AUSTRALIAN PRODUCT INFORMATION

EPLERENONE VIATRIS

(eplerenone) film coated tablet

1 NAME OF THE MEDICINE

Eplerenone

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each EPLERENONE VIATRIS film coated tablet contains 25 or 50 mg of eplerenone as the active ingredient.

Excipients with known effect: lactose.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

EPLERENONE VIATRIS is supplied as yellow, arc diamond shape, film-coated tablets.

25 mg tablet: debossed with 'NSR' over '25' on one side and 'VLE' on the other.

50 mg tablet: debossed with 'NSR' over '50' on one side and 'VLE' on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

EPLERENONE VIATRIS is indicated:

- to reduce the risk of cardiovascular death in combination with standard therapy in patients who have evidence of heart failure and left ventricular impairment within 3-14 days of an acute myocardial infarction (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

- to reduce the risk of cardiovascular mortality and morbidity in adult patients with NYHA Class II (chronic) heart failure and left ventricular systolic dysfunction (LVEF ≤30% or LVEF ≤35% in addition to QRS duration of > 130 msec), in addition to standard optimal therapy (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

4.2 DOSE AND METHOD OF ADMINISTRATION

For post-myocardial infarction heart failure patients

EPLERENONE VIATRIS is usually administered in combination with standard therapies. The recommended dose of EPLERENONE VIATRIS is 50 mg once daily. Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily within 4 weeks as tolerated by the patient.

In the pivotal clinical study EPHESUS, eplerenone was added to standard medical therapy within 3-14 days after an acute qualifying myocardial infarction. There is evidence that the reduction in mortality occurred mostly within the first 12 months of eplerenone treatment. Patients with chronic heart failure should be reassessed no longer than 12 months after commencing therapy and options for the management of chronic heart failure considered.

For patients with NYHA Class II (chronic) heart failure

Patients with eGFR ≥50 mL/min/1.73m^2 (CKD stages 1,2 and partly 3) - treatment should be initiated at a dose of 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks; taking into account the serum potassium levels (see serum potassium table below).

Serum potassium levels

Serum potassium should be measured before initiating eplerenone therapy, within the first week and at 1-month after the start of treatment or dosage adjustment. Serum potassium should be assessed periodically thereafter, and the dose of eplerenone adjusted based on the serum potassium level (see Table 1 below).

Table 1: Dose adjustment based on serum potassium levels

Serum potassium (mmol/L)	Action	Dose adjustment
<5.0	Increase	25 mg QOD to 25 mg QD 25 mg QD to 50 mg QD*
5.0–5.4	Maintain	No dose adjustment
5.5–5.9	Decrease	50 mg QD to 25 mg QD 25 mg QD to 25 mg QOD 25 mg QOD to withhold
≥6.0	Withhold	N/A

QOD: take eplerenone every other day; QD: take eplerenone once daily

* Only increase if baseline eGFR >50 mL/min/1.73m^2. See Table 2 below for detail on maximum dose for each cohort

EPLERENONE VIATRIS should be suspended when serum potassium is ≥6.0 mmol/L. It can be restarted at a dose of 25 mg every other day when serum potassium levels have fallen below 5.0 mmol/L. Serum potassium monitoring should continue once eplerenone has been re-started again.

Concomitant treatment

In case of concomitant treatment with mild to moderate CYP3A4 inhibitors, e.g. amiodarone, diltiazem, erythromycin, saquinavir, fluconazole and verapamil, dosing should not exceed 25 mg once daily.

EPLERENONE VIATRIS may be administered with or without food.

Special populations

Children

There are insufficient data to recommend the use of EPLERENONE VIATRIS in the paediatric population, and therefore, use in this age group is not recommended.

Elderly Patients

No dose adjustment is required in the elderly.

Patients with Chronic Kidney Disease

Periodic monitoring of serum potassium is recommended, in particular in patients with chronic kidney disease, to avoid serum potassium levels >5.5 mmol/L (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION - Serum Potassium Levels and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Chronic Kidney Disease).

Dosage should be initiated as shown in Table 2 and adjusted based on serum potassium levels as described above in Table 1.

Table 2: Dose adjustment based on renal function

<table>
<tr><th colspan="4">Baseline renal function and dose adjustment</th><th colspan="2">Kidney Health Australia CKD staging</th></tr>
<tr><td>Baseline eGFR (mL/min/1.73m^2)</td><td>Eplerenone starting dose (mg)</td><td>Eplerenone dose at 4 weeks (mg)</td><td>Maximum dose (mg)</td><td>CKD function stage</td><td>eGFR (ml/min/1.73m^2)</td></tr>
<tr><td rowspan="2">≥ 50</td><td rowspan="2">25 mg once daily</td><td rowspan="2">50 mg daily, if serum potassium remains <5.0 mmol/L</td><td rowspan="2">50 mg daily</td><td>1</td><td>≥90</td></tr>
<tr><td>2</td><td>60 – 89</td></tr>
<tr><td>30 – 49</td><td>25 mg once every other day</td><td>25 mg daily, if serum potassium remains <5.0 mmol/L</td><td>25 mg daily</td><td>3</td><td>30 – 59</td></tr>
<tr><td>< 30</td><td colspan="3">Eplerenone is contraindicated in patients with Stage 4 and 5 CKD (eGFR less than 30 mL/min/1.73m^2). (See Section 4.3 CONTRAINDICATIONS and Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).</td><td>4</td><td>15 – 29</td></tr>
<tr><td colspan="3"></td><td>5</td><td><15 or on dialysis</td></tr>
</table>

Doses above 25 mg daily have not been studied in patients with eGFR <50 mL/min/1.73m^2.

Eplerenone is not dialysable.

Patients with Hepatic Insufficiency

No initial dosage adjustment is necessary for patients with mild to moderate hepatic impairment. EPLERENONE VIATRIS is contraindicated in patients with severe hepatic insufficiency (see Section 4.3 CONTRAINDICATIONS).

4.3 CONTRAINDICATIONS

Hypersensitivity to eplerenone or any of the excipients.

Eplerenone should not be administered to patients with clinically significant hyperkalaemia (serum potassium >5.0 mmol/L at initiation) (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Eplerenone should not be administered to patients with severe renal insufficiency (eGFR <30 mL per minute per 1.73 m^2, CKD stages 4 and 5) (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

Eplerenone should not be administered to patients with severe hepatic insufficiency (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Eplerenone should not be co-administered to patients receiving potassium-sparing diuretics or strong inhibitors of CYP3A4 e.g. itraconazole, ketoconazole, ritonavir and clarithromycin. (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hyperkalaemia

The principal risk of eplerenone is hyperkalaemia. Hyperkalaemia can cause serious, sometimes fatal, arrhythmias. Patients who develop hyperkalaemia (>5.5 mmol/L) may still benefit from eplerenone with proper dose adjustment.

Serum potassium should be measured before initiating eplerenone therapy, and measured periodically thereafter, as clinically warranted (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Hyperkalaemia can be minimized by patient selection, avoidance of certain concomitant treatments, and periodic monitoring until the effect of eplerenone has been established. Eplerenone should generally not be administered to patients taking potassium supplements, or salt substitutes containing potassium. For patient selection and avoidance of certain concomitant medications, see Section 4.3 CONTRAINDICATIONS, Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS, and Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Clinical Laboratory Test Findings, Potassium. Dose reduction of eplerenone has been shown to decrease potassium levels (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Diabetic patients with CHF post-MI, including those with proteinuria, should also be treated with caution. The subset of patients in EPHESUS with both diabetes and proteinuria on the baseline urinalysis had increased rates of hyperkalaemia (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Clinical Laboratory Test Findings - Potassium).

The risk of hyperkalaemia may increase when eplerenone is used in combination with an angiotensin converting enzyme (ACE) inhibitor and an angiotensin receptor blocker (ARB) and therefore this combination is not recommended.

Use in Hepatic Impairment

Due to an increased systemic exposure to eplerenone in patients with mild-to-moderate hepatic impairment, frequent and regular monitoring of serum potassium is recommended in these patients, especially when elderly. In 16 subjects with mild-to-moderate hepatic impairment who received 400 mg of eplerenone no elevations of serum potassium above 5.5 mmol/L were observed. The mean increase in serum potassium was 0.12 mmol/L in patients with hepatic impairment and 0.13 mEq/L in normal controls. The use of eplerenone in patients with severe hepatic impairment has not been evaluated, and is therefore contraindicated (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.3 CONTRAINDICATIONS, and Section 5.2 PHARMACOKINETIC PROPERTIES - Special Populations).

Use in Renal Impairment

Eplerenone should not be administered to patients with severe renal insufficiency (CKD stages 4 and 5, eGFR <30 mL/min/1.73m^2), the risk of hyperkalaemia increases with declining renal function. Eplerenone cannot be removed by haemodialysis. (See Section 4.2 DOSE AND METHOD OF ADMINISTRATION, Section 4.3 CONTRAINDICATIONS, and Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials.)

Use in the Elderly

Of the total number of patients in EPHESUS, 3,340 (50%) were 65 and over, while 1,326 (20%) were 75 and over. Patients greater than 75 years did not appear to benefit from the use of eplerenone (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials). No differences in overall incidence of adverse events were observed between elderly and younger patients. However, due to age-related decreases in creatinine clearance, the incidence of laboratory-documented hyperkalaemia was increased in patients 65 and older (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hyperkalaemia).

Post-hoc analyses in the EMPHASIS-HF study to explore potential age-related blood pressure (BP) changes suggest that there may be a greater sensitivity to treatment in older individuals and thus potentially greater reductions in blood pressure with the use of eplerenone, compared to younger patients. In patients aged below

75 years, 28.3% treated with eplerenone recorded (maximum drop, at any time during study) systolic BP reductions from baseline of greater than 20 mmHg, while patients with placebo had a 23.9% incidence of these reductions. Of those aged at or over 75, the respective observations were 37.9% for eplerenone and 24.4% for placebo.

These blood pressure reductions noted in the EMPHASIS-HF study were independent of any reports of adverse events reported in the EMPHASIS-HF study (see Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

Paediatric Use

The safety and effectiveness of eplerenone has not been established in paediatric patients.

Effects on Laboratory Tests

See Section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS) - Post-marketing experience - Clinical Laboratory Test Findings.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Inhibitors of CYP3A4

Eplerenone metabolism is predominantly mediated via CYP3A4. A pharmacokinetic study evaluating the administration of a single dose of eplerenone 100 mg with ketoconazole 200 mg twice daily, a potent inhibitor of the CYP3A4 pathway, showed a 1.7-fold increase in C_{max} of eplerenone and a 5.4-fold increase in AUC of eplerenone. Eplerenone should not be used with drugs described as strong inhibitors of CYP3A4 in their labelling (see Section 4.3 CONTRAINDICATIONS). Administration of eplerenone with other CYP3A4 inhibitors (e.g. erythromycin 500 mg twice daily, verapamil 240 mg once daily, saquinavir 1,200 mg three times daily, fluconazole 200 mg once daily) resulted in increases in C_{max} of eplerenone ranging from 1.4- to 1.6-fold and AUC from 2.0- to 2.9-fold.

Inducers of CYP3A4

Co-administration of St John's Wort (a potent CYP3A4 inducer) with eplerenone caused a decrease in eplerenone AUC. A more pronounced decrease in eplerenone AUC may occur with more potent CYP3A4 inducers and the concomitant use of potent CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) with eplerenone is not recommended.

ACE inhibitors and angiotensin II receptor antagonists

In EPHESUS, 3,020 (91%) patients receiving eplerenone 25 to 50 mg also received ACE inhibitors or angiotensin II receptor antagonists (ACEI/ARB). Rates of patients with maximum potassium levels >5.5 mmol/L were similar regardless of the use of ACEI/ARB.

The risk of hyperkalaemia may increase when eplerenone is used in combination with an angiotensin converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB). A close monitoring of serum potassium and renal function is recommended, especially in patients at risk for impaired renal function, e.g., the elderly (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION and Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Lithium

A drug interaction study of eplerenone with lithium has not been conducted. Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors. Co-administration of eplerenone and lithium should be avoided. If this combination appears necessary, serum lithium levels should be monitored frequently.

Ciclosporin and tacrolimus

Ciclosporin and tacrolimus may lead to impaired renal function and increase the risk of hyperkalaemia. The concomitant use of eplerenone and ciclosporin or tacrolimus should be avoided. If needed, close monitoring of serum potassium and renal function are recommended when ciclosporin and tacrolimus are to be administered during treatment with eplerenone.

Trimethoprim

The concomitant administration of trimethoprim with eplerenone increases the risk of hyperkalaemia. Monitoring of serum potassium and renal function should be made, particularly in patients with renal impairment and in the elderly.

Alpha-1-blockers

When alpha-1-blockers (e.g. prazosin, alfuzosin) are combined with eplerenone, there is the potential for increased hypotensive effect and/or postural hypotension. Clinical monitoring for postural hypotension is recommended during alpha-1-blocker co-administration.

Tricyclic anti-depressants, neuroleptics, amifostine and baclofen

Co-administration of these drugs with eplerenone may potentially increase antihypertensive effects and risk of postural hypotension.

Non-steroidal anti-inflammatory drugs (NSAIDs)

A drug interaction study of eplerenone with an NSAID has not been conducted. The administration of other potassium-sparing antihypertensives with NSAIDs has been shown to reduce the antihypertensive effect in some patients and result in severe hyperkalaemia in patients with impaired renal function. Therefore, when eplerenone and NSAIDs are used concomitantly, patients should be observed to determine whether the desired effect on blood pressure is obtained.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Male rats treated with eplerenone at 1,000 mg/kg/day for 10 weeks (AUC 24 times that at the clinical dose of 50 mg/day) had decreased weights of seminal vesicles and epididymides and slightly decreased fertility; the no effect dose was 300 mg/kg/day (10 times clinical AUC at 50 mg/day). Dogs administered eplerenone at dosages of 15 mg/kg/day and higher (AUC six times that at the clinical dose of 50 mg/day) had dose-related prostate atrophy, and the NOEL (5 mg/kg/day) for prostate atrophy in dogs resulted in plasma AUC approximately three times the clinical value at 50 mg/day. Androgen receptor binding was identified as a possible cause of prostate atrophy. The effect was reversible following drug withdrawal. Dogs with prostate atrophy showed no decline in libido, sexual performance, or semen quality. Testicular weight and histology were not affected by eplerenone in mouse, rat or dog studies.

Use in Pregnancy – Pregnancy Category B3

There are no adequate data on the use of eplerenone in pregnant women. Studies in rats and rabbits showed no teratogenic effects, although decreased maternal and fetal weights in rats and decreased maternal body weights and post-implantation loss in rabbits were observed at the highest administered dose of 1,000 mg/kg/day in rats and 300 mg/kg/day in rabbits (for both species approximately 40 times the clinical exposure based on AUC). The potential risk for humans is unknown. Eplerenone should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Lactation

It is unknown if eplerenone is excreted in human breast milk after oral administration. Preclinical data show that eplerenone and/or metabolites are present in rat breast milk and that rat pups exposed by this route had decreased body weight gain at a maternal dose of 1,000 mg/kg/day (maternal exposure 43 times the clinical

AUC). Because many drugs are excreted in human milk and because of the unknown potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Dizziness and syncope have been reported to occur in some patients. Caution is advised when driving or operating machinery until the response to initial treatment has been determined.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Eplerenone has been evaluated for safety in 1,360 patients with heart failure and 3,307 patients treated for heart failure post-myocardial infarction (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical trials).

In the EPHESUS study, the overall incidence of adverse events reported with eplerenone (78.9%) was similar to placebo (79.5%). The discontinuation rate due to adverse events in this study was 4.4% for patients receiving eplerenone and 4.3% for patients receiving placebo.

In the EMPHASIS-HF study, the overall incidence of adverse events (% subjects) reported with eplerenone (72%) was similar to placebo (73.6%). The discontinuation rate due to adverse events in this study was 13.8% for patients receiving eplerenone and 16.2% for patients receiving placebo.

Adverse events reported are those with suspected relationship to treatment and in excess of placebo, or are serious and significantly in excess of placebo, or have been observed during post marketing surveillance. Adverse events are listed by body system and absolute frequency. Frequencies are defined as common (>1% to ≤10%) or uncommon (>0.1% to ≤1%).

Blood and Lymphatic System Disorders

Uncommon: eosinophilia

Cardiac Disorders

Common: myocardial infarction

Uncommon: left ventricular failure, atrial fibrillation, tachycardia

Endocrine Disorders

Uncommon: hypothyroidism

Gastrointestinal Disorders

Common: diarrhoea, nausea, constipation

Uncommon: flatulence, vomiting

General Disorders and Administration Site Conditions

Uncommon: asthenia, malaise

Hepatobiliary Disorders

Uncommon: cholecystitis

Infections and Infestations

Common: infection

Uncommon: pyelonephritis, pharyngitis

Investigations

Common: blood urea increased

Uncommon: blood creatinine increased, epidermal growth factor receptor decreased, blood glucose increased

Metabolic and Nutrition Disorders

Common: hyperkalaemia, dehydration

Uncommon: hypercholesterolaemia, hypertriglyceridaemia, hyponatraemia

Musculoskeletal and Connective Tissue Disorders

Common: muscle spasms, musculoskeletal pain

Uncommon: back pain

Nervous System Disorders

Common: dizziness, syncope

Uncommon: headache, hypoaesthesia

Psychiatric Disorders

Uncommon: insomnia

Renal and Urinary Disorders

Common: renal impairment

Reproductive System and Breast Disorders

Uncommon: gynaecomastia

Respiratory, Thoracic and Mediastinal Disorders

Common: cough

Skin and Subcutaneous Tissue Disorders

Common: pruritus

Uncommon: hyperhidrosis

Vascular Disorders

Common: hypotension

Uncommon: arterial thrombosis limb, orthostatic hypotension

The rates of sex hormone related events are shown in Table 3.

Table 3: Rates of sex hormone related adverse events in EPHESUS

	Rates in males (%)			Rates in females (%)
	Gynaecomastia	**Mastodynia**	**Either**	**Abnormal vaginal bleeding**
Eplerenone	0.4	0.1	0.5	0.4
Placebo	0.5	0.1	0.6	0.4

Table 4: Rates (%) of adverse events reported in EPHESUS with greater than 2% incidence on active treatment including the placebo arm

Body system **Adverse event**	**Placebo** **n=3,301**	**Eplerenone** **25-50 mg QD** **n=3,307**
Autonomic nervous system disorders		
Hypotension	109 (3.3%)	119 (3.6%)
Syncope	58 (1.8%)	71 (2.1%)
Body as a whole – general disorders		
Asthenia	68 (2.1%)	89 (2.7%)
Back pain	95 (2.9%)	91 (2.7%)
Chest pain non-cardiac	206 (6.2%)	213 (6.4%)
Oedema peripheral	110 (3.3%)	87 (2.6%)
Fatigue	91 (2.8%)	95 (2.9%)
Fever	65 (2.0%)	67 (2.0%)
Injury – accidental	69 (2.1%)	50 (1.5%)
Peripheral pain	68 (2.1%)	62 (1.9%)
Sudden death	177 (5.4%)	116 (3.5%)
Cardiovascular disorders, general		
Cardiac failure	460 (13.9%)	376 (11.4%)
Cardiac failure left	194 (5.9%)	153 (4.6%)
Unstable angina	315 (9.5%)	305 (9.2%)
Central and peripheral nervous system disorders		
Dizziness	197 (6.0%)	214 (6.5%)
Headache	119 (3.6%)	126 (3.8%)
Gastrointestinal systems disorders		
Abdominal pain	103 (3.1%)	97 (2.9%)
Constipation	92 (2.8%)	98 (3.0%)
Diarrhoea	113 (3.4%)	115 (3.5%)
Dyspepsia	120 (3.6%)	129 (3.9%)

Body system **Adverse event**	**Placebo** **n=3,301**	**Eplerenone** **25-50 mg QD** **n=3,307**
Nausea Vomiting	133 (4.0%) 59 (1.8%)	139 (4.2%) 76 (2.3%)
Heart rate and rhythm disorders Ventricular arrhythmia Atrial fibrillation Ventricular tachycardia	 73 (2.2%) 161 (4.9%) 63 (1.9%)	 73 (2.2%) 150 (4.5%) 70 (2.1%)
Metabolic and nutritional disorders Hypercholesterolaemia Hyperglycaemia Hyperkalaemia Hyperuricaemia	 119 (3.6%) 79 (2.4%) 66 (2.0%) 111 (3.4%)	 102 (3.1%) 67 (2.0%) 113 (3.4%) 87 (2.6%)
Musculoskeletal system disorders Arthralgia	 89 (2.7%)	 71 (2.1%)
Myo endo pericardial and valve disorders Angina pectoris Coronary artery disorder Myocardial infarction	 415 (12.6%) 91 (2.8%) 270 (8.2%)	 459 (13.9%) 100 (3.0%) 267 (8.1%)
Psychiatric disorders Depression Insomnia	 66 (2.0%) 105 (3.2%)	 48 (1.5%) 88 (2.7%)
Red blood cell disorders Anaemia	 98 (3.0%)	 115 (3.5%)
Respiratory system disorders Bronchitis Coughing Dyspnoea Pneumonia Upper respiratory tract infection	 137 (4.2%) 207 (6.3%) 307 (9.3%) 123 (3.7%) 171 (5.2%)	 111 (3.4%) 167 (5.0%) 243 (7.3%) 92 (2.8%) 156 (4.7%)
Urinary system disorders Creatinine increase Haematuria Renal function abnormal Urinary tract infection	 51 (1.5%) 55 (1.7%) 79 (2.4%) 113 (3.4%)	 81 (2.4%) 70 (2.1%) 96 (2.9%) 111 (3.4%)

Body system Adverse event	Placebo n=3,301	Eplerenone 25-50 mg QD n=3,307
Vascular disorders		
Cerebrovascular disorder	101 (3.1%)	103 (3.1%)

Table 5: Treatment-emergent serious adverse events occurring in >2% of subjects in either treatment group in EMPHASIS-HF, all causality

SOC/MedDRA Preferred Term	Placebo N=1,369 n (%)	Eplerenone N=1,360 n (%)
Cardiac disorders	393 (28.7)	306 (22.5)
Atrial fibrillation	30 (2.2)	22 (1.6)
Cardiac failure	243 (17.8)	187 (13.8)
Myocardial infarction	29 (2.1)	29 (2.1)
Ventricular tachycardia	27 (2.0)	17 (1.3)
General disorders and administration site conditions	119 (8.7)	82 (6.0)
Chest pain	28 (2.0)	21 (1.5)
Death	34 (2.5)	26 (1.9)
Infections and infestations	105 (7.7)	79 (5.8)
Pneumonia	29 (2.1)	22 (1.6)
Respiratory, thoracic and mediastinal disorders	77 (5.6)	57 (4.2)
Dyspnoea	28 (2.0)	14 (1.0)

A total of 3,353 patients have been treated with eplerenone in clinical studies of hypertension. The overall rates of adverse events in placebo-controlled studies were similar between eplerenone (49%) and placebo (48%). Adverse events with suspected relationship to treatment and in excess of placebo from the monotherapy arms of five placebo-controlled studies for patients who received eplerenone 25 to 400 mg are listed below by absolute frequency. Frequencies are defined as common (>1% to ≤10%) or uncommon (>0.1% to ≤1%).

Common: ALT increased, GGT increased

Uncommon: Anaemia, angina pectoris, arthralgia, AST increased, bilirubinaemia, coughing, creatine phosphokinase increased, dyspepsia, dyspnoea, ECG abnormal, flushing, gastroesophageal reflux, haematuria, hyperuricaemia, libido decreased, menstrual disorder, myalgia, prothrombin decreased, tinnitus, urine abnormal, URT infection.

Post-marketing experience

In post-marketing experience, the following additional undesirable effects have been reported:

Skin and Subcutaneous Tissues Disorders

Angioedema, rash.

Clinical Laboratory Test Findings

Creatinine

Increases of more than 44.2 µmol/d were reported for 6.5% of patients administered eplerenone and for 4.9% of placebo-treated patients.

Potassium

In EPHESUS, the frequency of patients with changes in potassium (<3.5 mmol/L or >5.5 mmol/L or ≥6.0 mmol/L) receiving eplerenone compared with placebo are displayed in Table 6.

Table 6: Hypokalaemia (<3.5 mmol/L) or hyperkalaemia (>5.5 mmol/L or ≥6.0 mmol/L) in EPHESUS

Potassium (mmol/L)	**Number of patients (%)**	
	Eplerenone (n=3,251)	**Placebo (n=3,237)**
<3.5	273 (8.4)	424 (13.1)
>5.5	508 (15.6)	363 (11.2)
≥6.0	180 (5.5)	126 (3.9)

Table 7 shows the rates of hyperkalaemia in EPHESUS as assessed by baseline renal function (creatinine clearance).

Table 7: Rates of hyperkalaemia (>5.5 mmol/L) in EPHESUS by baseline creatinine clearance*

Baseline creatine clearance (mL/min)	**Eplerenone (%)**	**Placebo (%)**
≤30	31.5	22.6
31–50	24.1	12.7
51–70	16.9	13.1
>70	10.8	8.7

*Estimated using Cockroft-Gault formula

Table 8 shows the rates of hyperkalaemia in EPHESUS as assessed by two baseline characteristics: presence/absence of proteinuria from baseline urinalysis and presence/absence of diabetes (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Hyperkalaemia).

Table 8: Rates of hyperkalaemia (>5.5 mmol/L) in EPHESUS by proteinuria and history of diabetes*

	Eplerenone (%)	Placebo (%)
Proteinuria	16	11
Diabetes, no proteinuria	18	13
Proteinuria and diabetes	26	16

*Diabetes assessed as positive medical history at baseline; proteinuria assessed by positive dipstick urinalysis at baseline.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No cases of adverse events associated with overdosage of eplerenone in humans have been reported. The most likely manifestation of human overdosage would be anticipated to be hypotension or hyperkalaemia.

There is no specific antidote; treatment is symptomatic and supportive. Eplerenone cannot be removed by haemodialysis. Eplerenone has been shown to bind extensively to charcoal. Activated charcoal is most effective when administered within 1-hour of ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via nasogastric tube once the airway is protected. If symptomatic hypotension should occur, supportive treatment should be initiated. If hyperkalaemia develops, standard treatment should be initiated.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Eplerenone is a relatively selective mineralocorticoid receptor antagonist with weak binding to androgen, glucocorticoid and progesterone 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.

Eplerenone has been shown to produce sustained increases in plasma renin and serum aldosterone, consistent with inhibition of the negative regulatory feedback of aldosterone on renin secretion. The resulting increased plasma renin activity and aldosterone circulating levels do not overcome the effects of eplerenone on blood pressure.

Eplerenone attenuates progression of heart failure in animal models with both ischaemic and non-ischaemic aetiologies. Independent of blood pressure lowering, eplerenone preserves diastolic and systolic function and reduces left ventricular remodelling. In animal models, eplerenone reduces vascular inflammation and injury in the heart and kidney.

Clinical Trials

EPHESUS Trial

Eplerenone was studied in the **E**plerenone **P**ost-acute myocardial infarction **H**eart failure **E**fficacy and **SU**rvival **S**tudy (EPHESUS). EPHESUS was a large multi-centre, double-blind, placebo-controlled study, of 3-year duration, in 6,632 patients with acute myocardial infarction (AMI), left ventricular dysfunction (as measured by left ventricular ejection fraction [LVEF] ≤40%), and clinical evidence of heart failure. Patients were randomized 3 to 14 days after an acute MI. Following randomization, patients received eplerenone or placebo in addition to standard therapies at an initial dose 25 mg once daily and titrated to the target dose of 50 mg once daily after 4 weeks if serum potassium was <5.0 mmol/L. Dosage was reduced or suspended anytime during the study if serum potassium levels were ≥5.5 mmol/L.

In EPHESUS, the co-primary endpoints were all-cause mortality and the combined endpoint of cardiovascular (CV) death (defined as sudden cardiac death or death due to progression of congestive heart failure [CHF], stroke, or other CV causes) or CV hospitalisation (defined as hospitalisation for progression of CHF, ventricular arrhythmias, AMI or stroke). Because of the increased CV risk associated with diabetes, patients with diabetes and LV dysfunction were eligible for randomization in the absence of symptoms of heart failure; 10% of the population met this criterion. Patients with CHF of valvular or congenital aetiology or patients with unstable post-infarct angina and patients with serum potassium >5.0 mmol/L or serum creatinine >221 µmol/L were excluded. Patients were also allowed to undergo revascularization by angioplasty or coronary artery bypass graft surgery.

The mean time to enrolment was 7 days, and the mean duration of follow-up was approximately 16 months. During the study patients received standard post-MI drug therapy including aspirin (92%), ACE inhibitors (90%), ß-blockers (83%), nitrates (72%), loop diuretics (66%), or HMG CoA reductase inhibitors (60%).

For the co-primary endpoint for all-cause mortality, 478 (14.4%) patients on eplerenone and 554 (16.7%) on placebo died. Consequently, a significant (p=0.008) risk reduction (RR=15%; HR=0.85; 95% CI, 0.75–0.96) was observed with eplerenone when compared to placebo. The risk benefit for all-cause mortality was primarily due to CV mortality (12.3%). Most CV deaths were attributed to sudden death, AMI and CHF. Kaplan-Meier curves for all-cause mortality are shown in Figure 2, and the efficacy analyses for the components of mortality are provided in Table 9.

With respect to the composite endpoint of CV death or CV hospitalisation, 885 (26.7%) patients on eplerenone and 993 (30%) on placebo experienced the endpoint. With respect to the above endpoint, a significant (p=0.002) risk reduction (RR=13%; HR=0.87; 95% CI: 0.79–0.95) was observed with eplerenone when compared to placebo (Table 10; Figure 3).

Table 9: Components of all-cause mortality in EPHESUS

	Number of patients (%)		**Hazard ratio**	**p-value**
	Eplerenone (n=3,319)	**Placebo (n=3,313)**		
Death from any cause	478 (14.4)	554 (16.7)	0.85	0.008
CV death	407 (12.3)	483 (14.6)	0.83	0.005
Non-CV death	60 (1.8)	54 (1.6)		
Unknown or unwitnessed death	11 (0.3)	17 (0.5)		

Table 10: Rates of death or hospitalisation in EPHESUS

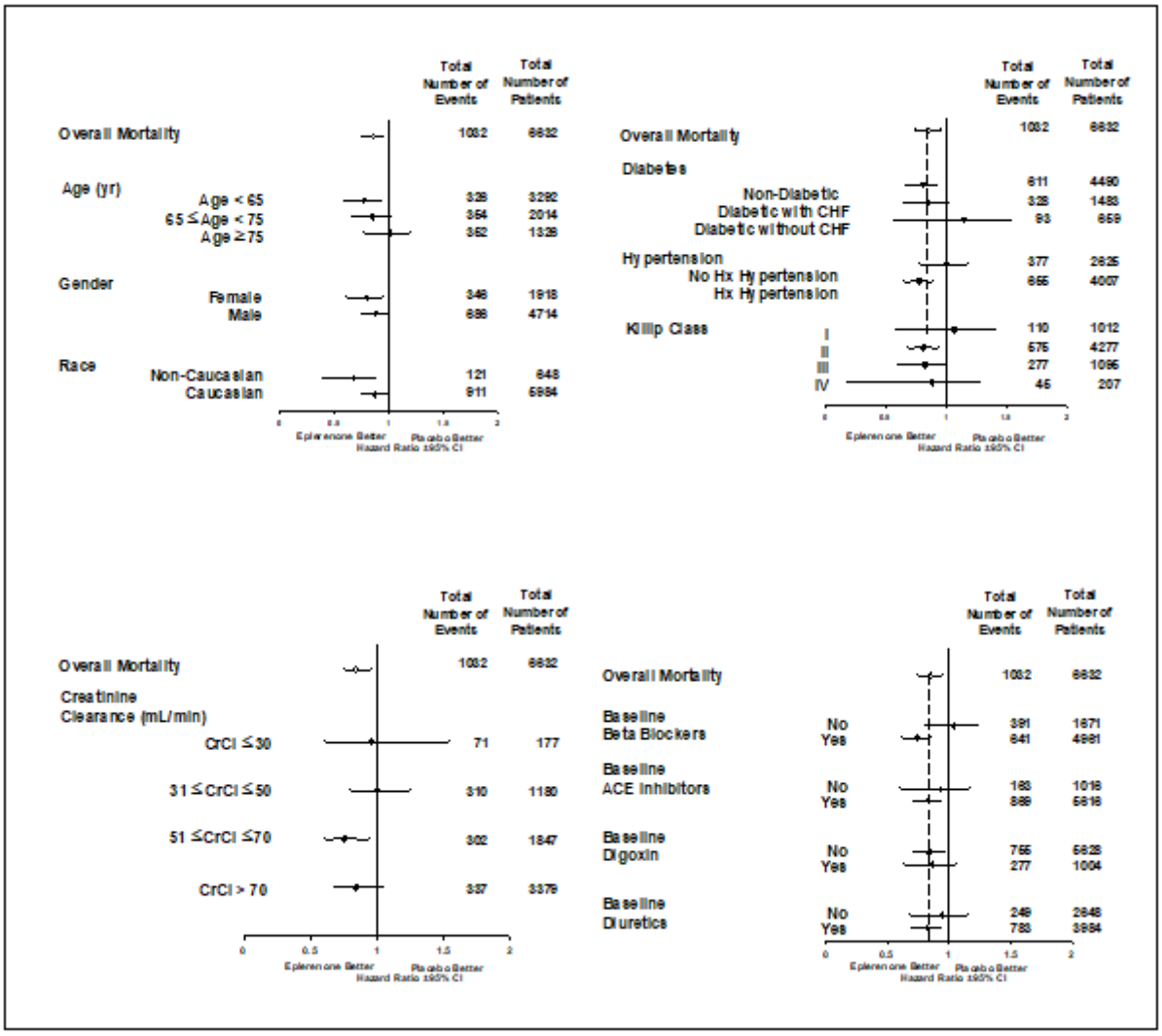
Event	Eplerenone n (%)	Placebo n (%)
CV death or hospitalisation for progression of CHF, stroke, MI or ventricular arrhythmia1	885 (26.7)	993 (30.0)
Death	407 (12.3)	483 (14.6)
Hospitalisation	606 (18.3)	649 (19.6)
CV death or hospitalisation for progression of CHF, stroke, MI, ventricular arrhythmia, atrial arrhythmia, angina, CV procedures, or other CV causes (PVD; hypotension)	1,516 (45.7)	1,610 (48.6)
Death	407 (12.3)	483 (14.6)
Hospitalisation	1,281 (38.6)	1,307 (39.5)
All-cause death or hospitalisation	1,734 (52.2)	1,833 (55.3)
Death[1]	478 (14.4)	554 (16.7)
Hospitalisation	1,497 (45.1)	1,530 (46.2)

[1]Co-primary endpoint.

The reduction in mortality observed in patients treated with eplerenone compared to those who received placebo is mainly the result of a reduction in the rate of sudden death after myocardial infarction. In the first 12 months of treatment the rate of all cause mortality was 11.68% among patients treated with eplerenone compared to 13.63% for patients treated with placebo. Among patients who remained alive after 12 months of therapy, the all cause mortality rates at month 27 in the eplerenone and placebo groups were 7.97% and 9.58%, respectively.

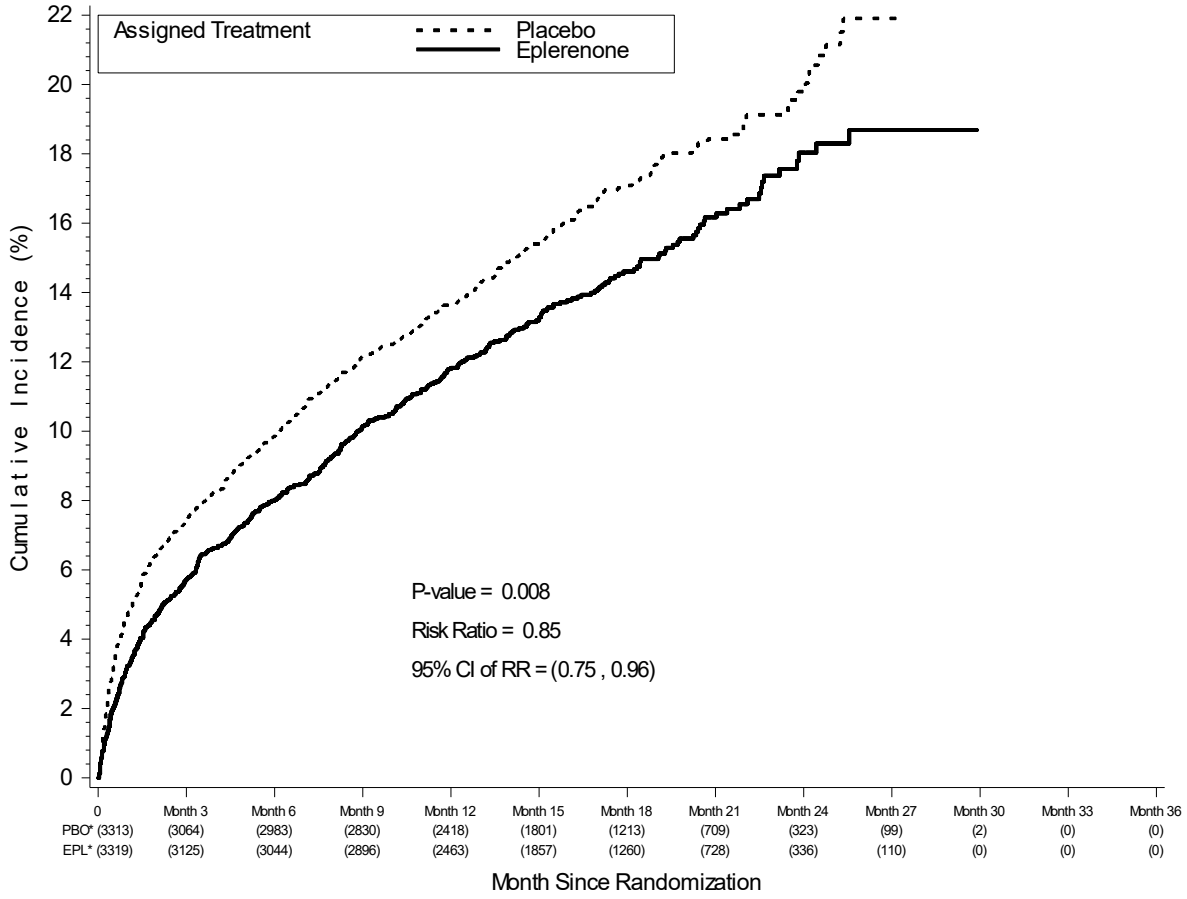
Mortality hazard ratios varied for some subgroups as shown in Figure 1. Mortality hazard ratios appeared favourable for eplerenone for both genders and for all races or ethnic groups, although the numbers of non-Caucasians was low (10%). Patients with diabetes without clinical evidence of CHF and patients greater than 75 years did not appear to benefit from the use of eplerenone. Such subgroup analyses must be interpreted cautiously.

Figure 1: Hazard ratios of all-cause mortality by subgroups



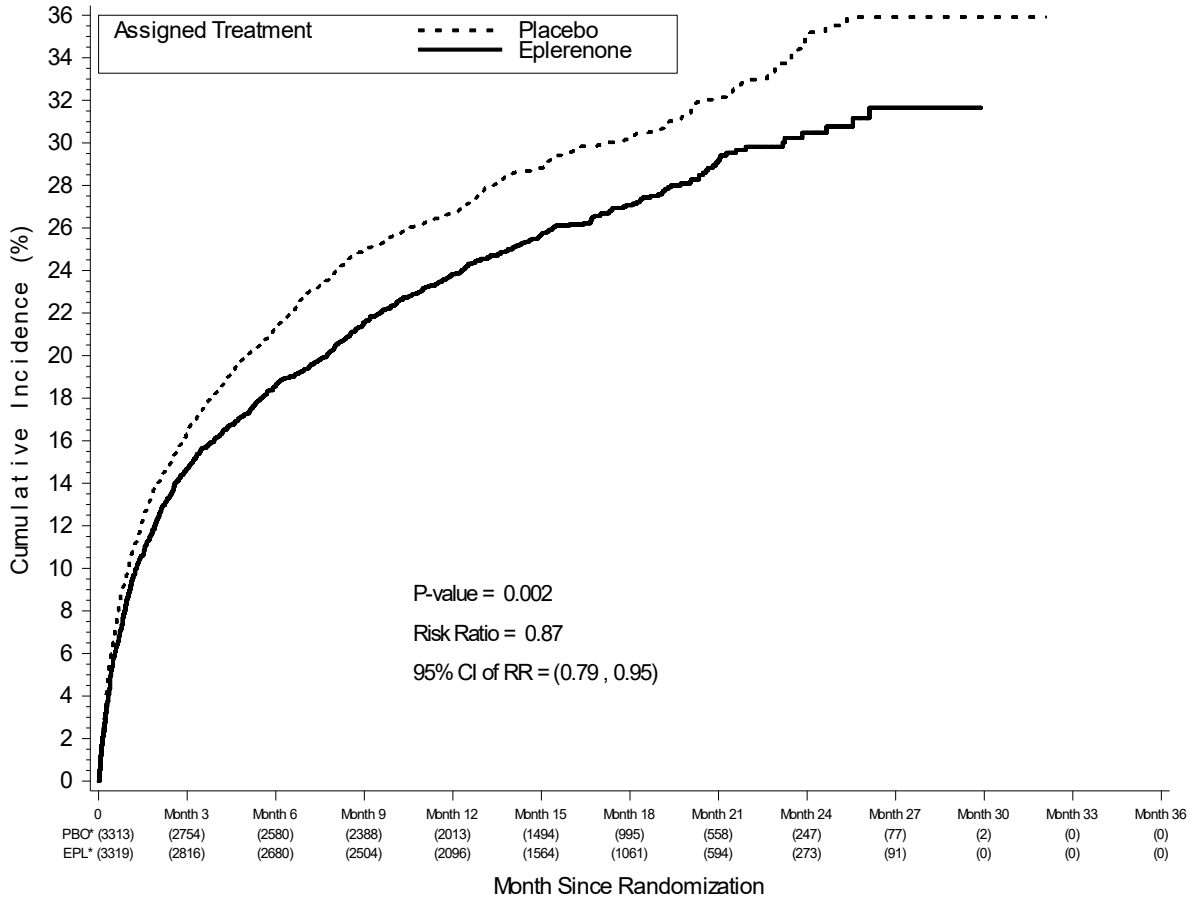
Analyses conducted for a variety of CV biomarkers did not confirm a mechanism of action by which mortality was reduced.

Figure 2: Cumulative incidence of all cause mortality (EPHESUS)



*: Number of Patients at risk.

Figure 3: Cumulative incidence of CV mortality/hospitalisation (EPHESUS)



*: Number of Patients at risk.

In dose-ranging studies of chronic heart failure (NYHA classification II–IV), the addition of eplerenone to standard therapy resulted in expected dose-dependent increases in aldosterone. Similarly, in a cardiorenal substudy of EPHESUS, therapy with eplerenone led to a significant increase in aldosterone. These results confirm the blockade of mineralocorticoid receptors in these populations.

No consistent effects of eplerenone on heart rate, QRS duration, or PR or QT interval were observed in 147 normal subjects evaluated for electrocardiographic changes during pharmacokinetic studies.

EMPHASIS-HF Trial

In the Eplerenone in Mild Patients Hospitalisation And SurvIval Study in Heart Failure trial, the effect of eplerenone when added to standard therapy was investigated on clinical outcomes in patients with systolic heart failure and mild symptoms (NYHA functional class II).

Patients were included if they were at least 55 years old, had a left ventricular ejection fraction (LVEF) ≤30% or LVEF ≤35% in addition to QRS duration of >130 msec and were either hospitalised for cardiovascular (CV) reasons 6 months prior to inclusion or had a plasma level of B-type natriuretic peptide (BNP) of at least 250 pg/mL or a plasma level of N-terminal pro-BNP of at least 500 pg/mL in men (750 pg/mL in women). Subjects were required to have a serum potassium level ≤5.0 mmoL/L and an eGFR ≥30 mL/min/1.73m^2 within 24 hours prior to randomisation. Eplerenone was started at a dose of 25 mg once daily and was increased after 4 weeks to 50 mg once daily if the serum potassium level was <5.0 mmol/L. Alternatively, if the estimated GFR was 30-49 mL/min/1.73m^2, eplerenone was started at 25 mg on alternate days, and increased to 25 mg once daily.

In total, 2,737 patients were randomised (double-blind) to the treatment with eplerenone (1,364 patients) or placebo (1,373 patients) including baseline therapy of diuretics (85%), ACE inhibitors (78%), angiotensin II receptor blockers (19%), beta blockers (87%), antithrombotic drugs (88%), and lipid lowering agents (63%).

Out of the randomised patients (1,360 treated with eplerenone, 1,369 treated with placebo; four patients in each group were not treated), the majority were white (1,141 subjects; 83.1% in the placebo group and 1,127 subjects; 82.6% in the eplerenone group). Subjects were predominately male (78.1% and 77.3% 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. The mean follow-up time was 21.1 months, the median was 20.6 months and the maximum follow-up time was 49.7 months.

The primary endpoint, death from cardiovascular causes or hospitalisation for heart failure occurred in 249 patients (18.3%) in the eplerenone group and 356 patients (25.9%) in the placebo group resulting in a relative risk reduction of 37% (hazard ratio 0.63, 95% CI, 0.54-0.74; p<0.0001), as shown in Table 11. A Kaplan-Meier plot of time to first event is provided in Figure 4 and a summary of the hazard ratios of the primary endpoint by sub-groups is presented in Figure 5.

The secondary endpoint of all cause mortality was met by 171 patients (12.5%) in the eplerenone group and 213 patients (15.5%) in the placebo group resulting in a relative risk reduction of 24% (hazard ratio 0.76; 95% CI, 0.62-0.93; p=0.008). Death from CV causes was reported in 147 (10.8%) patients in the eplerenone group and 185 (13.5%) patients in the placebo group resulting in a relative risk reduction of 24% (hazard ratio 0.76; 95% CI, 0.61-0.94; p=0.01).

Table 11: 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

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

Figure 4: Cumulative incidence of CV mortality/HF hospitalisation (EMPHASIS-HF) (full analysis set)

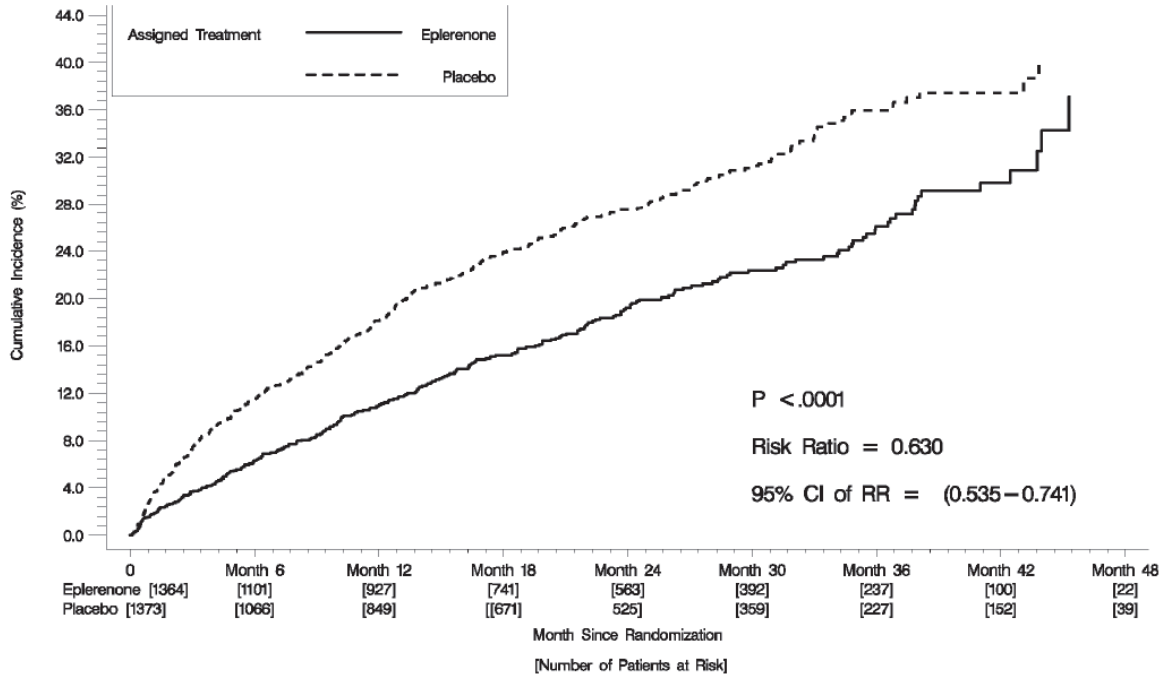
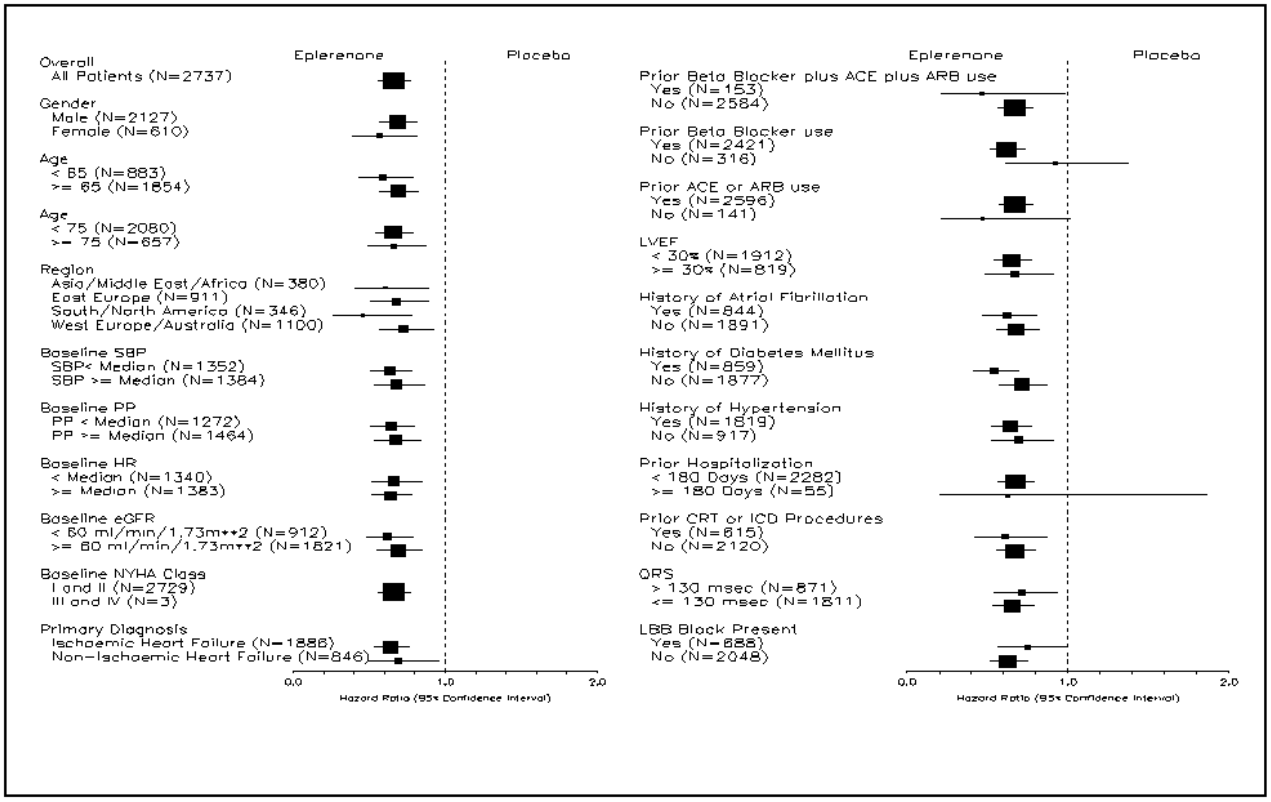


Figure 5: Sub-group analyses of HF hospitalisation or CV death (full analysis set)



Serum Potassium Levels

Serum potassium levels were assessed periodically during the study and the dosage adjusted accordingly (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION). During the EMPHASIS-HF study, hyperkalaemia (serum potassium level >5.5 mmol/L) was reported in 158 patients (11.8%) in the eplerenone group and 96 patients (7.2%) in the placebo group ($p<0.001$). Hypokalaemia, defined as serum potassium levels <3.5 mmol/L, was statistically lower with eplerenone when compared to placebo (7.5% for eplerenone compared to 11.0% for placebo, $p<0.002$). There is limited data available on the patient population with baseline serum potassium levels between 5.0 and 5.5 mmol/L.

Chronic Kidney Disease (CKD)

The distribution of subjects enrolled in the EMPHASIS-HF study based on renal function stratification is shown in Table 12 below.

Table 12: Distribution of Subjects Enrolled, Based on Renal Function Stratification

Renal Function	**eGFR (mL/min/1.73m^2)** Analysis Group	**Eplerenone N (%)**	**Placebo N (%)**	**Kidney function stage**	**eGFR (mL/min/1.73m^2) (KHA)**
Normal function	≥90	234 (17.2%)	239 (17.4%)	1	≥90
Mild Impairment	60 - 89	689 (50.6%)	659 (48.1%)	2	60 – 89
Moderate impairment	30 - 59	437 (32.1%)	471 (34.4%)	3	30 – 59

Renal Function	**eGFR (mL/min/1.73m^2)** Analysis Group	**Eplerenone N (%)**	**Placebo N (%)**	**Kidney function stage**	**eGFR (mL/min/1.73m^2) (KHA)**
Severe Impairment	<30	2 (0.1%)	2 (0.1%)	4	15 – 29
		0 (0.0%)	0 (0.0%)	5	<15 or on dialysis
Total		1362	1371		

Note the left hand side of this table refers to the EMPHASIS-HF trial, and the right hand side relates to the Kidney Health Australia classification for Chronic Kidney Disease

Patients with stage 1 and 2 CKD were started on eplerenone 25 mg or matching placebo daily. They could be up-titrated to eplerenone 50 mg daily, or matching placebo, if serum potassium at 4 weeks was <5.0 mmol/L. Subsequently, patients received a maintenance dose that ensured that serum potassium did not exceed 5.0 mmol/L. If serum potassium rose above 5.0 mmol/L, patients were down-titrated to a daily dose of 25 mg or matching placebo. Similarly, patients taking 25 mg or matching placebo, daily, were down-titrated to 25 mg or matching placebo, every other day, if serum potassium was >5.0 mmol/L.

Patients with stage 3 CKD and eGFR 50-59 mL/min/1.73m^2 were started on a dose of eplerenone 25 mg, or matching placebo, daily. At the end of 4 weeks, they were up-titrated to 50 mg or matching placebo, daily, if serum potassium was <5.0 mmol/L. However, if serum potassium was >5.0 mmol/L, patients were down-titrated to a dose of 25 mg or matching placebo, every other day.

Patients with stage 3 CKD and eGFR 30-49 mL/min/1.73m^2 were started on eplerenone 25 mg, or matching placebo, every other day. They were up-titrated to 25 mg or matching placebo daily, if serum potassium was <5.0 mmol/L at the end of 4 weeks. However, if serum potassium was >5.0 mmol.L, dosing was temporarily withheld and serum potassium repeated after 72 hours. If the repeated value of serum potassium was <5.0 mmol/L, eplerenone was re-introduced at 25 mg every other day, or if serum potassium increased again, eplerenone was discontinued.

While stratification to a dosing group at baseline was based on renal function, dose adjustments were always and solely based on serum potassium, a value of serum potassium >5.0 mmol/L always necessitating a downward dose adjustment.

Eplerenone has not been evaluated in subjects with severe (Stage 4 and 5) CKD (eGFR less than 30 mL/min/l.73 m^2).

Open Label Phase

The EMPHASIS-HF study protocol included pre-specified interim analyses. During the second interim analysis, the Data Safety Monitoring Committee confirmed that the study had reached its primary efficacy endpoint early and that the pre-specified stopping rules regarding early attainment of positive efficacy results had been met. A recommendation was made to terminate the double blind (DB) study and to provide a mechanism to make eplerenone available to all participating subjects. As a result, enrolment into the study was stopped and all subjects who were participating in the double blind phase of EMPHASIS-HF were given the opportunity to receive open label treatment for 12 months.

All efficacy data collected during the DB phase up to termination of enrolment were analysed according to the pre-specified protocol and are presented in Table 11 and Figure 4 & Figure 5. Although enrolment was stopped, the DB phase of the study continued until all consenting patients were transitioned into the open-label extension (OLE) phase of the study. The all cause mortality figures collected up to start of the OLE phase are 205/1367 (15.0%) for eplerenone and 253/1376 (18.4%) for placebo. These figures were not subject to statistical analysis.

A total of 1245 subjects were treated in the OLE phase, and 56 (4.5%) deaths were reported during the 12 months. No efficacy evaluations were conducted on the open label extension (OLE) phase.

5.2 PHARMACOKINETIC PROPERTIES

Eplerenone is cleared predominantly by cytochrome P450 (CYP) 3A4 metabolism, with an elimination half-life of 3 to 5 hours. Steady state is reached within 2 days. Absorption is not affected by food. Inhibitors of CYP3A4 (e.g. ketoconazole, saquinavir) increase blood levels of eplerenone.

Absorption

Mean peak plasma concentrations of eplerenone are reached approximately 1.5 hours following oral administration. The absolute bioavailability of eplerenone 100 mg tablet is 69%. Both peak plasma levels (C_{max}) and area under the curve (AUC) are dose proportional for doses of 25 to 100 mg and less than proportional at doses above 100 mg.

Distribution

The plasma protein binding of eplerenone is about 50% and is primarily bound to alpha-1-acid glycoproteins. The apparent volume of distribution at steady state ranged from 43 to 90 L. Eplerenone does not preferentially bind to red blood cells.

Metabolism

Eplerenone metabolism is primarily mediated via CYP3A4. No active metabolites of eplerenone have been identified in human plasma.

Excretion

Less than 5% of an eplerenone dose is recovered as unchanged drug in the urine and faeces. Following a single oral dose of radiolabelled drug, approximately 32% of the dose was excreted in the faeces and approximately 67% was excreted in the urine. The elimination half-life of eplerenone is approximately 3 to 5 hours. The apparent plasma clearance is approximately 10 L/hr.

Special populations

Age, gender, and race

The pharmacokinetics of eplerenone at a dose of 100 mg once daily have been investigated in the elderly (≥65 years), in males and females, and in blacks. The pharmacokinetics of eplerenone did not differ significantly between males and females. At steady state, elderly subjects had increases in C_{max} (22%) and AUC (45%) compared with younger subjects (18 to 45 years). At steady state, C_{max} was 19% lower and AUC was 26% lower in blacks (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Chronic Kidney Disease

The pharmacokinetics of eplerenone were evaluated in patients with varying degrees of chronic kidney disease and in patients undergoing haemodialysis. Compared with control subjects, steady-state AUC and C_{max} were increased by 38% and 24%, respectively, in patients with severe chronic kidney disease and were decreased by 26% and 3%, respectively, in patients undergoing haemodialysis. No correlation was observed between plasma clearance of eplerenone and creatinine clearance. Eplerenone is not removed by haemodialysis (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Hepatic insufficiency

The pharmacokinetics of eplerenone 400 mg have been investigated in patients with moderate (Child-Pugh Class B) hepatic impairment and compared with normal subjects. Steady-state C_{max} and AUC of eplerenone were increased by 3.6% and 42%, respectively (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Heart failure

The pharmacokinetics of eplerenone 50 mg were evaluated in patients with heart failure (NYHA classification II–IV). Compared with healthy subjects matched according to age, weight and gender, steady state AUC and C_{max} in heart failure patients were 38% and 30% higher, respectively. Consistent with these results, a population pharmacokinetic analysis of eplerenone based on a subset of patients from EPHESUS indicates that clearance of eplerenone in patients with heart failure was similar to that in healthy elderly subjects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Eplerenone was non-genotoxic in a battery of assays including *in vitro* bacterial gene mutation (*Salmonella typhimurium* and *E. coli*), *in vitro* mammalian cell gene mutation (mouse lymphoma cells), *in vitro* chromosomal aberration (Chinese hamster ovary cells), *in vivo* rat bone marrow micronucleus formation, and *in vivo/ex vivo* unscheduled DNA synthesis in rat hepatocytes.

Carcinogenicity

There was no drug-related tumour response in heterozygous P53 deficient mice when tested for 6 months at oral dosages up to 1,000 mg/kg/day (systemic AUC exposures up to 10-15 times the exposure in humans receiving the 50 mg/day therapeutic dose, based on unbound AUC). Statistically significant increases in benign thyroid tumours were observed after 2 years in both male and female rats when administered eplerenone 250 mg/kg/day (highest dose tested) and in male rats only at 75 mg/kg/day. The incidence of renal tubular adenomas was increased in females at 250 mg/kg/day. These dosages provided systemic AUC exposures three to 16 times the average human therapeutic exposure at 50 mg/day. The thyroid tumours were associated with thyroid hypertrophy resulting from increases in the hepatic enzyme responsible for conjugation and clearance of levothyroxine sodium, which results in increased levels of TSH by a compensatory mechanism. The benign renal tumours were associated with chronic progressive nephropathy, which commonly occur in ageing rats and which is exacerbated by some human therapeutic agents. Drugs that have produced thyroid tumours and renal tubular adenomas by these rodent-specific mechanisms have not shown a similar effect in humans.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each film coated tablet contains: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hypromellose, sodium lauryl sulfate, purified talc, magnesium stearate, titanium dioxide, macrogol 400, polysorbate 80, iron oxide yellow (CI77492), iron oxide red (CI77491)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Packed in PVC/Al blister packs of 10, 30, 50 and 60 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

Australian Register of Therapeutic Goods (ARTG)

AUST R 508245 – EPLERENONE VIATRIS eplerenone 25 mg tablet blister pack

AUST R 508246 – EPLERENONE VIATRIS eplerenone 50 mg tablet blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

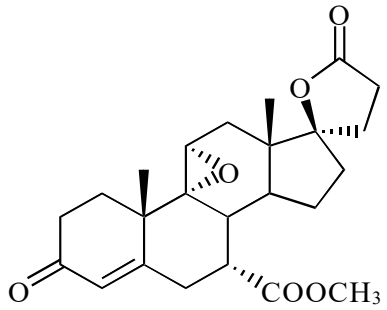
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Eplerenone is an odourless, white to off-white crystalline powder. It is very slightly soluble in water, with its solubility essentially pH independent. The octanol/water partition coefficient of eplerenone is approximately 7.1 at pH 7.0.

Chemical Structure

Eplerenone is pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo, γ-lactone, methyl ester, (7α,11α,17α). The empirical formula of eplerenone is $C_{24}H_{30}O_6$ and its molecular weight 414.50. The structural formula of eplerenone is shown below:



CAS Number

107724-20-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Viatris Pty Ltd

Level 1, 30 The Bond

30-34 Hickson Road

Millers Point NSW 2000

www.viatris.com.au

Phone: 1800 274 276

9 DATE OF FIRST APPROVAL

28/04/2026

10 DATE OF REVISION

N/A

Summary Table of Changes

Section Changed	Summary of New Information
All	New document.

EPLERENONE VIATRIS_pi\Apr26/00