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 tablet.

25 mg tablet: yellow tablet with stylized “VLE” on one side of tablet, “NSR” over “25” on the other side of tablet.

50 mg tablet: yellow tablet with stylized “VLE” on one side of tablet, “NSR” over “50” on the other side of tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Heart Failure - Post Myocardial Infarction (MI)

Eplerenone is indicated, in addition to standard therapy, to reduce the risk of cardiovascular (CV) mortality and morbidity in stable patients with left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤40%) and clinical evidence of heart failure after recent myocardial infarction (MI).

4.2 Posology and Method of Administration

Posology

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 post-MI heart failure patients:
The recommended maintenance dose of eplerenone is 50 mg once daily (OD). Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks, taking into account the serum potassium level (see Table 1). Eplerenone therapy should usually be started within 3-14 days after an acute MI.

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 in Heart Failure - Post-MI

Serum potassium (mmol/L or mEq/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).

Following withholding eplerenone due to serum potassium ≥6.0 mmol/L (or ≥6.0 mEq/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 (or 5.0 mEq/L).

General Considerations

Potassium: 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 periodically thereafter.

Food: Eplerenone may be administered with or without food.

Concomitant CYP3A4 Medications: Patients receiving mild to moderate CYP3A4 inhibitors, such as erythromycin, saquinavir, verapamil, and fluconazole should receive the dose of 25 mg once daily (see section **4.5 Interaction with Other Medicinal Products and Other Forms of Interaction**).

Special Populations and Special Considerations for Dosing

Use in children
Safety and efficacy of eplerenone has not been studied in pediatric patients with heart failure.

Elderly

No initial dose adjustment is required in the elderly. Due to an age-related decline in renal function, the risk of hyperkalaemia is increased in elderly patients. This risk may be further increased when co-morbidity associated with increased systemic exposure is also present, in particular mild-to-moderate hepatic impairment. Periodic monitoring of serum potassium is recommended (see section **4.4 Special Warnings and Precautions for Use**).

Use in renal impairment
No initial dose adjustment is required in patients with mild renal impairment. Periodic monitoring of serum potassium with dose adjustment according to Table 1 is recommended (see section **4.4 Special Warnings and Precautions for Use**).

Patients with moderate renal impairment (CrCl 30-60 mL/min) 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**).

In patients with post-MI heart failure, there is no experience in patients with CrCl < 50 mL/min.

Use in patients with severe renal impairment (CrCl < 30 mL/min) is contraindicated (see section **4.3 Contraindications**). Eplerenone is not dialysable.

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**).

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 (Eplerenone Post-acute Myocardial Infarction Heart failure Efficacy and Survival Study [EPHESUS]).
- 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**).

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).

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.

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**).

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

Pharmacodynamic interactions

Potassium-sparing diuretics and potassium supplements
Due to increased risk of hyperkalaemia, eplerenone should not be administered to patients receiving other potassium-sparing diuretics and potassium supplements (see section **4.3 Contraindications**). Potassium-sparing diuretics may also potentiate the effect of antihypertensive agents and other diuretics.

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. The triple combination of an ACE inhibitor and an ARB with eplerenone should not be used (see sections **4.3 Contraindications** and **4.4 Special Warnings and Precautions for Use**).

Lithium
Drug interaction studies of eplerenone have not been conducted with lithium. However, lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors (see section **4.4 Special Warnings and Precautions for Use**). Co-administration of eplerenone and lithium should be avoided. If this combination appears necessary, lithium plasma concentrations should be monitored (see section **4.4 Special Warnings and Precautions for Use**).

Cyclosporin, tacrolimus
Cyclosporin and tacrolimus may lead to impaired renal function and increase the risk of hyperkalaemia. The concomitant use of eplerenone and cyclosporin or tacrolimus should be avoided. If needed, close monitoring of serum potassium and renal function are recommended when cyclosporin and tacrolimus are to be administered during treatment with eplerenone (see section **4.4 Special Warnings and Precautions for Use**).

Non-steroidal anti-inflammatory drugs (NSAIDs)
Acute renal failure may occur in at risk patients (elderly, dehydrated subjects, using diuretics, with impaired renal function) due to decreased glomerular filtration (inhibition of vasodilatory prostaglandins due to non-steroidal anti-inflammatory drugs). These effects are generally reversible. Furthermore, there may be a reduction of the antihypertensive effect. Hydrate the patient and monitor renal function at the beginning of treatment and regularly during the combination (see sections **4.2 Posology and Method of Administration** and **4.4 Special Warnings and Precautions for Use**).

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 (e.g. prazosin, alfuzosin)
When alpha-1-blockers 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, baclofen
Co-administration of these drugs with eplerenone may potentially increase antihypertensive effects and risk of postural hypotension.

Glucocorticoids, tetracosactide
Co-administration of these drugs with eplerenone may potentially decrease antihypertensive effects (sodium and fluid retention).

Pharmacokinetic interactions

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.

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 pharmacokinetic interactions have been observed with warfarin. Caution is warranted when warfarin is dosed near the upper limit of therapeutic range.

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

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

- Mild to moderate CYP3A4 inhibitors: Co-administration with erythromycin, saquinavir, amiodarone, diltiazem, 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 sections **4.2 Posology and Method of Administration**).

CYP3A4 inducers
Co-administration of St. John's wort (a strong CYP3A4 inducer) with eplerenone caused a 30% decrease in eplerenone AUC. A more pronounced decrease in eplerenone AUC may occur with stronger CYP3A4 inducers, such as rifampicin. Due to the risk of decreased eplerenone efficacy, the concomitant use of strong CYP3A4 inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort) with eplerenone is not recommended (see section **4.4 Special Warnings and Precautions for Use**).

Antacids
Based on the results of a pharmacokinetic clinical study, no significant interaction is expected when antacids are co-administered with eplerenone.

4.6 Fertility, Pregnancy and Lactation

Fertility/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.

Lactation: It is unknown if eplerenone is excreted in human breast milk after oral administration. However, preclinical 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

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 may occur during treatment.

4.8 Undesirable Effects

Heart Failure Post MI

In the (EPHESUS) study, 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 study was hyperkalemia with an incidence rate of 3.4% 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 ≥1/1000 to <1/100	Frequency Not Known (cannot be estimated from available data)
Infections and Infestations	infection	pharyngitis	
Blood and Lymphatic System		eosinophilia	

Disorders			
Endocrine Disorders		hypothyroidism	
Metabolism and Nutrition Disorders	hyperkalemia, dehydration	hypertriglyceridaemia, hypercholesterolaemia, hyponatraemia	
Psychiatric Disorders		insomnia	
Nervous System Disorders	syncope, dizziness	headache, hypoaesthesia	
Cardiac Disorders	myocardial infarction	left ventricular failure, atrial fibrillation	
Vascular Disorders	hypotension	orthostatic hypotension	
Respiratory, Thoracic and Mediastinal Disorders	cough		
Gastrointestinal Disorders	diarrhoea, 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		
General Disorders and Administration Site Conditions		asthenia, malaise	
Investigations	blood urea increased	blood creatinine increased, epidermal growth factor receptor decreased, blood glucose increased	

*ADR identified post-marketing.

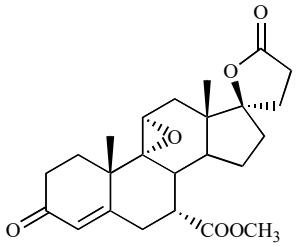
4.9 Overdose

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.

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 EPHESUS, a double-blind, placebo-controlled study in 6632 subjects with acute MI, left ventricular dysfunction (as measured by LVEF $\leq$ 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 patients assigned to eplerenone and 16.7% of subjects assigned to placebo died (all causes), while 26.7% of patients 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).

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 apparent 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 (E460)
Croscarmellose sodium (E468)
Hypromellose (E464)
Sodium laurilsulfate
Talc (E553b)
Magnesium stearate (E470b)

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

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

36 months

6.4 Special Precautions for Storage

No special precautions for storage.

6.5 Nature and Contents of Container

Cardboard cartons of 30 and 50 tablets containing opaque PVC/aluminum foil blister strips each of 10 tablets.

Some product strengths or pack sizes may not be available in your country.

6.6 Instructions for Use and Handling

No special requirements.

7. MANUFACTURER

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