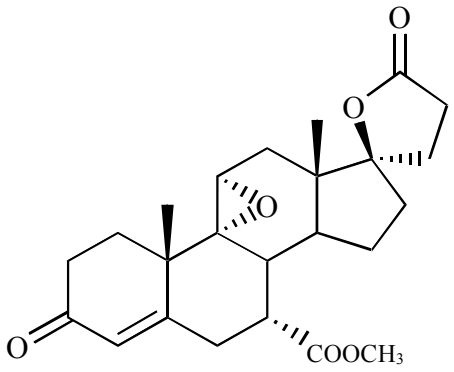
INSPRA™

eplerenone tablets

DESCRIPTION

INSPRA™ contains eplerenone, a blocker of aldosterone binding at the mineralocorticoid receptor.

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

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

INSPRA for oral administration contains 25 mg or 50 mg of eplerenone and the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hypromellose, sodium lauryl sulfate, talc, magnesium stearate, titanium dioxide, polyethylene glycol,

polysorbate 80, and iron oxide yellow and iron oxide red (25 mg tablet) and iron oxide red (50 mg tablet).

CLINICAL PHARMACOLOGY

Mechanism of Action

Eplerenone binds to the mineralocorticoid receptor and blocks the binding of aldosterone, a component of the renin-angiotensin-aldosterone-system (RAAS). Aldosterone synthesis, which occurs primarily in the adrenal gland, is modulated by multiple factors, including angiotensin II and non-RAAS mediators such as adrenocorticotropic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure through induction of sodium reabsorption and possibly other mechanisms.

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.

Eplerenone selectively binds to recombinant human mineralocorticoid receptors relative to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Pharmacokinetics

General: Eplerenone is cleared predominantly by cytochrome P450 (CYP) 3A4 metabolism, with an elimination half-life of 4 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 and Distribution: Mean peak plasma concentrations of eplerenone are reached approximately 1.5 hours following oral administration. The absolute bioavailability of

eplerenone is unknown. 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.

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

Metabolism 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 4 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 **PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Geriatric Use and DOSAGE AND ADMINISTRATION, Hypertension**.)

***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 **WARNINGS, Hyperkalemia in Patients Treated for Hypertension** and **PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure Post-Myocardial Infarction and Congestive Heart Failure Post-Myocardial Infarction and Hypertension**.)

***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 **DOSAGE AND ADMINISTRATION, Hypertension**.)

***Heart Failure*:** The pharmacokinetics of eplerenone 50 mg were evaluated in 8 patients with heart failure (NYHA classification II-IV) and 8 matched (gender, age, weight) healthy controls. Compared with the controls, steady state AUC and C_{max} in patients with stable heart failure were 38% and 30% higher, respectively.

Drug-Drug Interactions

(See **PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions**.)

Drug-drug interaction studies were conducted with a 100 mg dose of eplerenone.

Eplerenone is metabolized primarily by CYP3A4. A potent inhibitor of CYP3A4 (ketoconazole) caused increased exposure of about 5-fold while less potent CYP3A4 inhibitors (erythromycin, saquinavir, verapamil, and fluconazole) gave approximately 2-fold increases. Grapefruit juice caused only a small increase (about 25%) in exposure. (See **PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions** and **DOSAGE AND ADMINISTRATION, Hypertension**.)

Eplerenone is not an inhibitor of CYP1A2, CYP3A4, CYP2C19, CYP2C9, or CYP2D6. Eplerenone did not inhibit the metabolism of chlorzoxazone, diclofenac, methylphenidate, losartan, amiodarone, dexamethasone, mephobarbital, phenytoin, phenacetin, dextromethorphan,

metoprolol, tolbutamide, amlodipine, astemizole, cisapride, 17α-ethinyl estradiol, fluoxetine, lovastatin, methylprednisolone, midazolam, nifedipine, simvastatin, triazolam, verapamil, and warfarin in vitro. Eplerenone is not a substrate or an inhibitor of P-Glycoprotein at clinically relevant doses.

No clinically significant drug-drug pharmacokinetic interactions were observed when eplerenone was administered with digoxin, warfarin, midazolam, cisapride, cyclosporine, simvastatin, glyburide, or oral contraceptives (norethindrone/ethinyl estradiol). St. Johns Wort (a CYP3A4 inducer) caused a small (about 30%) decrease in eplerenone AUC.

No significant changes in eplerenone pharmacokinetics were observed when eplerenone was administered with aluminum and magnesium-containing antacids.

CLINICAL STUDIES

Congestive Heart Failure Post-Myocardial Infarction

The eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS) was a multinational, multicenter, double-blind, randomized, placebo-controlled study in patients clinically stable 3-14 days after an acute myocardial infarction (MI) with left ventricular dysfunction (as measured by left ventricular ejection fraction [LVEF] ≤40%) and either diabetes or clinical evidence of congestive heart failure (CHF) (pulmonary congestion by exam or chest x-ray or S_3). Patients with CHF of valvular or congenital etiology, patients with unstable post-infarct angina, and patients with serum potassium >5.0 mEq/L or serum creatinine >2.5 mg/dL were to be excluded. Patients were allowed to receive standard post-MI drug therapy and to undergo revascularization by angioplasty or coronary artery bypass graft surgery.

Patients randomized to INSPRA were given 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 mEq/L. Dosage was reduced or suspended anytime during the study if serum potassium levels were ≥ 5.5 mEq/L. (See **DOSAGE AND ADMINISTRATION, Congestive Heart Failure Post-Myocardial Infarction**.)

EPHESUS randomized 6,632 patients (9.3% U.S.) at 671 centers in 27 countries. The study population was primarily white (90%, with 1% black, 1% Asian, 6% Hispanic, 2% other) and male (71%). The mean age was 64 years (range, 22-94 years). The majority of patients had pulmonary congestion (75%) by exam or x-ray and were Killip Class II (64%). The mean ejection fraction was 33%. The average time to enrollment was 7 days post-MI. Medical histories prior to the index MI included hypertension (60%), coronary artery disease (62%), dyslipidemia (48%), angina (41%), type 2 diabetes (30%), previous MI (27%), and HF (15%).

The mean dose of INSPRA was 43 mg/day. Patients also received standard care including aspirin (92%), ACE inhibitors (90%), ß-blockers (83%), nitrates (72%), loop diuretics (66%), or HMG-CoA reductase inhibitors (60%).

Patients were followed for an average of 16 months (range, 0-33 months). The ascertainment rate for vital status was 99.7%.

The co-primary endpoints for EPHESUS were (1) the time to death from any cause, and (2) the time to first occurrence of either cardiovascular (CV) mortality [defined as sudden cardiac death or death due to progression of congestive heart failure (CHF), stroke, or other CV causes] or CV hospitalization (defined as hospitalization for progression of CHF, ventricular arrhythmias, acute myocardial infarction, or stroke). For the co-primary endpoint for death from any cause, there were 478 deaths in the INSPRA group (14.4%) and 554 deaths in the placebo group (16.7%). The risk of death with INSPRA was reduced by 15% [hazard ratio equal to 0.85 (95% confidence interval 0.75 to 0.96; p = 0.008 by log rank test)]. Kaplan-Meier estimates of all-cause mortality are shown in Figure 1 and the components of mortality are provided in Table 1.

Figure 1. Kaplan-Meier Estimates of All-Cause Mortality

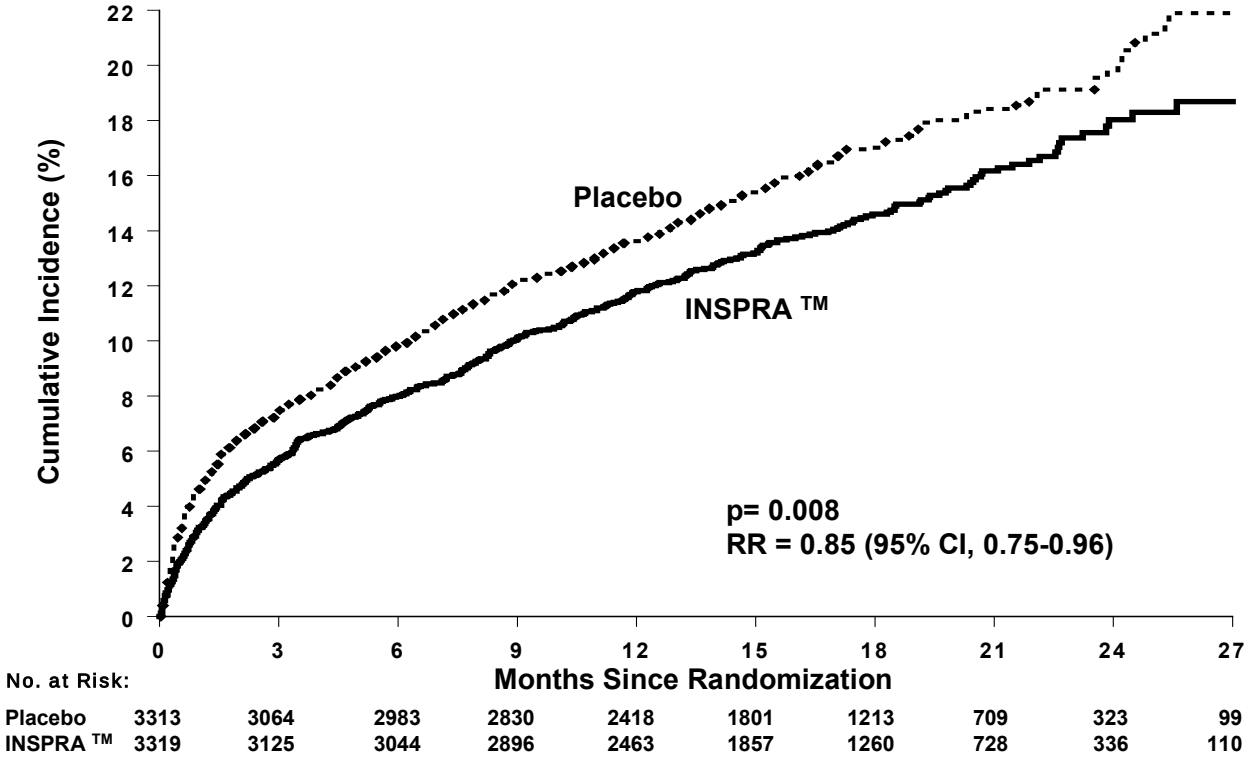


Table 1. Components of All-Cause Mortality in EPHESUS

	INSPRA™ (N=3319) n (%)	Placebo (N=3313) n (%)	Hazard Ratio	p-value
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, acute MI, and CHF.

The time to first event for the co-primary endpoint of CV death or hospitalization as defined above, was longer in the INSPRA group (hazard ratio 0.87, 95% confidence interval 0.79 to 0.95, p = 0.002). An analysis that included the time to first occurrence of CV mortality and all CV hospitalizations (atrial arrhythmia, angina, CV procedures, progression of CHF, MI, stroke, ventricular arrhythmia, or other CV causes) showed a smaller effect with a hazard ratio of 0.92 (95% confidence interval 0.86 to 0.99; p = 0.028). The combined endpoints, including combined all-cause hospitalization and mortality were driven primarily by CV mortality. The combined endpoints in EPHESUS, including all-cause hospitalization and all-cause mortality, are presented in Table 2.

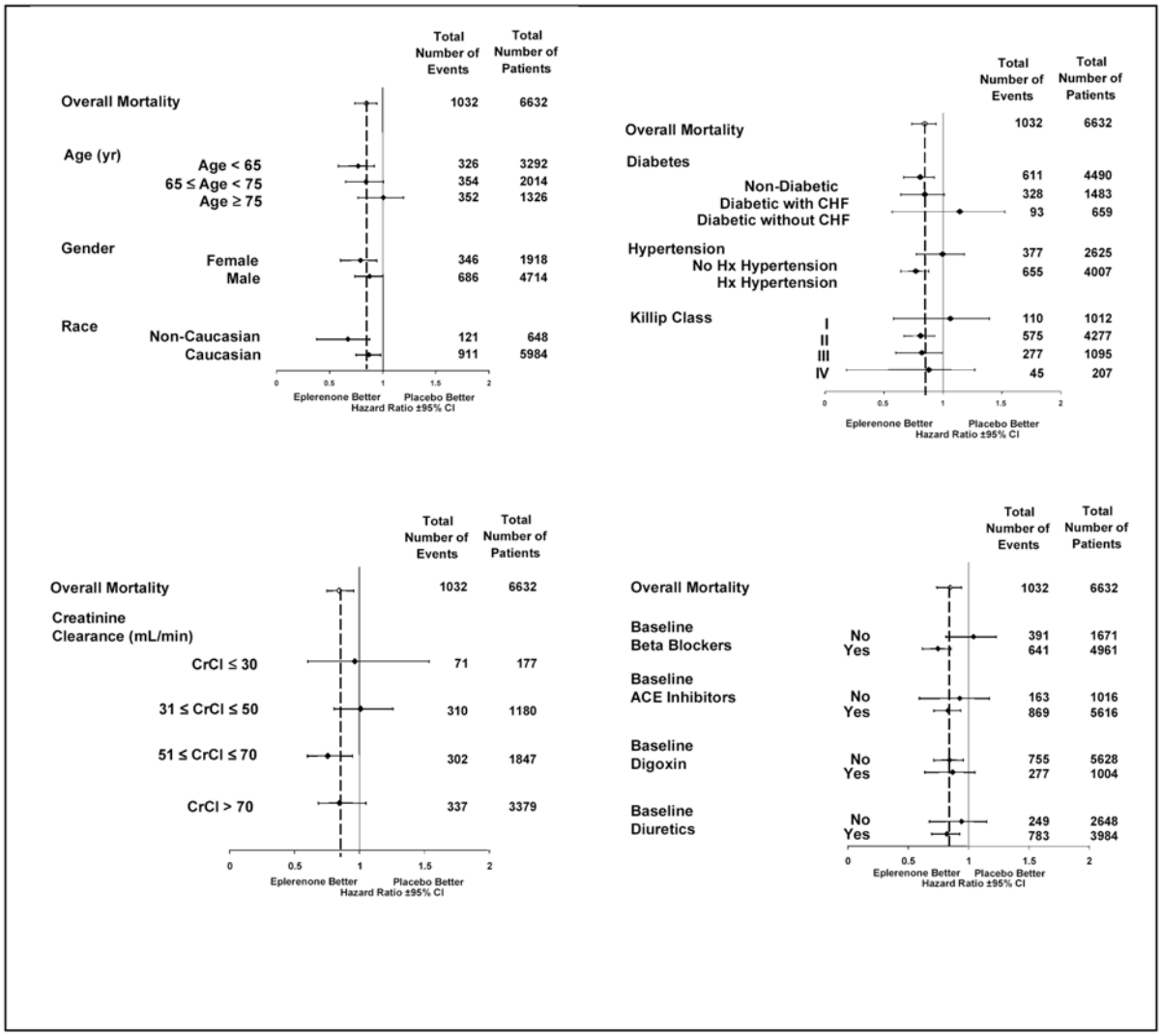
Table 2. Rates of Death or Hospitalization in EPHESUS

Event	INSPRA™ n (%)	Placebo n (%)
CV death or hospitalization for progression of CHF, stroke, MI or ventricular arrhythmia[1]	885 (26.7)	993 (30.0)
Death	407 (12.3)	483 (14.6)
Hospitalization	606 (18.3)	649 (19.6)
CV death or hospitalization for progression of CHF, stroke, MI, ventricular arrhythmia, atrial arrhythmia, angina, CV procedures, or other CV causes (PVD; Hypotension)	1516 (45.7)	1610 (48.6)
Death	407 (12.3)	483 (14.6)
Hospitalization	1281 (38.6)	1307 (39.5)
All-cause death or hospitalization	1734 (52.2)	1833 (55.3)
Death[1]	478 (14.4)	554 (16.7)
Hospitalization	1497 (45.1)	1530 (46.2)

[1] Co-Primary Endpoint.

Mortality hazard ratios varied for some subgroups as shown in Figure 2. Mortality hazard ratios appeared favorable for INSPRA for both genders and for all races or ethnic groups, although the numbers of non-caucasians were low (648, 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 2. 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.

Hypertension

The safety and efficacy of INSPRA have been evaluated alone and in combination with other antihypertensive agents in clinical studies of 3091 hypertensive patients. The studies included 46% women, 14% blacks, and 22% elderly (age ≥65). The studies excluded patients with

elevated baseline serum potassium (>5.0 mEq/L) and elevated baseline serum creatinine (generally >1.5 mg/dL in males and >1.3 mg/dL in females).

Two fixed-dose, placebo-controlled, 8- to 12-week monotherapy studies in patients with baseline diastolic blood pressures of 95 to 114 mm Hg were conducted to assess the antihypertensive effect of INSPRA. In these two studies, 611 patients were randomized to INSPRA and 140 patients to placebo. Patients received INSPRA in doses of 25 to 400 mg daily as either a single daily dose or divided into two daily doses. The mean placebo-subtracted reductions in trough cuff blood pressure achieved by INSPRA in these studies at doses up to 200 mg are shown in Figures 3 and 4.

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Figure 3. INSPRA™ Dose Response - Trough Cuff SBP Placebo-Subtracted Adjusted Mean Change from Baseline in Hypertension Studies

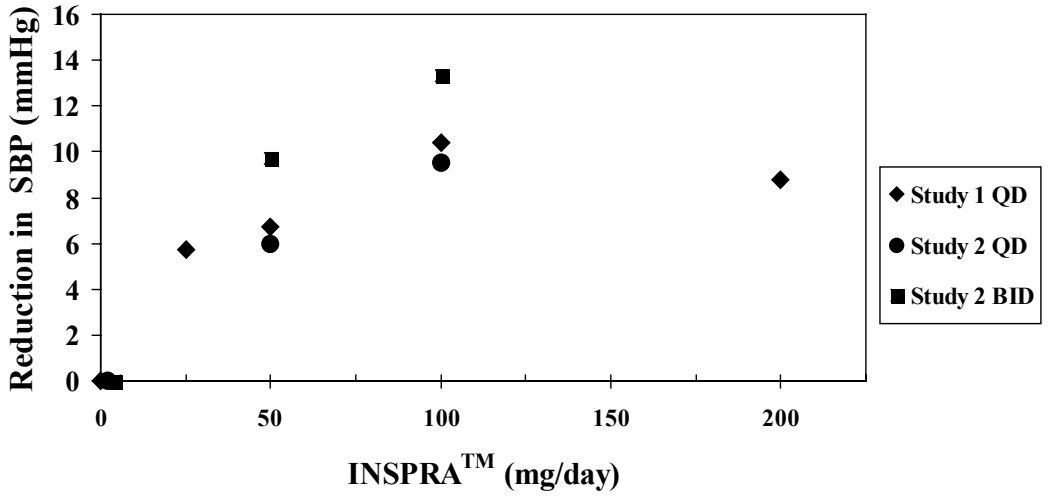

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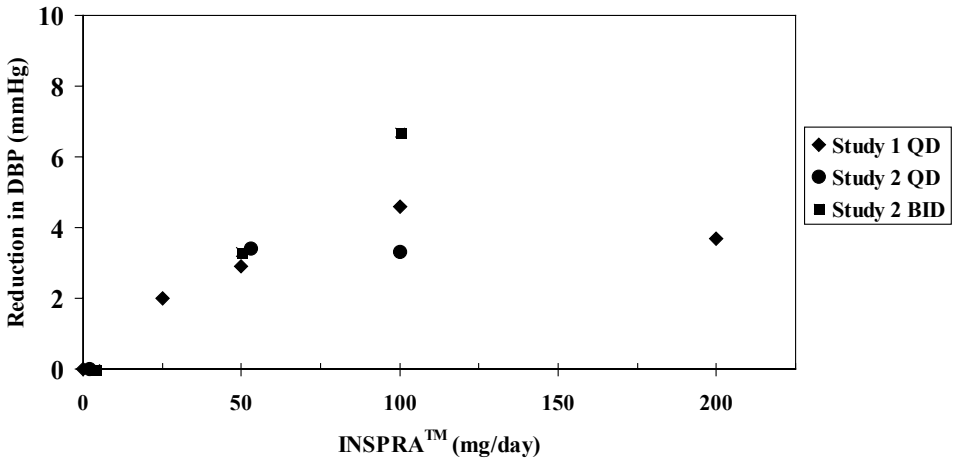
Figure 4. INSPRA™ Dose Response - Trough Cuff DBP Placebo-Subtracted Adjusted Mean Change from Baseline in Hypertension Studies



Patients treated with INSPRA 50 to 200 mg daily experienced significant decreases in sitting systolic and diastolic blood pressure at trough with differences from placebo of 6-13 mm Hg (systolic) and 3-7 mm Hg (diastolic). These effects were confirmed by assessments with 24-hour ambulatory blood pressure monitoring (ABPM). In these studies, assessments of 24-hour ABPM data demonstrated that INSPRA, administered once or twice daily, maintained antihypertensive efficacy over the entire dosing interval. However, at a total daily dose of 100 mg, INSPRA administered as 50 mg twice per day produced greater trough cuff (4/3 mm Hg) and ABPM (2/1 mm Hg) blood pressure reductions than 100 mg given once daily.

Blood pressure lowering was apparent within 2 weeks from the start of therapy with INSPRA, with maximal antihypertensive effects achieved within 4 weeks. Stopping INSPRA following treatment for 8 to 24 weeks in six studies did not lead to adverse event rates in the week following withdrawal of INSPRA greater than following placebo or active control withdrawal. Blood pressures in patients not taking other antihypertensives rose 1 week after withdrawal of INSPRA by about 6/3 mm Hg, suggesting that the antihypertensive effect of INSPRA was maintained through 8 to 24 weeks.

Blood pressure reductions with INSPRA in the two fixed-dose monotherapy studies and other studies using titrated doses, as well as concomitant treatments, were not significantly different when analyzed by age, gender, or race with one exception. In a study in patients with low renin hypertension, blood pressure reductions in blacks were smaller than those in whites during the initial titration period with INSPRA.

INSPRA 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 INSPRA usually produced its expected antihypertensive effects.

There was no significant change in average heart rate among patients treated with INSPRA in the combined clinical studies. No consistent effects of INSPRA on heart rate, QRS duration, or PR

or QT interval were observed in 147 normal subjects evaluated for electrocardiographic changes during pharmacokinetic studies.

INDICATIONS AND USAGE

Congestive Heart Failure Post-Myocardial Infarction

INSPRA is indicated to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction ≤40%) and clinical evidence of congestive heart failure after an acute myocardial infarction. (See **CLINICAL STUDIES, Congestive Heart Failure Post-Myocardial Infarction**.)

Hypertension

INSPRA is indicated for the treatment of hypertension. INSPRA may be used alone or in combination with other antihypertensive agents. (See **CLINICAL STUDIES, Hypertension**.)

CONTRAINDICATIONS

INSPRA is contraindicated in all patients with the following:

- serum potassium >5.5 mEq/L at initiation
- creatinine clearance ≤30 mL/min
- concomitant use with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, and nelfinavir. Inspra should also not be used with other drugs noted in the **CONTRAINDICATIONS**, **WARNINGS** or **PRECAUTIONS** sections of their labeling to be potent CYP3A4 inhibitors. (See **CLINICAL PHARMACOLOGY, Drug-Drug Interactions; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions** and **DOSAGE AND ADMINISTRATION, Hypertension**.)

Hypertension

INSPRA is also contraindicated for the treatment of hypertension in patients with the following:

- type 2 diabetes with microalbuminuria

- serum creatinine >2.0 mg/dL in males or >1.8 mg/dL in females
- creatinine clearance <50 mL/min
- concomitant use of potassium supplements or potassium-sparing diuretics (amiloride, spironolactone, or triamterene)

(See **CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions; WARNINGS, Hyperkalemia in Patients Treated for Hypertension; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions;** and **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Hypertension, Potassium**.)

WARNINGS

Hyperkalemia in Patients Treated for Hypertension

The principal risk of INSPRA is hyperkalemia. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. This risk can be minimized by patient selection, avoidance of certain concomitant treatments, and monitoring. For patient selection and avoidance of certain concomitant medications, see **CONTRAINDICATIONS; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions;** and **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Potassium**. Periodic monitoring is recommended in patients at risk for the development of hyperkalemia (including patients receiving concomitant ACE inhibitors or angiotensin II receptor antagonists) until the effect of INSPRA is established. Dose reduction of INSPRA has been shown to decrease potassium levels. (See **DOSAGE AND ADMINISTRATION, Congestive Heart Failure Post-Myocardial Infarction and Hypertension**.)

PRECAUTIONS

Hyperkalemia in Patients Treated for Congestive Heart Failure Post-Myocardial Infarction

The principal risk of INSPRA is hyperkalemia. Hyperkalemia can cause serious, sometimes fatal, arrhythmias. Patients who develop hyperkalemia (>5.5 mEq/L) may still benefit from INSPRA with proper dose adjustment. Hyperkalemia can be minimized by patient selection, avoidance of certain concomitant treatments, and periodic monitoring until the effect of INSPRA has been established. For patient selection and avoidance of certain concomitant medications, see **CONTRAINDICATIONS; PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions;** and **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium**. Dose reduction of INSPRA has been shown to decrease potassium levels. (See **DOSAGE AND ADMINISTRATION, Congestive Heart Failure Post-Myocardial Infarction**.)

Patients with CHF post MI who have serum creatinine levels >2.0 mg/dL (males) or >1.8 mg/dL (females) or creatinine clearance ≤50mL/min should be treated with caution. The rates of hyperkalemia increased with declining renal function. (See **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium**.)

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 hyperkalemia. (See **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium**.)

Congestive Heart Failure Post-Myocardial Infarction and Hypertension

***Impaired Hepatic Function*:** In 16 subjects with mild-to-moderate hepatic impairment who received 400 mg of eplerenone no elevations of serum potassium above 5.5 mEq/L were

observed. The mean increase in serum potassium was 0.12 mEq/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. (See **DOSAGE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY**, **Special Populations**.)

***Impaired Renal Function*: (**See **CONTRAINDICATIONS; WARNINGS;** and **PRECAUTIONS**.)

***Information for Patients*:** Patients receiving INSPRA should be informed not to use potassium supplements, salt substitutes containing potassium, or contraindicated drugs without consulting the prescribing physician. (See **CONTRAINDICATIONS; WARNINGS;** and **PRECAUTIONS**.)

***Drug Interactions*:**

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 BID, 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 drugs described as strong inhibitors of CYP3A4 in their labeling. (See **CONTRAINDICATIONS**.)

Administration of eplerenone with other CYP3A4 inhibitors (e.g., erythromycin 500 mg BID, verapamil 240 mg QD, saquinavir 1200 mg TID, fluconazole 200 mg QD) 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. (See **CLINICAL PHARMACOLOGY**, **Pharmacokinetics, Drug-Drug Interactions** and **DOSAGE AND ADMINISTRATION, Hypertension**.)

ACE Inhibitors and Angiotensin II Receptor Antagonists (Congestive Heart Failure Post-Myocardial Infarction)- In EPHESUS, 3020 (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 mEq/L were similar regardless of the use of ACEI/ARB.

ACE Inhibitors and Angiotensin II Receptor Antagonists (Hypertension)- In clinical studies of patients with hypertension, the addition of INSPRA 50 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 INSPRA 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%. (See **CONTRAINDICATIONS**.)

Lithium- A drug interaction study of eplerenone with lithium has not been conducted. Lithium toxicity has been reported in patients receiving lithium concomitantly with diuretics and ACE inhibitors. Serum lithium levels should be monitored frequently if INSPRA is administered concomitantly with lithium.

Nonsteroidal 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 INSPRA and NSAIDs are used concomitantly, patients should be observed to determine whether the desired effect on blood pressure is obtained.

Pregnancy:

Pregnancy Category B- There are no adequate and well-controlled studies in pregnant women. INSPRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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, INSPRA should be used during pregnancy only if clearly needed.

***Nursing Mothers*:** The concentration of eplerenone in human breast milk after oral administration is unknown. However preclinical data show that eplerenone and/or metabolites are present in rat breast milk (0.85:1 [milk:plasma] AUC ratio) obtained after a single oral dose. Peak concentrations in plasma and milk were obtained from 0.5 to 1 hour after dosing. 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.

***Pediatric Use*:** The safety and effectiveness of INSPRA has not been established in pediatric patients.

***Geriatric Use*:**

Congestive Heart Failure Post-Myocardial Infarction- Of the total number of patients in EPHESUS, 3340 (50%) were 65 and over, while 1326 (20%) were 75 and over. Patients greater than 75 years did not appear to benefit from the use of INSPRA. (See **CLINICAL STUDIES, Congestive Heart Failure Post-Myocardial Infarction**.) 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 hyperkalemia was increased in patients 65 and older. (See **PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure**.)

Hypertension- Of the total number of subjects in clinical hypertension studies of INSPRA, 1123 (23%) were 65 and over, while 212 (4%) were 75 and over. No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Eplerenone was non-genotoxic in a battery of assays including in vitro bacterial mutagenesis (Ames test in *Salmonella* spp. and *E.*

Coli), in vitro mammalian cell mutagenesis (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 liver.

There was no drug-related tumor response in heterozygous P53 deficient mice when tested for 6 months at dosages up to 1000 mg/kg/day (systemic AUC exposures up to 9 times the exposure in humans receiving the 100-mg/day therapeutic dose). Statistically significant increases in benign thyroid tumors 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. These dosages provided systemic AUC exposures approximately 2 to 12 times higher than the average human therapeutic exposure at 100 mg/day. Repeat dose administration of eplerenone to rats increases the hepatic conjugation and clearance of thyroxin, which results in increased levels of TSH by a compensatory mechanism. Drugs that have produced thyroid tumors by this rodent-specific mechanism have not shown a similar effect in humans.

Male rats treated with eplerenone at 1000 mg/kg/day for 10 weeks (AUC 17 times that at the 100-mg/day human therapeutic dose) had decreased weights of seminal vesicles and epididymides and slightly decreased fertility. Dogs administered eplerenone at dosages of 15 mg/kg/day and higher (AUC 5 times that at the 100-mg/day human therapeutic dose) had dose-related prostate atrophy. The prostate atrophy was reversible after daily treatment for 1 year at 100 mg/kg/day. Dogs with prostate atrophy showed no decline in libido, sexual performance, or semen quality. Testicular weight and histology were not affected by eplerenone in any test animal species at any dosage.

ADVERSE REACTIONS

Congestive Heart Failure Post-Myocardial Infarction

In EPHESUS, safety was evaluated in 3307 patients treated with INSPRA and 3301 placebo-treated patients. The overall incidence of adverse events reported with INSPRA (78.9%) was similar to placebo (79.5%). Adverse events occurred at a similar rate regardless of age, gender,

or race. Patients discontinued treatment due to an adverse event at similar rates in either treatment group (4.4% INSPRA vs. 4.3% placebo).

Adverse events that occurred more frequently in patients treated with INSPRA than placebo were hyperkalemia (3.4% vs 2.0%) and increased creatinine (2.4% vs 1.5%). Discontinuations due to hyperkalemia or abnormal renal function were less than 1.0% in both groups. Hypokalemia occurred less frequently in patients treated with INSPRA (0.6% vs. 1.6%).

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

Table 3. Rates of Sex Hormone Related Adverse Events in EPHESUS

	Rates in Males			Rates in Females
	Gynecomastia	**Mastodynia**	**Either**	**Abnormal Vaginal Bleeding**
INSPRA™	0.4%	0.1%	0.5%	0.4%
Placebo	0.5%	0.1%	0.6%	0.4%

Hypertension

INSPRA has been evaluated for safety in 3091 patients treated for hypertension. A total of 690 patients were treated for over 6 months and 106 patients were treated for over 1 year.

In placebo-controlled studies, the overall rates of adverse events were 47% with INSPRA and 45% with placebo. Adverse events occurred at a similar rate regardless of age, gender, or race. Therapy was discontinued due to an adverse event in 3% of patients treated with INSPRA and 3% of patients given placebo. The most common reasons for discontinuation of INSPRA were headache, dizziness, angina pectoris/myocardial infarction, and increased GGT. The adverse events that were reported at a rate of at least 1% of patients and at a higher rate in patients treated with INSPRA in daily doses of 25 to 400 mg versus placebo are shown in Table 4.

494

Table 4. Rates (%) of Adverse Events Occurring in Placebo-Controlled Hypertension Studies in ≥1% of Patients Treated with INSPRA™ (25 to 400 mg) and at a More Frequent Rate than in Placebo-Treated Patients

	INSPRA™ (n=945)	Placebo (n=372)
Metabolic		
Hypercholesterolemia	1	0
Hypertriglyceridemia	1	0
Digestive		
Diarrhea	2	1
Abdominal pain	1	0
Urinary		
Albuminuria	1	0
Respiratory		
Coughing	2	1
Central/Peripheral Nervous System		
Dizziness	3	2
Body as a Whole		
Fatigue	2	1
Influenza-like symptoms	2	1

495 **Note: Adverse events that are too general to be informative or are very common in the treated population are**
496 **excluded.**
497

498 Gynecomastia and abnormal vaginal bleeding were reported with INSPRA but not with placebo.
499 The rates of these sex hormone related adverse events are shown in Table 5. The rates increased
500 slightly with increasing duration of therapy. In females, abnormal vaginal bleeding was also
501 reported in 0.8% of patients on antihypertensive medications (other than spironolactone) in
502 active control arms of the studies with INSPRA.

Table 5. 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%

Clinical Laboratory Test Findings

***Congestive Heart Failure Post-Myocardial Infarction*:**

Creatinine- Increases of more than 0.5 mg/dL 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 mEq/L or >5.5 mEq/L or ≥6.0 mEq/L) receiving INSPRA compared with placebo are displayed in Table 6.

Table 6. Hypokalemia (<3.5 mEq/L) or Hyperkalemia (>5.5 or ≥6.0 mEq/L) in EPHESUS

Potassium (mEq/L)	**INSPRA™ (N=3251) n (%)**	**Placebo (N=3237) n (%)**
< 3.5	273 (8.4)	424 (13.1)
>5.5	508 (15.6)	363 (11.2)
≥ 6.0	180 (5.5)	126 (3.9)

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

Table 7. Rates of Hyperkalemia (>5.5 mEq/L) in EPHESUS by Baseline Creatinine Clearance*

Baseline Creatinine Clearance	INSPRA™	Placebo
≤30 mL/min	31.5%	22.6%
31-50 mL/min	24.1%	12.7%
51-70 mL/min	16.9%	13.1%
>70 mL/min	10.8%	8.7%

* Estimated using the Cockroft-Gault formula.

Table 8 shows the rates of hyperkalemia in EPHESUS as assessed by two baseline characteristics: presence/absence of proteinuria from baseline urinalysis and presence/absence of diabetes. (See **PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure**.)

Table 8. Rates of Hyperkalemia (>5.5 mEq/L) in EPHESUS by Proteinuria and History of Diabetes*

	INSPRA™	Placebo
Proteinuria, no Diabetes	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.

Hypertension:

Potassium- In placebo-controlled fixed-dose studies, the mean increases in serum potassium were dose related and are shown in Table 9 along with the frequencies of values >5.5 mEq/L.

Table 9. Changes in Serum Potassium in the Placebo-Controlled, Fixed-Dose Hypertension Studies of INSPRA™

		Mean Change mEq/L	% >5.5 mEq/L
Daily Dosage	**n**		
Placebo	194	0	1
25	97	0.08	0
50	245	0.14	0
100	193	0.09	1
200	139	0.19	1
400	104	0.36	8.7

Patients with both type 2 diabetes and microalbuminuria are at increased risk of developing persistent hyperkalemia. In a study in such patients taking INSPRA 200 mg, the frequencies of maximum serum potassium levels >5.5 mEq/L were 33% with INSPRA given alone and 38% when INSPRA was given with enalapril.

Rates of hyperkalemia increased with decreasing renal function. In all studies serum potassium elevations >5.5 mEq/L were observed in 10.4% of patients treated with INSPRA with baseline calculated creatinine clearance <70 mL/min, 5.6% of patients with baseline creatinine clearance of 70 to 100 mL/min, and 2.6% of patients with baseline creatinine clearance of >100 mL/min. (See **WARNINGS, Hyperkalemia in Patients Treated for Hypertension**.)

Sodium- Serum sodium decreased in a dose-related manner. Mean decreases ranged from 0.7 mEq/L at 50 mg daily to 1.7 mEq/L at 400 mg daily. Decreases in sodium (<135 mEq/L) were reported for 2.3% of patients administered INSPRA and 0.6% of placebo-treated patients.

Triglycerides- Serum triglycerides increased in a dose-related manner. Mean increases ranged from 7.1 mg/dL at 50 mg daily to 26.6 mg/dL at 400 mg daily. Increases in triglycerides (above 252 mg/dL) were reported for 15% of patients administered INSPRA and 12% of placebo-treated patients.

Cholesterol- Serum cholesterol increased in a dose-related manner. Mean changes ranged from a decrease of 0.4 mg/dL at 50 mg daily to an increase of 11.6 mg/dL at 400 mg daily. Increases in serum cholesterol values greater than 200 mg/dL were reported for 0.3% of patients administered INSPRA and 0% of placebo-treated patients.

Liver Function Tests- Serum alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) increased in a dose-related manner. Mean increases ranged from 0.8 U/L at 50 mg daily to 4.8 U/L at 400 mg daily for ALT and 3.1 U/L at 50 mg daily to 11.3 U/L at 400 mg daily for GGT. Increases in ALT levels greater than 120 U/L (3 times upper limit of normal) were reported for 15/2259 patients administered INSPRA and 1/351 placebo-treated patients. Increases in ALT levels greater than 200 U/L (5 times upper limit of normal) were reported for 5/2259 of patients administered INSPRA and 1/351 placebo-treated patients. Increases of ALT greater than 120 U/L and bilirubin greater than 1.2 mg/dL were reported 1/2259 patients administered INSPRA and 0/351 placebo-treated patients. Hepatic failure was not reported in patients receiving INSPRA.

BUN/Creatinine- Serum creatinine increased in a dose-related manner. Mean increases ranged from 0.01 mg/dL at 50 mg daily to 0.03 mg/dL at 400 mg daily. Increases in blood urea nitrogen to greater than 30 mg/dL and serum creatinine to greater than 2 mg/dL were reported for 0.5% and 0.2%, respectively, of patients administered INSPRA and 0% of placebo-treated patients.

Uric Acid- Increases in uric acid to greater than 9 mg/dL were reported in 0.3% of patients administered INSPRA and 0% of placebo-treated patients.

OVERDOSAGE

No cases of human overdosage with eplerenone have been reported. Lethality was not observed in mice, rats, or dogs after single oral doses that provided C_{max} exposures at least 25 times higher than in humans receiving eplerenone 100 mg/day. Dogs showed emesis, salivation, and tremors at a C_{max} 41 times the human therapeutic C_{max}, progressing to sedation and convulsions at higher exposures.

The most likely manifestation of human overdosage would be anticipated to be hypotension or hyperkalemia. Eplerenone cannot be removed by hemodialysis. Eplerenone has been shown to bind extensively to charcoal. If symptomatic hypotension should occur, supportive treatment should be instituted. If hyperkalemia develops, standard treatment should be initiated.

DOSAGE AND ADMINISTRATION

Congestive Heart Failure Post-Myocardial Infarction

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 preferably within 4 weeks as tolerated by the patient. INSPRA may be administered with or without food.

Serum potassium should be measured before initiating INSPRA therapy, within the first week and at one month after the start of treatment or dose adjustment. Serum potassium should be assessed periodically thereafter. Factors such as patient characteristics and serum potassium levels may indicate that additional monitoring is appropriate. (See **PRECAUTIONS, Hyperkalemia in Patients Treated for Congestive Heart Failure** and **ADVERSE REACTIONS, Clinical Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction, Potassium**.) In EPHESUS, the majority of hyperkalemia was observed within the first three months after randomization. The dose should be adjusted based on the serum potassium level and the dose adjustment table shown below (Table 10).

Table 10. Dose Adjustment in Congestive Heart Failure

Serum Potassium (mEq/L)	Action	Dose Adjustment
< 5.0	Increase	25mg QOD to 25mg QD 25mg QD to 50mg QD
5.0-5.4	Maintain	No adjustment
5.5-5.9	Decrease	50mg QD to 25mg QD 25mg QD to 25mg QOD 25mg QOD to withhold
≥ 6.0	Withhold	

Following withholding INSPRA due to serum potassium ≥6.0 mEq/L, INSPRA can be restarted at a dose of 25 mg QOD when serum potassium levels have fallen below 5.5 mEq/L.

Hypertension

INSPRA may be used alone or in combination with other antihypertensive agents. The recommended starting dose of INSPRA is 50 mg administered once daily. The full therapeutic effect of INSPRA is apparent within 4 weeks. For patients with an inadequate blood pressure response to 50 mg once daily the dosage of INSPRA should be increased to 50 mg twice daily. Higher dosages of INSPRA are not recommended either because they have no greater effect on blood pressure than 100 mg or because they are associated with an increased risk of hyperkalemia. (See **CLINICAL STUDIES, Hypertension**.)

No adjustment of the starting dose is recommended for the elderly or for patients with mild-to-moderate hepatic impairment. For patients receiving weak CYP3A4 inhibitors, such as erythromycin, saquinavir, verapamil, and fluconazole the starting dose should be reduced to 25 mg once daily. (See **CONTRAINDICATIONS** and **PRECAUTIONS, Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions**.)

HOW SUPPLIED

INSPRA Tablets, 25 mg, are yellow diamond biconvex film-coated tablets. They are debossed with *PHA* on one side and 1710 on the other. They are supplied as follows:

NDC Number	Size
0025-1710-01	Bottle of 30 tablets
0025-1710-02	Bottle of 90 tablets
0025-1710-03	Hospital Unit Dose

INSPRA Tablets, 50 mg, are pink diamond biconvex film-coated tablets. They are debossed with *PHA* on one side and 1720 on the other. They are supplied as follows:

NDC Number	Size
0025-1720-03	Bottle of 30 tablets
0025-1720-01	Bottle of 90 tablets

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

Rx only Revised: Date

U.S. Patent No. 4,559,332

INSPRA Tablets are manufactured for:

G.D. Searle LLC

A subsidiary of Pharmacia Corporation

Chicago, IL 60680, USA.

Date Copy Code

October 7, 2003