INSPRA
Eplerenone

1. NAME OF THE MEDICINAL PRODUCT

INSPRA

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: eplerenone
The tablets for oral administration contain either 25 mg or 50 mg of eplerenone.

3. PHARMACEUTICAL FORM

Film-coated tablets

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Hypertension
Eplerenone is indicated for the treatment of hypertension. In these patients, eplerenone may be used alone or in combination with other antihypertensive agents.

Heart Failure - Post-Myocardial Infarction (MI)
Eplerenone is indicated, in addition to standard therapy, to reduce the risk of cardiovascular mortality and cardiovascular hospitalization in stable patients with left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤40%) and clinical evidence of heart failure after recent MI.

New York Heart Association (NYHA) Class II (Chronic) Heart Failure
Eplerenone is indicated, in addition to standard optimal therapy to reduce the risk of cardiovascular mortality and hospitalization in heart failure 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) (see section **5.1 Pharmacodynamic Properties**).

4.2 Posology and Method of Administration

For the individual adjustment of dose, the strengths of 25 mg and 50 mg are available. The maximum dose regimen is 50 mg daily for heart failure and 100 mg daily for hypertension.

For Patients with Hypertension:

The recommended starting dose of eplerenone is 50 mg administered once daily. The full therapeutic effect of eplerenone is apparent within 4 weeks. For patients with an inadequate blood pressure response to 50 mg once daily the dosage of eplerenone should be increased to 50 mg twice daily. Higher dosages of eplerenone are not recommended because they have no greater effect on blood pressure than 100 mg and are associated with an increased risk of hyperkalemia.

For Post-myocardial Infarction Heart Failure Patients:

The recommended maintenance dose of eplerenone is 50 mg once daily. Treatment should be initiated at 25 mg once daily and titrated in one step to the target dose of 50 mg once daily preferably within 4 weeks, taking into account the serum potassium level (see Table 1).

Eplerenone therapy should usually be started within 3-14 days after an acute myocardial infarction.

For Patients with NYHA Class II (Chronic) Heart Failure:

For chronic heart failure NYHA class II patients, 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 level (see Table 1 and section **4.4 Special Warnings and Precautions for Use**).

General Considerations:

Patients with a serum potassium of >5.0 mmol/L should not be started on eplerenone (see section **4.3 Contraindications**).

Serum potassium should be measured before initiating eplerenone therapy, within the first week and at one month after the start of treatment or dose adjustment. Serum potassium should be assessed as needed periodically thereafter.

After initiation, the dose should be adjusted based on the serum potassium level as shown in Table 1.

Table 1: Dose Adjustment after Initiation

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

EOD (Every Other Day), OD (Once Daily).
^Do not increase if: on concurrent mild-moderate CYP3A4 inhibitor or in patients with eGFR 30-49 mL/min/1.73 m^2.

Following withholding eplerenone due to serum potassium ≥6.0 mmol/L, eplerenone can be re-started at a dose of 25 mg every other day when potassium levels have fallen below 5.0 mmol/L.

Food: Eplerenone may be administered with or without food.

Concomitant CYP3A4 Medications: In patients receiving mild to moderate CYP3A4 inhibitors, such as amiodarone, diltiazem, erythromycin, saquinavir, verapamil, and fluconazole, dosing should not exceed 25 mg once daily.

Special Populations and Special Considerations for Dosing

Use in Hepatic Impairment

Mild-to-Moderate Hepatic Impairment: No initial dose adjustment is necessary (see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**).

Use in Renal Impairment

For post-myocardial infarction heart failure patients:

No initial dose adjustment is required in patients with mild renal impairment (creatinine clearance ≥50 mL/min). The rates of hyperkalemia increase with declining renal function. Periodic monitoring of serum potassium with dose adjustment according to Table 1 is recommended (see section **4.4 Special Warnings and Precautions for Use**).

There is no experience in patients with moderate to severe renal impairment (creatinine clearance <50 mL/min) or Type 2 Diabetes with microalbuminuria. The use of eplerenone in these patients is contraindicated.

For patients with NYHA class II (chronic) heart failure:

No initial dose adjustment is required in patients with mild renal impairment (eGFR ≥50 mL/min/1.73 m^2). The rates of hyperkalemia increase with declining renal function. Periodic monitoring of serum potassium is recommended (see section **4.4 Special Warnings and Precautions for Use**) and doses adjusted according to Table 1.

Patients with moderate renal impairment (eGFR 30 – 49 mL/min/1.73 m^2) should be started at 25 mg every other day, and dose should be adjusted based on the potassium level (see Table 1). Periodic monitoring of serum potassium is recommended (see section **4.4 Special Warnings and Precautions for Use**). Doses above 25 mg daily have not been studied in patients with eGFR 30-49 mL/min/1.73 m^2.

There is no experience in patients with severe renal impairment eGFR <30 mL/min/1.73 m^2. The use of eplerenone in these patients is contraindicated.

Eplerenone is not dialyzable.

For patients with hypertension:

For hypertensive patients with moderate-to-severe renal impairment or Type 2 diabetes with microalbuminuria, see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**.

Use in the Elderly

No initial adjustment of the dose is required in the elderly patients (see section **4.4 Special Warnings and Precautions for Use**).

Use in Children

Safety and efficacy of eplerenone has not been studied in pediatric patients with heart failure. Eplerenone has not been studied in hypertensive patients less than 4 years old and the study in older pediatric patients did not demonstrate efficacy. Currently available data are described in section **5.1 Pharmacodynamic Properties**.

4.3 Contraindications

Eplerenone is contraindicated in all patients with the following:

- hypersensitivity to eplerenone or any component of this medication
- clinically significant hyperkalemia or with conditions associated with hyperkalemia
- serum potassium level >5.0 mmol/L (mEq/L) at initiation

- moderate to severe renal impairment (creatinine clearance <50 mL/min) in post-MI heart failure (based on Eplerenone Post-acute Myocardial Infarction Heart failure Efficacy and Survival Study [EPHESUS], see section **5.1 Pharmacodynamic Properties**)
- severe renal impairment (eGFR <30 mL/min/1.73 m^2) in NYHA class II (chronic) heart failure (based on Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure [EMPHASIS-HF] study, see section **5.1 Pharmacodynamic Properties**)
- severe hepatic impairment (Child-Pugh Class C)
- concomitant use with potassium-sparing diuretics or potent inhibitors of CYP450 3A4, such as ketoconazole, itraconazole, and ritonavir (see section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**)

Eplerenone is also contraindicated in patients with HYPERTENSION and the following:
- Type 2 diabetes with microalbuminuria
- serum creatinine >2.0 mg/dL (or >177 µmol/L) in males, or >1.8 mg/dL (or >159 µmol/L) in females
- concomitant use with potassium supplements

4.4 Special Warnings and Precautions for Use

Hyperkalemia
Eplerenone is associated with an increased risk of hyperkalemia. This risk can be minimized by patient selection, avoidance of certain concomitant treatments, and monitoring. Eplerenone should generally not be administered to patients who are receiving potassium supplements (see section **4.3 Contraindications**). Potassium levels should be monitored regularly in patients with impaired renal function, including diabetic microalbuminuria (see below). Dose reduction of eplerenone has been shown to decrease serum potassium levels (see section **4.2 Posology and Method of Administration**).

The risk of hyperkalemia may increase when eplerenone is used in combination with an Angiotensin-converting enzyme (ACE) inhibitor and/or an angiotensin receptor blocker (ARB).

The rates of hyperkalemia increase with declining renal function. Patients with hypertension who have serum creatinine levels >2.0 mg/dL (males) or >1.8 mg/dL (females) or creatinine clearance ≤50 mL/min should not be treated with eplerenone.

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. The use of eplerenone in patients with severe hepatic impairment (Child-Pugh Class C) has not been evaluated and is therefore contraindicated (see sections **4.2 Posology and Method of Administration** and **4.3 Contraindications**).

Impaired Renal Function
See **hyperkalemia** above and also section **4.3 Contraindications.**

Elderly
Due to age-related decline in renal function, the risk of hyperkalemia is increased in elderly patients. Periodic monitoring of serum potassium is recommended.

Post-hoc analyses in the EMPHASIS-HF study to explore 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 (see section **5.1 Pharmacodynamic Properties**).

CYP3A4 Inducers
Co-administration of eplerenone with potent CYP3A4 inducers is not recommended (see section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Lithium, cyclosporine, tacrolimus should be avoided during treatment with eplerenone (see section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Information for Patients
Patients receiving eplerenone should be informed not to use potassium supplements, salt substitutes containing potassium, or contraindicated medications without consulting the prescribing healthcare professional.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Potassium-sparing diuretics: Eplerenone should not be administered to patients receiving other potassium-sparing diuretics (see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use - Hyperkalemia**).

ACE inhibitors, ARBs: The risk of hyperkalemia may increase when eplerenone is used in combination with an ACE inhibitor and/or an 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.

Hypertension
In clinical studies of patients with hypertension, the addition of eplerenone 50 mg to 100 mg to ACE inhibitors and angiotensin II receptor antagonists increased mean serum potassium slightly (about 0.09–0.13 mEq/L). In a study in diabetics with microalbuminuria, eplerenone 200 mg combined with the ACE inhibitor enalapril 10 mg increased the frequency of hyperkalemia (serum potassium >5.5 mEq/L) from 17% on enalapril alone to 38%.

Digoxin: No clinically significant drug-drug pharmacokinetic interactions have been found with digoxin. Systemic exposure (AUC) to digoxin increases by 16% (90% CI: 4%-30%) when co-administered with eplerenone. Caution is warranted when digoxin is dosed near the upper limit of therapeutic range.

Warfarin: No clinically significant drug-drug pharmacodynamic interactions have been found with warfarin.

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 hyperkalemia 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 and monitored for changes in serum potassium levels.

Lithium: Drug interaction studies of eplerenone have not been conducted with lithium. Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors.

Co-administration of INSPRA and lithium should be avoided. If this combination appears necessary, serum lithium levels should be monitored frequently.

Cyclosporine, tacrolimus: Cyclosporine and tacrolimus may lead to impaired renal function and increase the risk of hyperkalemia. The concomitant use of eplerenone and cyclosporine or tacrolimus should be avoided. If needed, close monitoring of serum potassium and renal function are

recommended when cyclosporine and tacrolimus are to be administered during treatment with eplerenone.

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

Tricyclic anti-depressants, neuroleptics, amifostine and baclofen: Co-administration of these drugs with INSPRA may potentially increase antihypertensive effects and risk of postural hypotension.

In vitro **studies indicate that eplerenone is not an inhibitor of CYP1A2, CYP2C19, CYP2C9, CYP2D6 or CYP3A4 isozymes. Eplerenone is not a substrate or an inhibitor of P-glycoprotein.**

CYP3A4 substrates: Results of pharmacokinetic studies with CYP3A4 probe-substrates, i.e. midazolam and cisapride, showed no significant pharmacokinetic interactions when these drugs were co-administered with eplerenone.

CYP3A4 inhibitors: Because eplerenone metabolism is predominantly mediated via CYP3A4, do not use eplerenone with drugs that are strong inhibitors of CYP3A4. In patients with hypertension taking moderate CYP3A4 inhibitors, reduce the starting dose of eplerenone to 25 mg once daily.

Potent CYP3A4 inhibitors: Significant pharmacokinetic interactions may occur when eplerenone is co-administered with drugs that inhibit the CYP3A4 enzyme. A potent inhibitor of CYP3A4 (ketoconazole 200 mg twice daily) led to a 441% increase in AUC of eplerenone (see section **4.3 Contraindications**). The concomitant use of eplerenone with potent CYP3A4 inhibitors, such as ketoconazole, itraconazole, and ritonavir is contraindicated (see section **4.3 Contraindications**).

Mild to moderate CYP3A4 inhibitors: Co-administration with erythromycin, saquinavir, verapamil, or fluconazole has led to significant pharmacokinetic interactions with rank order increases in AUC ranging from 98% to 187%. Eplerenone dosing should therefore not exceed 25 mg daily when mild to moderate inhibitors of CYP3A4 are co-administered with eplerenone (see section **4.2 Posology and Method of Administration**).

CYP3A4 inducers: Co-administration of St. John's wort (a potent CYP3A4 inducer) with eplerenone caused a 30% 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 (see section **4.4 Special Warnings and Precautions for Use**).

4.6 Pregnancy and Lactation

Pregnancy: Eplerenone has not been studied in pregnant women. Animal studies did not indicate direct or indirect adverse effects with respect to pregnancy, embryofetal development, parturition or post-natal development (see section **5.3 Preclinical Safety Data**). Caution should be exercised when prescribing eplerenone to pregnant women.

Teratogenic Effects
Embryo-fetal development studies were conducted with doses up to 1000 mg/kg/day in rats and 300 mg/kg/day in rabbits (exposures up to 32 and 31 times the human AUC for the 100 mg/day therapeutic dose, respectively). No teratogenic effects were seen in rats or rabbits, although decreased body weight in maternal rabbits and increased rabbit fetal resorptions and post-implantation loss were observed at the highest administered dosage. Because animal reproduction studies are not always predictive of human response, eplerenone should be used during pregnancy only if clearly needed.

Lactation: It is unknown if eplerenone is excreted in human breast milk after oral administration. However, pre-clinical data show that eplerenone and/or metabolites are present in rat breast milk and

that rat pups exposed by this route developed normally. 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 Undesirable Effects

Hypertension

The following adverse events are those with suspected relationship to treatment and are from the monotherapy arms of four placebo-controlled trials in subjects with hypertension who received eplerenone 25 mg to 400 mg. Events with incidence greater than 1% and greater than placebo are provided below.
Note: Adverse events that are too general to be informative or are very common in the treated population are excluded.

System Organ Class	**Common** **≥1/100 to <1/10**
Infections and Infestations	influenza-like illness
Metabolism and Nutrition Disorders	hyperkalemia, hypertriglyceridaemia, hypercholesterolaemia
Nervous System Disorders	dizziness
Respiratory, Thoracic and Mediastinal Disorders	cough
Gastrointestinal Disorders	abdominal pain, diarrhoea
Hepatobiliary Disorders	gamma glutamyl transferase increased, alanine aminotransferase increased
Renal and Urinary Disorders	albuminuria
General Disorders and Administration Site Conditions	fatigue

Gynecomastia and abnormal vaginal bleeding were reported with eplerenone but not with placebo. The rates of these sex hormone-related adverse events are shown in Table 2. The rates increased slightly with increasing duration of therapy. In females, abnormal vaginal bleeding was also reported in 0.8% of patients on antihypertensive medications (other than spironolactone) in active control arms of the studies with eplerenone.

Table 2. Rates of Sex Hormone-Related Adverse Events with INSPRA in Hypertension Clinical Studies

	Rates in Males			**Rates in Females**
	Gynecomastia	**Mastodynia**	**Either**	**Abnormal Vaginal Bleeding**
All controlled studies	0.5%	0.8%	1.0%	0.6%
Controlled studies lasting ≥6 months	0.7%	1.3%	1.6%	0.8%
Open-label, long-term study	1.0%	0.3%	1.0%	2.1%

Heart Failure Post-MI and NYHA Class II (Chronic) Heart Failure

In two studies (EPHESUS and EMPHASIS-HF), the overall incidence of adverse events and the discontinuation rate due to adverse events reported with eplerenone was similar to placebo.

The most frequent adverse event reported in the EPHESUS and EMPHASIS-HF studies was hyperkalemia with an incidence rate of 3.4% and 8.7% for eplerenone, respectively.

Adverse events reported below are those with suspected relationship to treatment. Adverse events are listed by body system and absolute frequency.

Adverse Reactions Table

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Frequency Not Known (cannot be estimated from available data)
Infections and Infestations	infection	pharyngitis, pyelonephritis	
Blood and Lymphatic System Disorders		eosinophilia	
Endocrine Disorders		hypothyroidism	
Metabolism and Nutrition Disorders	hyperkalemia, dehydration	hypertriglyceridemia, hypercholesterolemia, hyponatraemia	
Psychiatric Disorders		insomnia	
Nervous System Disorders	syncope, dizziness	headache, hypoesthesia	
Cardiac Disorders	myocardial infarction	left ventricular failure, atrial fibrillation, tachycardia	
Vascular Disorders	hypotension	orthostatic hypotension, arterial thrombosis limb	
Respiratory, Thoracic and Mediastinal Disorders	cough		
Gastrointestinal Disorders	diarrhea, nausea, constipation	flatulence, vomiting	
Hepatobiliary Disorders		cholecystitis	
Skin and Subcutaneous Tissue Disorders	pruritus	hyperhidrosis	angioedema,* rash*
Musculoskeletal, Connective Tissue and Bone Disorders	muscle spasms, musculoskeletal pain	back pain	
Renal and Urinary Disorders	renal impairment		
Reproductive System and Breast Disorders		gynecomastia	
General Disorders and Administration Site Conditions		asthenia, malaise	
Investigations	blood urea increased	blood creatinine increased, epidermal	

Adverse Reactions Table

System Organ Class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Frequency Not Known (cannot be estimated from available data)
		growth factor receptor decreased, blood glucose increased	

* ADR identified post-marketing

In EPHESUS, there were numerically more cases of stroke in the very elderly group (≥75 years old). There was however no statistical significant difference between the occurrence of stroke in the eplerenone (30) vs. placebo (22) groups. In EMPHASIS-HF, the number of cases of stroke in the very elderly (≥75 years old) was 9 in the eplerenone group and 8 in the placebo group.

4.9 Overdose

No cases of adverse events associated with overdose of eplerenone in humans have been reported.

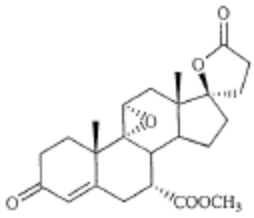
The most likely manifestation of human overdose would be hypotension and/or hyperkalemia, consequently patients should be treated symptomatically and supportive measures, instituted, as required.

Eplerenone cannot be removed by hemodialysis. Eplerenone has been shown to bind extensively to charcoal.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Eplerenone is chemically described as Pregn-4-ene-7,21-dicarboxylic acid, 9,11-epoxy-17-hydroxy-3-oxo-, γ-lactone, methyl ester, (7α,11α,17α)-. Its empirical formula is $C_{24}H_{30}O_6$ and it has a molecular weight of 414.50. The structural formula of eplerenone is represented below:



Eplerenone

Mechanism of Action of Eplerenone

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.

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 circulating aldosterone levels do not overcome the effects of eplerenone.

Hypertension
Eplerenone was studied in 3091 hypertensive patients, comprising 46% women, 14% blacks and 22% ≥65 years. Patients were excluded if they had elevated baseline serum potassium >5.0 mmol/L or creatinine >133 μmol/L for men and >115 μmol/L for women). Two fixed-dose, placebo-controlled 8- to 12-week monotherapy studies in hypertensive patients randomized 611 subjects to eplerenone (doses ranging from 25 mg to 400 mg daily as either a single daily dose or two daily doses) and 140 subjects to placebo. Patients treated with 50 mg to 200 mg daily experienced significant decreases in sitting blood pressure at trough with differences from placebo of 6-13 mmHg (systolic) and 3-7 mmHg (diastolic), effects confirmed with 24-hour ambulatory measurements.

Blood pressure lowering was apparent by 2 weeks and the maximal effect by 4 weeks of treatment. In 6 studies, after 8 to 24 weeks of therapy the discontinuation of eplerenone, placebo or active control resulted in similar adverse event rates in the week following withdrawal. In eplerenone-treated patients blood pressure rose in patients not taking other antihypertensives, suggesting that eplerenone's effect was maintained through 8 to 24 weeks. Overall, eplerenone's effects are unaffected by age, gender or race with the exception of patients with low renin hypertension where a single study showed smaller blood pressure reductions with eplerenone in black than white patients during the initial titration period.

Eplerenone has been studied concomitantly with treatment with ACE inhibitors, angiotensin II receptor antagonists, calcium channel blockers, beta blockers, and hydrochlorothiazide. When administered concomitantly with one of these drugs eplerenone usually produced its expected antihypertensive effects.

Pediatric population:
In a 10-week study of pediatric patients with hypertension (age range 4 to 16 years, n = 304), eplerenone, at doses (from 25 mg up to 100 mg per day) that produced exposure similar to that in adults, did not lower blood pressure effectively. In this study and in a 1-year pediatric safety study in 149 subjects (age range 5 to 17 years), the safety profile was similar to that of adults. Eplerenone has not been studied in hypertensive patients less than 4 years old and the study in older pediatric patients showed a lack of efficacy (see section **4.2 Posology and Method of Administration**).

Heart Failure Post-MI
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.

Eplerenone was studied in the EPHESUS, a double-blind, placebo-controlled study in 6632 subjects with acute MI, left ventricular dysfunction (as measured by LVEF ≤40%), and clinical signs of heart failure. Within 3 to 14 days (median 7 days) after an acute MI, 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. During the study, patients received standard care including acetylsalicylic acid (92%), ACE inhibitors (90%), beta-blockers (83%), nitrates (72%), loop diuretics (66%), or HMG CoA reductase inhibitors (60%).

In EPHESUS, the co-primary endpoints were all-cause mortality and the combined endpoint of cardiovascular (CV) death or CV hospitalization; 14.4% of subjects assigned to eplerenone and 16.7% of subjects assigned to placebo died (all causes), while 26.7% of subjects assigned to eplerenone and 30.0% assigned to placebo met the combined endpoint of CV death or hospitalization. Thus, in EPHESUS, eplerenone reduced the risk of death from any cause by 15% (RR 0.85; 95% CI, 0.75-0.96; p = 0.008) compared to placebo, primarily by reducing CV mortality.

The combined risk of CV death or CV hospitalization was reduced by 13% with eplerenone (RR 0.87; 95% CI, 0.79-0.95; p=0.002). The absolute risk reductions for the endpoints all-cause mortality and combined CV mortality/hospitalization were 2.3% and 3.3%, respectively. Clinical efficacy was primarily demonstrated when eplerenone therapy was initiated in patients aged <75 years old. The benefits of therapy in those patients over the age of 75 are unclear. NYHA functional classification improved or remained stable for a statistically significant greater proportion of patients receiving eplerenone compared to placebo. The incidence of hyperkalemia was 3.4% in the eplerenone group vs. 2.0% in the placebo group (p <0.001). The incidence of hypokalemia was 0.5% in the eplerenone group vs. 1.5% in the placebo group (p <0.001).

NYHA Class II (Chronic) Heart Failure

In the EMPHASIS-HF 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 LVEF ≤30%, or LVEF ≤35% in addition to QRS duration of >130 msec, and were either hospitalized for 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). 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 glomerular filtration rate (GFR) was 30-49 mL/min/1.73 m^2, eplerenone was started at 25 mg on alternate days, and increased to 25 mg once daily.

In total, 2737 subjects were randomized (double-blind) to treatment with eplerenone or placebo including baseline therapy of diuretics (85%), ACE inhibitors (78%), angiotensin II receptor blockers (19%), beta blockers (87%), anti-thrombotic drugs (88%), lipid-lowering agents (63%), and digitalis glycosides (27%). The mean LVEF was ~26% and the mean QRS duration was ~122 msec. Most of the subjects (83.4%) were previously hospitalized for CV reasons within 6 months of randomization, with around 50% of them due to heart failure. Around 20% of the subjects had implantable defibrillators or cardiac resynchronization therapy.

The primary endpoint, death from cardiovascular causes or hospitalization for heart failure occurred in 249 (18.3%) subjects in the eplerenone group and 356 (25.9%) subjects in the placebo group (RR 0.63, 95% CI, 0.54-0.74; p <0.001). The effect of eplerenone on the primary endpoint outcomes was consistent across all pre-specified subgroups.

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

During the study, hyperkalemia (serum potassium level >5.5 mmol/L) was reported in 158 (11.8%) patients in the eplerenone group and 96 (7.2%) subjects in the placebo group (p <0.001). Hypokalemia, defined as serum potassium level <4.0 mmol/L, was statistically lower with eplerenone when compared to placebo (38.9% for eplerenone compared to 48.4% for placebo, p <0.0001).

In 330 eplerenone and 327 placebo subjects (≥75 years of age (subgroup analysis), the statistical significance of the composite primary endpoint rates (HR 0.66, p = 0.005) was driven by significant reduction in hospitalization for heart failure (HR 0.55, p = 0.0007) as there was no statistically significant reduction in cardiovascular mortality (HR 0.98, p = 0.92). The analysis also showed significant reductions (p <0.003) in both CV hospitalization and all cause hospitalization, while it did not show a difference for all-cause mortality, fatal/non-fatal MI or fatal/non-fatal stroke in these elderly patients.

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 subjects. In subjects aged below 75 years, 28.3% treated with eplerenone recorded (maximum drop, at any time during study) systolic BP reductions from baseline greater than 20 mmHg, while subjects 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.

Electrocardiography
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

Absorption and Distribution
The absolute bioavailability of eplerenone is 69% following administration of a 100 mg oral tablet. Maximum plasma concentrations are reached after approximately 1.5 to 2 hours. Both peak plasma levels (C_{max}) and area under the curve (AUC) are dose proportional for doses of 10 mg to 100 mg and less than proportional at doses above 100 mg. Steady state is reached within 2 days. Absorption is not affected by food.

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 is estimated to be 42-90 L. Eplerenone does not preferentially bind to red blood cells.

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

Less than 5% of an eplerenone dose is recovered as unchanged drug in the urine and feces. Following a single oral dose of radiolabeled drug, approximately 32% of the dose was excreted in the feces 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 Posology and Method of Administration**).

Renal Insufficiency: The pharmacokinetics of eplerenone were evaluated in patients with varying degrees of renal insufficiency and in patients undergoing hemodialysis. 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 hemodialysis. No correlation was observed between plasma clearance of eplerenone and creatinine clearance. Eplerenone is not removed by hemodialysis (see section **4.9 Overdose**).

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 Posology and Method of Administration**). Since the use of eplerenone has not been investigated in patients with severe hepatic impairment, eplerenone is contraindicated in this patient group (see section **4.3 Contraindications**).

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
Preclinical studies of safety pharmacology, genotoxicity, carcinogenic potential and reproductive toxicity revealed no special hazard for humans.

In repeated dose toxicity studies, prostate atrophy was observed in rats and dogs at exposure levels several-fold above clinical exposure levels. The prostatic changes were not associated with adverse functional consequences. The clinical relevance of these findings is unknown.

Studies in rats and rabbits showed no teratogenic effects, although decreased body weight in maternal rabbits and increased rabbit fetal resorptions and post-implantation loss were observed at the highest administered dosage.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core:
Lactose monohydrate, Microcrystalline cellulose (E460i), Croscarmellose sodium (E466), Hypromellose (E464), Sodium laurilsulfate, Talc (E553b), Magnesium stearate (E470b).

Tablet coating:
Hypromellose (E464), Titanium dioxide (E171), Macrogol 400, Polysorbate 80 (E433), Iron oxide yellow (E172), Iron oxide red (E172).

6.2 Incompatibilities

None.

6.3 Shelf-life

Refer to outer carton for expiration date.

6.4 Special Precautions for Storage

Store below 30°C.

6.5 Nature and Contents of Container

Cardboard cartons of 30 and 50 tablets containing Foil/PVC blister strips each of 10 tablets.

Not all pack sizes may be marketed.

6.6 Special Precautions for Disposal of a Used Medicinal Product or Waste Materials Derived from such Medicinal Product and Other Handling of the Product

No special requirements.

7. PRODUCT OWNER

Viatris Inc
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