NEW ZEALAND DATA SHEET

INSPRA®

1. Product Name

INSPRA 25 mg and 50 mg film-coated tablets

2. Qualitative and Quantitative Composition

Each 25 mg film-coated tablet contains 25 mg eplerenone.

Each 50 mg film-coated tablets contains 50 mg eplerenone.

Excipients with known effects: lactose monohydrate

Allergen declaration: contains lactose

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

INSPRA is supplied as yellow, arc diamond, film-coated tablets.

25 mg tablet: stylised with “VLE” on one side of tablet, “NSR” over “25” on other side of tablet

50 mg tablet: stylised with “VLE” on one side of tablet, “NSR” over “50” on other side of tablet

4. Clinical Particulars

4.1 Therapeutic indications

Inspra is indicated to reduce the risk of cardiovascular death in combination with standard therapy in patients who have evidence of heart failure and left ventricular impairment within 3 to 14 days of an acute myocardial infarction.

4.2 Dose and method of administration

Dose

Inspra is usually administered in combination with standard therapies. The recommended dose of Inspra 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, 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 Inspra 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. Serum potassium should be measured before initiating Inspra 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 adjusted based on the serum potassium level (see table 1).

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	

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

Inspra 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 5.5 mmol/L. Serum potassium monitoring should continue once eplerenone has been re-started again. Inspra may be administered with or without food.

Patients taking mild to moderate CYP3A4 inhibitors, such as erythromycin, saquinavir, verapamil, and fluconazole, should not be administered Inspra in doses exceeding 25 mg once daily.

Special populations

Elderly

No dose adjustment is required in the elderly.

Renal impairment

No initial dose adjustment is required in patients with mild renal impairment (see section 4.4). The rates of hyperkalaemia increase with declining renal function. Periodic monitoring of serum potassium with dose adjustment according to the table above is recommended. Inspra is contraindicated in patients with severe renal insufficiency (see section 4.3).

Hepatic impairment

No initial dosage adjustment is necessary for patients with mild-to-moderate hepatic impairment. Inspra is contraindicated in patients with severe hepatic insufficiency (see section 4.3).

Paediatric

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

4.3 Contraindications

- Hypersensitivity to eplerenone or any of the excipients.
- Inspra should not be administered to patients with clinically significant hyperkalaemia (serum potassium >5.0 mmol/L at initiation).
- Inspra should not be administered to patients with moderate to severe renal insufficiency (creatinine clearance <50 mL/min) (see section 4.2).
- Inspra should not be administered to patients with severe hepatic insufficiency (see section 4.2).
- Inspra should not be co-administered to patients receiving potassium-sparing diuretics, potassium supplements, or strong inhibitors of CYP3A4 such as ketoconazole, itraconazole and ritonavir (see section 4.4 and 4.5).

4.4 Special warnings and precautions for use

Hyperkalaemia

The principal risk of Inspra is hyperkalaemia. Hyperkalaemia can cause serious, sometimes fatal, arrhythmias. Patients who develop hyperkalaemia (>5.5 mmol/L) may still benefit from Inspra with proper dose adjustment. Hyperkalaemia can be minimized by patient selection, avoidance of certain concomitant treatments, and periodic monitoring until the effect of Inspra has been established. Inspra 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, 4.5 and 4.8). Dose reduction of Inspra has been shown to decrease potassium levels (see section 4.2).

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).

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).

Impaired Hepatic Function

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 Inspra in patients with severe hepatic impairment has not been evaluated, and is therefore contraindicated (see section 4.2, 4.3, and 5.2).

Impaired Renal Function

See section 4.3 and 4.4.

Paediatric Use

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

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 Inspra (see section 5.1). 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).

4.5 Interaction with other medicines and other forms of interaction

Inhibitors of CYP3A4

Eplerenone metabolism is predominantly mediated via CYP3A4. A pharmacokinetic study evaluating the administration of a single dose of Inspra 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. Inspra should not be used with medicines described as strong inhibitors of CYP3A4 in their labelling (see section 4.3).

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 with eplerenone is not recommended.

ACE Inhibitors and Angiotensin II Receptor Antagonists

In EPHESUS, 3,020 (91%) patients receiving Inspra 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.

Lithium

A medication 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. Serum lithium levels should be monitored frequently if Inspra is administered concomitantly with lithium.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

A medication 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 Inspra 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

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. Inspra should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Breastfeeding

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 medications 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 medicine, taking into account the importance of the medicine to the mother.

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 medication 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.

4.7 Effects on ability to drive and use machines

No studies on the effect of eplerenone on the ability to drive or use machines have been performed. Eplerenone does not cause drowsiness or impairment of cognitive function but when driving vehicles or operating machines it should be taken into account that dizziness and syncope may occur during treatment.

4.8 Undesirable effects

Inspra has been evaluated for safety in 3,307 patients treated for heart failure post-myocardial infarction (see section 5.1). In EPHESUS, the overall incidence of adverse events reported with Inspra (78.9%) was similar to placebo (79.5%). The discontinuation rate due to adverse events in these studies was 4.4% for patients receiving Inspra and for 4.3% patients receiving placebo.

Adverse events reported below are those with suspected relationship to treatment and in excess of placebo. 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: atrial fibrillation, left ventricular failure

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: 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

Respiratory, Thoracic and Mediastinal Disorders

Common: cough

Skin and Subcutaneous Tissue Disorders

Common: pruritus

Uncommon: hyperhidrosis

Vascular Disorders

Common: hypotension

Uncommon: orthostatic hypotension.

The rates of sex hormone related events are shown in Table 2.

TABLE 2. Rates of sex hormone related adverse events in EPHESUS

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

Table 3: 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**
<u>Autonomic nervous system disorders</u>		
Hypotension	109 (3.3%)	119 (3.6%)
Syncope	58 (1.8%)	71 (2.1%)

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

Body system Adverse event	Placebo n=3,301	Eplerenone 25-50 mg QD n=3,307
Urinary tract infection	113 (3.4%)	111 (3.4%)
Vascular disorders Cerebrovascular disorder	 101 (3.1%)	 103 (3.1%)

A total of 3,353 patients have been treated with Inspra in clinical studies of hypertension. The overall rates of adverse events in placebo-controlled studies were similar between Inspra (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 Inspra 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: angioneurotic oedema, rash.

Clinical Laboratory Test Findings

Creatinine

Increases of more than 44.2 µmol/d were reported for 6.5% of patients administered Inspra 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 Inspra compared with placebo are displayed in Table 4.

TABLE 4. Hypokalaemia (<3.5 mmol/L) or hyperkalaemia (>5.5 mmol/L or ≥6.0 mmol/L) in EPHESUS

Potassium (mmol/L)	Number of patients (%)	
	Inspra (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 5 shows the rates of hyperkalaemia in EPHESUS as assessed by baseline renal function (creatinine clearance).

TABLE 5. Rates of hyperkalaemia (>5.5 mmol/L) in EPHESUS by baseline creatinine clearance*

Baseline creatine clearance (mL/min)	Inspra (%)	Placebo (%)
≤30	31.5	22.6
31–50	24.1	12.7
51–70	16.9	13.1

Baseline creatine clearance (mL/min)	Inspra (%)	Placebo (%)
>70	10.8	8.7

*Estimated using Cockroft-Gault formula

Table 6 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).

TABLE 6. Rates of hyperkalaemia (>5.5 mmol/L) in EPHESUS by proteinuria and history of diabetes*

	Inspra (%)	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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

Signs and Symptoms

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

Treatment

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 further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

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

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 of 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 medication 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 7.

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 8; Figure 3).

TABLE 7. Components of all-cause mortality in EPHESUS

	Number of patients (%)		Hazard ratio	p-value
	Inspra (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)		

Most CV deaths were attributed to sudden death, AMI, and congestive heart failure (CHF).

TABLE 8. Rates of death or hospitalisation in EPHESUS

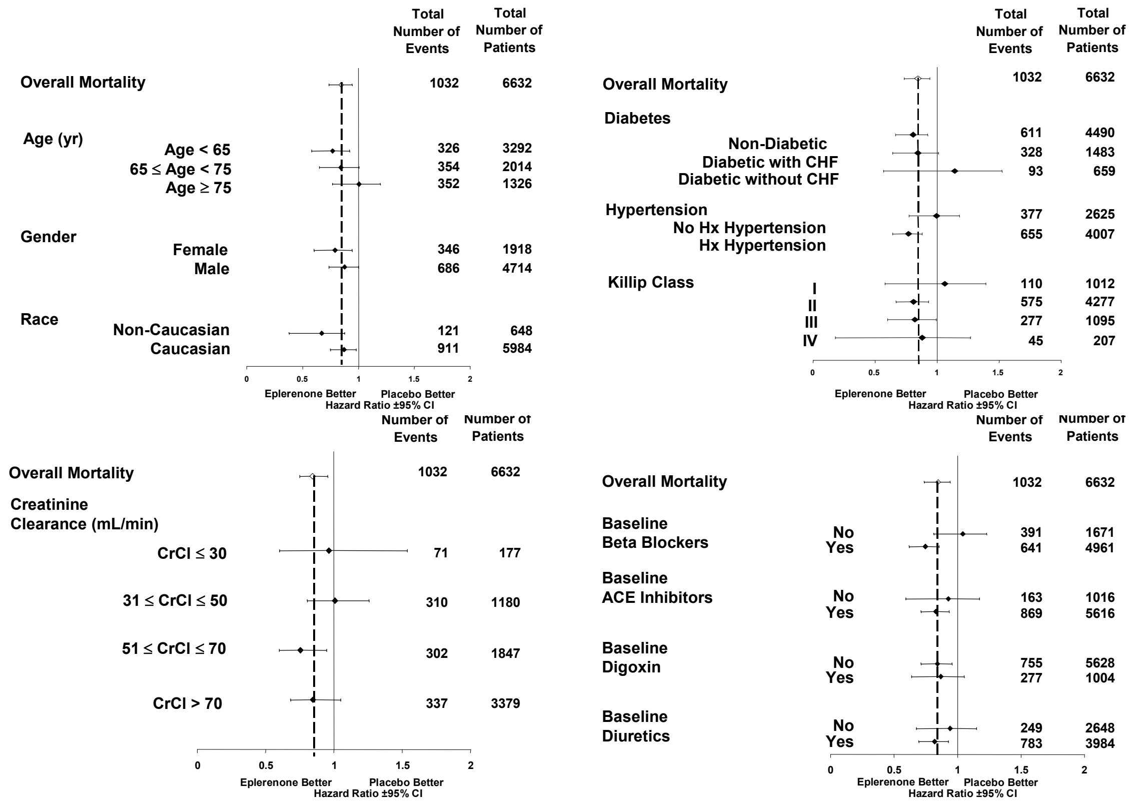
Event	Inspra n (%)	Placebo n (%)
CV death or hospitalisation for progression of CHF, stroke, MI or ventricular arrhythmia[1]	885 (26.7)	993 (30.0)
Death	407 (12.3)	483 (14.6)
Hospitalisation	606 (18.3)	649 (19.6)
CV death or hospitalisation for progression of CHF, stroke, MI, ventricular arrhythmia, 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 Inspra 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 Inspra 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.

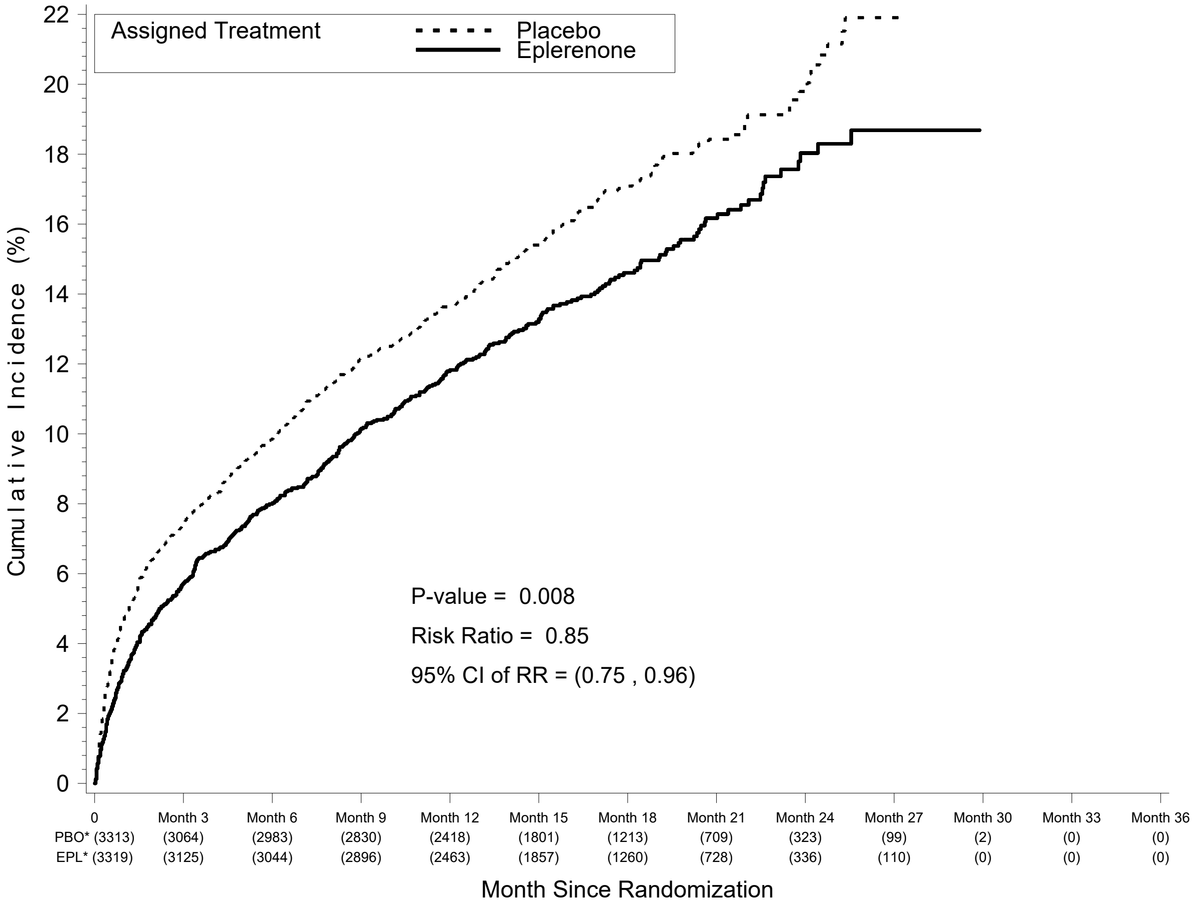
Mortality hazard ratios varied for some subgroups as shown in Figure 1. Mortality hazard ratios appeared favourable for Inspra for both genders and for all races or ethnic groups, although the numbers of non-Caucasians were low (10%). Patients with diabetes without clinical evidence of CHF and patients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

FIGURE 1. Hazard ratios of all-cause mortality by subgroups



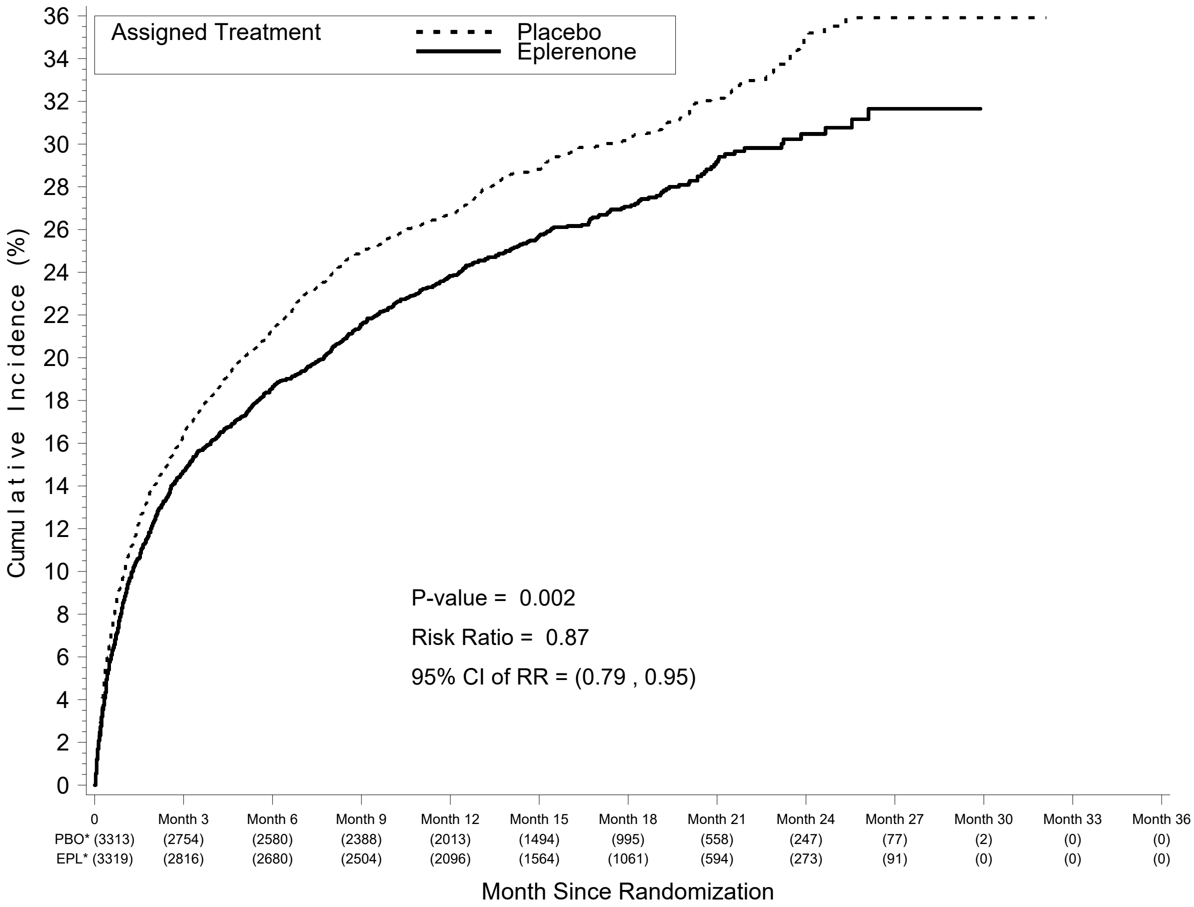
Analyses conducted for a variety of CV biomarkers did not confirm a mechanism of action by which mortality was reduced.

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.

5.2 Pharmacokinetic properties

Eplerenone is cleared predominantly by cytochrome P450 (CYP) 3A4 metabolism, with an elimination half-life of 3 to 6 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 42 to 90 L. Eplerenone does not preferentially bind to red blood cells.

Biotransformation

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

Elimination

Less than 5% of an eplerenone dose is recovered as unchanged medication in the urine and faeces. Following a single oral dose of radiolabelled medication, 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 6 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).

Renal insufficiency: The pharmacokinetics of eplerenone were evaluated in patients with varying degrees of renal insufficiency 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 renal impairment 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).

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 –).

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.

Mutagenicity

There was no medication-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 thyroxine, which results in increased levels of TSH by a compensatory mechanism.

The benign renal tumours were associated with chronic progressive nephropathy, which commonly occurs in ageing rats and which is exacerbated by some human therapeutic agents. Medications 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

Inspra film coated tablets also contains

- Lactose monohydrate
- Microcrystalline cellulose
- Croscarmellose sodium
- Hypromellose
- Sodium laurylsulfate
- Purified talc
- Magnesium stearate
- Opadry yellow YS-1-12524-A
- Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25ºC.

6.5 Nature and contents of container

Inspra 25 mg blisters. Pack size of 10, 30, 50 and 60 film coated tablets.

Inspra 50 mg blisters. Pack size of 10, 30, 50 and 60 film coated tablets.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

Not applicable

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
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Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

22 December 2005

10. Date of Revision of the Text

20 March 2024

Summary table of changes

Section	Summary of new information
All	Update to Viatris template Update "INSPRA" to "Inspra" Updated the word "drugs" to "medication" or "medicine" Addition of table title and consequential reordering of tables Minor formatting changes Minor editorial changes
2	Addition of allergen declaration
3	Updated tablet description
4.8	Updated ADR website
6.5	Addition of non-marketed pack sizes

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