerenone			Placebo			Fischer's Exact Test (P value)
PARAMETER	CRITERIA	N	n	(%)	N	n	(%)	
Total number of Subjects		691			664			
Potassium	>6 mEq/L	684	23	3.36	653	11	1.68	0.0567
	>5.5 mEq/L	684	79	11.55	653	47	7.20	0.0066
	<4 mEq/L	684	281	41.08	653	339	51.91	<.0001
	<3.5 mEq/L	684	66	9.65	653	80	12.25	0.1363

Safety Discussion and Conclusion:

The most commonly reported treatment related AE and serious AE in the eplerenone group was hyperkalaemia. This is a known AE associated with MRA therapy; the important issue is adequate monitoring and management. Current recommendations in the SPC are considered adequate to minimize the risk of hyperkalaemia. To ensure that such measures are adequate in actual clinical practice AEs related to hyperkalaemia should be monitored and presented regularly in PSURs.

Serious AE related to cardiac disorders were also more frequent in the eplerenone group (n=13) vs. 4 cases in the placebo group. The most frequent preferred term was cardiac failure (n=5 and n=3 respectively). Considering the favourable efficacy results in the eplerenone group, it can be assumed that these minor differences events, though serious, do not reflect negatively on morbidity or mortality.
Discontinuations due to treatment-related AEs were comparable in the eplerenone group (3.4%) compared to the placebo group (3.1%).
Regarding renal functions, a slight but significant increase in serum creatinine was recorded in the eplerenone group compared to the placebo group (p = 0.0157). There was also a higher median increase in BUN from baseline in the eplerenone group (2.2 mg/dl) compared to placebo (0.8 mg/dl). It is, on the other hand, reassuring that hospitalisations for worsening renal function measured as a secondary efficacy endpoint was observed at a comparable rate in both eplerenone (n=9; 0.7%) and placebo groups (n=8; 0.6%).

Subgroup analysis
Certain groups are at a higher risk of developing hyperkalaemia, e.g. elderly, patients with renal impairment and diabetics.

Elderly Patients. Hyperkalaemia is obviously a problem, though the results do not indicate that this risk is significantly exaggerated in the elderly. The results should also be considered in light of the favourable efficacy results. Currently, no change in posology is considered necessary in elderly patients per se; however, hyperkalaemia should be vigilantly monitored.
Deterioration in renal function measured by eGFR was more marked in patients > 75 years, in both the eplerenone and placebo groups, compared to the whole study cohort.

Patients with diabetes Mellitus. The presented data are in line with what is already known about the risk of hyperkalaemia in patients with diabetes mellitus and do not point to the need of any extra precautions for this group. The current warning in section 4.4 of the SPC is considered adequate.

Patients with renal impairment. Presented data are reassuring. However, the proposed dose in this subgroup deserves further discussion.

Mild renal impairment: Patients were administered the same dose as recommended for patients with HF post MI, that is 25 mg daily, to be up-titrated to 50 mg daily according to serum potassium. The reported efficacy results are in line with the general cohort. Safety results show that 3 (0.4%) patients in the eplerenone arm and no (0) patients in the placebo arm were hospitalised for worsening renal function while 3 (0.4%) patients in the eplerenone arm and 1 patient in the placebo arm (0.2%) were hospitalised for hyperkalaemia. Significantly more patients with hyperkalaemia > 5.5 mEq/L were reported in eplerenone group (11.55%) than the placebo group (7.2%) (p = 0.0066). Although the results show a tendency for more of hyperkalaemia, there is re-assurance that there is some experience with this dose in the more severe patients, that is patients with HF post MI. Therefore the current dose recommendations are endorsed.

Moderate renal impairment: This group was administered different doses in EPHESUS and EMPHASIS, based on the level of renal impairment. In EPHESUS, patients with CrCl ≤ 50 ml/min were excluded and accordingly were contraindicated in the SPC. In the same study, no dose adjustments were implemented in patients with CrCl ≥ 50 ml/min, which was mentioned in the SPC. In the current EMPAHSIS study, patients with CrCl 30-50 ml/min were administered 25 mg EOD to be up-titrated to 25 mg/day depending on serum potassium. Patients with CrCl 50-60 ml/min were administered 25 mg daily to be up-titrated to 50 mg/day depending on serum potassium. Efficacy and safety data appear comparable between these two groups utilising different dose recommendations.
To simplify dose calculation and avoid medication errors, it can be agreed that implementing the same dose recommendations for the whole group of moderate renal impairment CrCl 30-60 ml/min is acceptable. However, the recommended dose for this group was an issue for discussion. The currently approved dose recommendations are those implemented in the clinical study and the open-label extension. Also considering the risk in this patients group, it is advisable to maintain the cautious dosing of 25 mg every other day (used in patients with CrCl <50 ml/min) and titrate accordingly to 25 mg/day or to withhold. It is also noted that there is no experience in patients with CrCl <50 ml/min in the HF post MI

population, who are more acute than the patients represented in EMPHASIS. It can be agreed that current data negate the need for an explicit contraindication for these patients in section 4.3; however a warning about the lack of data for these patients is included.

Long term Extension phase:

This interim synopsis-type study report presents a snapshot of the safety data from the open-label extension (OLE) phase up to 14 June 2011.

Diagnosis and main criteria for inclusion: All subjects who had been randomised into the double-blind (DB) phase of the trial and had not withdrawn consent were eligible to participate in the OLE if their estimated glomerular filtration rate (eGFR) was >30 ml/min/1.73 m2 at the DB closeout visit.
Study treatment: Upon entry into the OLE phase, subjects received 25-mg eplerenone once daily. At 4 weeks, the dose of eplerenone could have been increased to 50 mg once daily. For subjects with an eGFR between 30 and 49 ml/min/1.73m2 at the DB screening visit, the initial dose of eplerenone was 25 mg once every other day. At 4 weeks, the dose of eplerenone could have been increased to 25 mg once daily based on the serum potassium level.
Efficacy evaluations: There was no efficacy analysis for the open-label phase.
Safety evaluations: Safety assessment was based on listing of adverse events (AEs), clinical laboratory measurements (serum potassium), and vital signs.

Results
Subject disposition and datasets analysed: A total of 1155 subjects have been enrolled in the OLE phase. This includes 497 (43.0%) subjects in Western Europe/Australia, 414 (35.8%) subjects in Eastern Europe, 162 (14.0%) subjects in South and North America, and 82 (7.1%) subjects in Asia/Middle East/Africa. There were a total of 58 (5.0%) subjects who discontinued from the study prior to the data snapshot date, including subjects who died (Table E11).

Table E11: Discontinuations from treatment

Number (%) of Subjects	Eplerenone N = 1155
Study drug discontinuation due to death	16 (1.4)
Relation to study drug not defined	27 (2.3)
Lost to follow-up	1 (0.1)
Protocol violation	1 (0.1)
Study terminated by sponsor[a]	3 (0.3)
Subject no longer willing to participate	20 (1.7)
Other	2 (0.2)
Related to study drug	12 (1.0)
Adverse event	9 (0.8)
Laboratory abnormality	3 (0.3)
Not related to study drug	3 (0.3)
Adverse event	2 (0.2)
Laboratory abnormality	1 (0.1)
Total	**58 (5.0)**

Incidence of adverse events: A total of 246 (21.3%) subjects reported 415 AEs in the OLE phase up to the data snapshot date (Table E12). The majority of AEs were considered to be unrelated to study treatment.

Table E12: Treatment-emergent adverse events (all causalities and treatment related)

Number (%) of Subjects	All Causality	Treatment Related
Subjects evaluable for AEs	1155	1155
Number of AEs	415	82
Subjects with AEs	246 (21.3)	66 (5.7)
Subjects with SAEs	82 (7.1)	16 (1.4)
Subjects with severe AEs	51 (4.4)	13 (1.1)
Subjects discontinued due to AEs	28 (2.4)	12 (1.0)
Subjects with dose reduced or temporary discontinuation due to AEs	31 (2.7)	23 (2.0)

The most common AEs reported in ≥ 5 patients included hyperkalaemia (17 [1.5%] subjects), cardiac failure (15 [1.3%] subjects), nasopharyngitis (13 [1.1%] subjects), and chest pain (11 [1.0%] subjects). The most common treatment-related AE was hyperkalaemia (15 [1.3%] subjects) (table E13).

Table E13: Incidence of adverse events reported in ≥ 5 subjects (all causalities and treatment related)

Number (%) of Subjects by: System Organ Class MedDRA (v14.0) Preferred Term	All Causality (N = 1155)	Treatment Related (N = 1155)
Cardiac disorders	41 (3.5)	6 (0.5)
Cardiac failure	15 (1.3)	3 (0.3)
Gastrointestinal disorders	29 (2.5)	6 (0.5)
Constipation	6 (0.5)	2 (0.2)
Nausea	6 (0.5)	2 (0.2)
General disorders and administration site conditions	32 (2.8)	4 (0.3)
Chest pain	11 (1.0)	1 (0.1)
Fatigue	5 (0.4)	1 (0.1)
Infections and infestations	69 (6.0)	6 (0.5)
Bronchitis	8 (0.7)	0
Nasopharyngitis	13 (1.1)	1 (0.1)
Pneumonia	8 (0.7)	0
Upper respiratory tract infection	8 (0.7)	2 (0.2)
Urinary tract infection	5 (0.4)	0
Metabolism and nutrition disorders	28 (2.4)	19 (1.6)
Hyperkalaemia	17 (1.5)	15 (1.3)
Musculoskeletal and connective tissue disorders	27 (2.3)	4 (0.3)
Pain in extremity	7 (0.6)	1 (0.1)
Nervous system disorders	24 (2.1)	9 (0.8)
Dizziness	7 (0.6)	4 (0.3)
Respiratory, thoracic and mediastinal disorders	24 (2.1)	2 (0.2)
Cough	6 (0.5)	1 (0.1)
Dyspnoea	8 (0.7)	1 (0.1)
Vascular disorders	18 (1.6)	5 (0.4)
Hypotension	7 (0.6)	3 (0.3)

The majority of AEs were mild or moderate in severity (177/415 AEs were mild, 160/415 AEs were moderate). A total of 70/415 all-causality AEs and 16/82 treatment-related AEs were considered severe. The only severe treatment-related AEs reported in more than 1 subject were hyperkalaemia (2 [0.2%] subjects) and acute renal failure (2 [0.2%] subjects).

Deaths: There were a total of 22 deaths in the OLE phase of this study prior to the data snapshot date. The MAH provided a detailed list of all the deaths. A total of 16 of the 22 subjects died while still on study drug. A similar number of deaths was reported in subjects who received placebo (12) or eplerenone (10) during the DB phase of the study. The majority of deaths (7/12) in subjects who received placebo during the DB phase occurred after more than 90 days treatment with eplerenone in the OLE of the study, while 4 subjects and 3 subjects who received eplerenone during the DB phase had received over 3 years treatment and over 2 years treatment prior to death, respectively.

The MAH was requested to submit supplementary data concerning the 8 deaths reported during this period with PT Death, sudden cardiac death and ventricular arrhythmia.
In their response, the MAH clarified that most of the cases were not properly documented, as they mostly occurred at home rather than in a clinical setting. None of these cases were considered to be related to the study drug by the investigator. Potassium levels were not available, except for three patients and not always directly before death. However such values did not indicate hyperkalaemia. Most of the patients suffered from multiple co-morbidities. All these cases were already administered eplerenone between 96 to 800 days prior to death, except one case was reported after 7 days of eplerenone administration in the OLE (she received placebo in the DB period).

Serious adverse events: A total of 82 (7.1%) subjects reported 128 SAEs in the OLE phase up to the data cut-off date (table E14). The majority of SAEs were considered unrelated to study treatment. The system organ class with the most treatment-related SAEs was metabolism and nutrition disorders (4 [0.3%] subjects). Treatment-related SAE of acute renal failure was reported in 2 (0.2%) subjects.

Table E14: Treatment-emergent serious adverse events (all causalities and treatment related)

Number (%) of Subjects	All Causality	Treatment Related
Subjects evaluable for SAEs	1155	1155
Number of SAEs	128	19
Subjects with SAEs	82 (7.1)	16 (1.4)
Subjects with severe SAEs	45 (3.9)	10 (0.9)
Subjects discontinued due to SAEs	13 (1.1)	4 (0.3)
Subjects with dose reduced or temporary discontinuation due to SAEs	8 (0.7)	3 (0.3)

Discontinuations due to adverse events: A total of 28 (2.4%) subjects discontinued the study due to AEs, with 12 (1.0%) subjects discontinuing due to treatment-related AEs.
Laboratory results: A summary of the incidence of hyperkalaemia and hypokalaemia in the laboratory tests is provided in Table E15.

Table E15: Incidence of hyperkalaemia and hypokalaemia

Parameter	Criteria	Eplerenone	
		N	n (%)
Potassium	>6 mEq/L	1099	57 (5.19)
	>5.5 mEq/L	1099	82 (7.46)
	<4 mEq/L	1099	230 (20.93)
	<3.5 mEq/L	1099	24 (2.18)

Conclusions:
No efficacy data were collected in the long-term extension phase. The main safety concern is still hyperkalaemia and its management. The most common treatment-related AE was hyperkalaemia (15 [1.3%] subjects). The only severe treatment-related AEs reported in more than 1 subject were hyperkalaemia (2 [0.2%] subjects) and acute renal failure (2 [0.2%] subjects). Also it appears to be the most frequent serious treatment related adverse event: metabolism and nutrition disorders (4 [0.3%] subjects). Hyperkalaemia (> 6 mEq/L) was reported more frequently in the open-label extension than in the double-blind phase (5.19% vs. 2.47% respectively) but levels > 5.5 mEq/L were reported less (7.46% vs. 11.83% respectively). The reported severe hyperkalaemia levels point that this will remain a major concern for the use of eplerenone. For the reported deaths, limited data are submitted concerning the events that led to death. However, available data indicate that these patients indeed suffered from multiple co-morbidities confounding causality. For the cases were potassium levels were available, no hyperkalaemia is observed.

III.4 Pharmacovigilance System and Risk Management Plan

Introduction
The targeted extension of the indication for use in the current variation necessitates the submission of a DDPS and RMP. The current PSUR cycle is on a 3-year basis. However, on the basis of the current variation and taking into account the important identified risk as discussed below, the PSUR is adjusted into a 6-months period. If the data in the PSUR are reassuring, the PSUR submission may be further adjusted into longer review periods.

Pharmacovigilance system
The MAH submitted a Detailed Description of the Pharmacovigilance (DDPS) version 3 dated 14 December 2010.

Risk Management Plan
The MAH submitted a Risk Management Plan version 1.0 dated 18 March 2011, focusing on the use in patients with NYHA class II (chronic) heart failure and its main concerns.
In this RMP the following identified risks have been addressed: myocardial infarction, hyperkalaemia, renal impairment, and pruritus. The following potential risk has been addressed: rash.

Overall Summary of the Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Myocardial infarction	PSURs, TME reviews, DME reviews, RMCs, Data mining	Information in section 4.8 of the proposed eplerenone SPC
Hyperkalaemia	PSURs, TME reviews DME reviews, RMCs, Data mining	Information in Sections 4.2, 4.3, 4.4, 4.5 and 4.8 of the proposed eplerenone SPC
Renal impairment	PSURs, TME reviews, DME reviews, RMCs, Data mining	Information in Sections 4.2, 4.4, and 4.8 of the proposed eplerenone SPC
Pruritus	PSURs, TME reviews, DME reviews, RMCs,	Information in Section 4.8 of the proposed eplerenone SPC
Rash	PSURs, TME reviews, DME reviews, RMCs,	Information in Section 4.8 of the proposed eplerenone SPC

TME = targeted medical event
DME = designated medical event
RMC = risk management committee

There are no additional risk minimisation activities planned at this time. The RMS considers hyperkalaemia and renal impairment as the most important identified risks that warrants close follow up.

This is due to submitted data and also the observed clinical practice for another product within the same class i.e. spironolactone (see further at the overall conclusion and B/R assessment in this report). The MAH will closely monitor these identified risks in the PSURs.

IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Non-clinical/environmental risk assessment

No new non-clinical data have been submitted. From the updated ERA it is concluded that the environmental risk is acceptable and unchanged by current variation.

Clinical

Eplerenone is a selective mineralocorticoid receptor antagonist (MRA) approved in the EU to reduce the risk of cardiovascular mortality and morbidity in stable patients with left ventricular dysfunction (LVEF ≤ 40%) and clinical evidence of heart failure after recent myocardial infarction (EPHESUS trial). The efficacy of aldosterone antagonists is also established in severely symptomatic heart failure patients to reduce CV morbidity and mortality (RALES trial).

Benefit

Beneficial effects
The current application shows the benefit of eplerenone in mildly symptomatic HF patients despite optimal standard treatment based on the results of one pivotal study EMPHASIS-HF. The design of the study and the investigated endpoints are in line with the relevant CHMP guideline CPMP/EWP/235/95, Rev1. The study was prematurely terminated because of the efficacy shown during the planned second interim analysis.
Eplerenone on top of standard therapy resulted in significant reduction in the composite primary endpoint of CV mortality or hospitalisation for HF (n=249; 18.3%) compared to the placebo group (n=356; 25.9%), representing a 37% relative risk reduction (p<0.0001). This represents an absolute risk reduction of 7.6%. This superiority was shown on the individual components of the endpoint as well as on all cause mortality (a secondary endpoint; 12.5% vs 15.5% respectively; ARR: 3%; RRR 24%).
Subgroups of specific importance are elderly, patients with renal impairment and diabetics. Efficacy results (primary and secondary endpoints) in elderly patients ≥ 75 years and patients with diabetes are comparable to the general population. In this study, patients with moderate renal impairment (eGFR 30-60 ml/min/1.73m^2) were recruited. The database consisted of n=912 patients in total. The results of the primary and secondary efficacy endpoints were generally in line with those of the overall population.

Uncertainty in the knowledge about the beneficial effects
The current beneficial results are not observed in a typically mildly symptomatic NYHA II population. The patients were recruited suffering from additional co-morbidities in order to accelerate the study duration. For example 85.4% of the recruited patients were previously hospitalised for CV reasons, with more than half already previously hospitalised for heart failure. Most of the recruited patients had a LVEF ≤ 35%. These characteristics show the veteran nature of the recruited patients, although still classified as NYHA II, compared to other HF studies.
The investigated secondary endpoints showed a beneficial effect except in the endpoint of fatal/non-fatal myocardial infarction which was slightly higher in the eplerenone group (n=45; 3.3% vs. n=33; 2.4%). Further analysis of the data show that this is probably a chance finding.

Dose recommendations in patients with moderate renal impairment (eGFR 30-60 ml/min/1.73m^2) was subject of discussion. Patients with eGFR 30-50 ml/min/1.73m^2 were excluded from the EPHESUS study, but patients with eGFR >50 ml/min/1.73m^2 were administered an un-adapted dose. In EMPHASIS patients with eGFR 30-49 ml/min/1.73 m^2 received a modified dose. To avoid medication errors and also to guard against hyperkalaemia, an adapted dose is currently recommended for the whole group of moderate renal impairment.

Risks

Unfavourable effects
The safety analysis comprised 1360 and 1369 patients in the eplerenone and placebo groups respectively. The mean follow-up time of the double-blind phase is 21.1 months. This is followed by an open-label phase that was planned after the premature study discontinuation.
The interim results of the open-label phase were submitted and included 1155 patients.
During the double-blind period, overall, the incidence of adverse events was comparable between the eplerenone and placebo groups; while treatment related AEs were slightly higher in the eplerenone group (20.6% vs 15.9% respectively). The only treatment-related AE that occurred in >2% of subjects in either treatment group was hyperkalaemia. Deaths (investigated as a secondary efficacy endpoint) was reported less frequently in the eplerenone group (n=171; 12.5%) than the placebo group (n=213; 15.5%). Serious AEs related to eplerenone were reported with a slightly higher frequency (2.7%) than in the placebo group (2.2%); hyperkalaemia was one of the most frequently reported serious AE.
Discontinuations due to AEs were comparable in the eplerenone group (3.4%) and the placebo group (3.1%). Hyperkalaemia >5.5 mEq ($p<0.0001$) and >6 mEq/L ($p = 0.291$) were more frequently reported in the eplerenone group. Certain subgroups are known to be more vulnerable to developing hyperkalaemia: elderly, patients with renal impairment and diabetics. Presented data do not indicate a significant concern in these patients. On the other hand, cases of hypokalaemia (< 4 mEq/L) were reported in a significantly lower rate in the eplerenone than the placebo group (38.85% vs 48.36 in the eplerenone and placebo groups respectively; $P< 0.0001$). A slight significant increase in serum creatinine (0.09±0.37 mg/dL in the eplerenone group compared to 0.04±0.40 mg/dL in the placebo group; $p = 0.0157$), together with a numerical increase in BUN (2.2 mg/dl vs 0.8 mg/dl respectively) were observed.
Results of the open label phase are in line with the double blind phase.

Uncertainty in the knowledge about the unfavourable effects
Current recommendations in the SPC (dose adaptations based on potassium level, recommendations for frequent monitoring in cases of renal impairment, or as necessary in other cases) are considered adequate to minimize the risk of hyperkalaemia; however the feasibility of the implementation of these recommendations in clinical practice is yet to be shown.

Balance

Importance of favourable and unfavourable effects
The demonstrated results are considered clinically relevant, as superiority was also shown in all cause mortality. The results compare favourably with previous studies. In the EPHESUS trial, eplerenone reduced the risk of CV death or CV hospitalisation by 13% (RR 0.87; 95% CI, 0.79-0.95; $p = 0.002$). In the RALES trial, the combined end point of death from cardiac causes or hospitalisation for cardiac causes revealed a 32% RRR in the spironolactone group ($P<0.001$). Favourable efficacy was also maintained in vulnerable subgroups.
Eplerenone is available on the market since 2004. It is a mineralocorticoid antagonist and its safety profile is accordingly predictable. This study specifically investigates the safety profile of NYHA II patients; a population not investigated previously. The duration and the exposure of the patients during the double-blind phase are considered adequate. Further presented data of patients with different degrees of renal impairment are not worrisome regarding renal function.

Benefit risk balance and discussion
In the current study, a clinically and statistically significant effect was shown for NYHA II heart failure patients. Cardiovascular mortality and morbidity in addition to total mortality were all reduced when eplerenone was added on top of standard therapy. This is an extension of the efficacy shown in more heart failure patients post myocardial infarction. It is doubtful if such impressive efficacy can be all translated to the general NYHA II population, so characteristics of this high risk recruited population is currently reflected in the indication, with more detailed description in section 5.1. Hyperkalaemia is the main risk associated with this beneficial effect. To minimise this risk, frequent monitoring and dose adjustments based on the potassium levels are advocated in the SPC. These measures are considered adequate, but their feasibility remains to be demonstrated in clinical practice as this necessitates vigilant monitoring; this may not always be the case. This has been shown in the past for spironolactone after the

release of the results of the RALES trial; there was a striking increase in hospital admissions and deaths related to hyperkalaemia (NEJM; 2004, 351 (6):543-551). This might be largely explained by the use of higher doses of spironolactone and the treatment of patients who had a lower glomerular filtration rate (NEJM; 2004, 351 (6) 526-528). This has been specifically studied for spironolactone, but caution is needed. Patients with moderate renal impairment are recruited and these need special attention as they are more vulnerable to hyperkalaemia. Further dose adaptations are requested in this group. Further data regarding vulnerable subgroups like patients above 75 years, or diabetics do not point to any additional concerns.
The benefits of administration of eplerenone in this veteran heart failure NYHA II population in the form of significant decrease in mortality and morbidity are considered to outweigh the risks, mainly hyperkalaemia**.**

Risk management plan/PSUR
The targeted indication for use necessitates the submission of a DDPS and RMP. Based on the current variation the PSUR cycle should be adjusted from a 3-yearly basis into a 6-months period. The RMS considers hyperkalaemia and renal impairment as the most important identified risks that warrants close follow up. The MAH will closely monitor these identified risks in the PSURs.

In **conclusion**, the overall benefit-risk balance of the sought extension of the indication is positive. The SPC, PIL and labelling are adapted as recommended. Procedure NL/H/0506/001-002/II/028 was finalised on 15 February 2012.