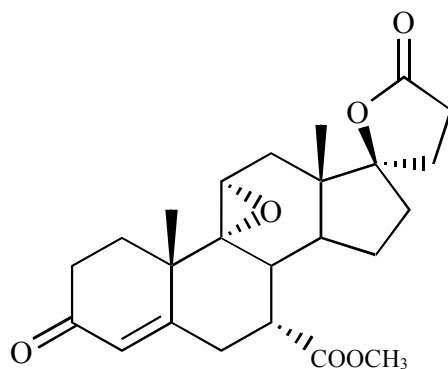

INSPRA™eplerenone tablets

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, (7 α ,11 α ,17 α)-. Its empirical formula is C₂₄H₃₀O₆ 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,

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

33

34

35 **CLINICAL PHARMACOLOGY**

36 **Mechanism of Action**

37 Eplerenone binds to the mineralocorticoid receptor and blocks the binding of aldosterone, a
38 component of the renin-angiotensin-aldosterone-system (RAAS). Aldosterone synthesis, which
39 occurs primarily in the adrenal gland, is modulated by multiple factors, including angiotensin II
40 and non-RAAS mediators such as adrenocorticotrophic hormone (ACTH) and potassium.

41 Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and
42 nonepithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure through
43 induction of sodium reabsorption and possibly other mechanisms.

44

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

49

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

52

53 **Pharmacokinetics**

54 **General:** Eplerenone is cleared predominantly by cytochrome P450 (CYP) 3A4 metabolism,
55 with an elimination half-life of 4 to 6 hours. Steady state is reached within 2 days. Absorption is
56 not affected by food. Inhibitors of CYP3A4 (e.g., ketoconazole, saquinavir) increase blood
57 levels of eplerenone.

58

59 **Absorption and Distribution:** Mean peak plasma concentrations of eplerenone are reached
60 approximately 1.5 hours following oral administration. The absolute bioavailability of

61 eplerenone is unknown. Both peak plasma levels (C_{\max}) and area under the curve (AUC) are
62 dose proportional for doses of 25 to 100 mg and less than proportional at doses above 100 mg.

63
64 The plasma protein binding of eplerenone is about 50% and it is primarily bound to alpha 1-acid
65 glycoproteins. The apparent volume of distribution at steady state ranged from 43 to 90 L.
66 Eplerenone does not preferentially bind to red blood cells.

67
68 **Metabolism and Excretion:** Eplerenone metabolism is primarily mediated via CYP3A4. No
69 active metabolites of eplerenone have been identified in human plasma.

70
71 Less than 5% of an eplerenone dose is recovered as unchanged drug in the urine and feces.
72 Following a single oral dose of radiolabeled drug, approximately 32% of the dose was excreted
73 in the feces and approximately 67% was excreted in the urine. The elimination half-life of
74 eplerenone is approximately 4 to 6 hours. The apparent plasma clearance is approximately 10
75 L/hr.

76 77 **Special Populations**

78 **Age, Gender, and Race:** The pharmacokinetics of eplerenone at a dose of 100 mg once daily
79 have been investigated in the elderly (≥ 65 years), in males and females, and in blacks. The
80 pharmacokinetics of eplerenone did not differ significantly between males and females. At
81 steady state, elderly subjects had increases in C_{\max} (22%) and AUC (45%) compared with
82 younger subjects (18 to 45 years). At steady state, C_{\max} was 19% lower and AUC was 26%
83 lower in blacks. (See **PRECAUTIONS, Congestive Heart Failure Post-Myocardial**
84 **Infarction and Hypertension, Geriatric Use and DOSAGE AND ADMINISTRATION,**
85 **Hypertension.**)

86
87 **Renal Insufficiency:** The pharmacokinetics of eplerenone were evaluated in patients with
88 varying degrees of renal insufficiency and in patients undergoing hemodialysis. Compared with
89 control subjects, steady-state AUC and C_{\max} were increased by 38% and 24%, respectively, in
90 patients with severe renal impairment and were decreased by 26% and 3%, respectively, in
91 patients undergoing hemodialysis. No correlation was observed between plasma clearance of

92 eplerenone and creatinine clearance. Eplerenone is not removed by hemodialysis. (See
93 **WARNINGS, Hyperkalemia in Patients Treated for Hypertension** and **PRECAUTIONS,**
94 **Hyperkalemia in Patients Treated for Congestive Heart Failure Post-Myocardial**
95 **Infarction and Congestive Heart Failure Post-Myocardial Infarction and Hypertension.**)

96
97 **Hepatic Insufficiency:** The pharmacokinetics of eplerenone 400 mg have been investigated in
98 patients with moderate (Child-Pugh Class B) hepatic impairment and compared with normal
99 subjects. Steady-state C_{max} and AUC of eplerenone were increased by 3.6% and 42%,
100 respectively. (See **DOSAGE AND ADMINISTRATION, Hypertension.**)

101
102 **Heart Failure:** The pharmacokinetics of eplerenone 50 mg were evaluated in 8 patients with
103 heart failure (NYHA classification II-IV) and 8 matched (gender, age, weight) healthy controls.
104 Compared with the controls, steady state AUC and C_{max} in patients with stable heart failure were
105 38% and 30% higher, respectively.

106 107 **Drug-Drug Interactions**

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

110
111 Drug-drug interaction studies were conducted with a 100 mg dose of eplerenone.

112
113 Eplerenone is metabolized primarily by CYP3A4. A potent inhibitor of CYP3A4 (ketoconazole)
114 caused increased exposure of about 5-fold while less potent CYP3A4 inhibitors (erythromycin,
115 saquinavir, verapamil, and fluconazole) gave approximately 2-fold increases. Grapefruit juice
116 caused only a small increase (about 25%) in exposure. (See **PRECAUTIONS, Congestive**
117 **Heart Failure Post-Myocardial Infarction and Hypertension, Drug Interactions** and
118 **DOSAGE AND ADMINISTRATION, Hypertension.**)

119
120 Eplerenone is not an inhibitor of CYP1A2, CYP3A4, CYP2C19, CYP2C9, or CYP2D6.
121 Eplerenone did not inhibit the metabolism of chlorzoxazone, diclofenac, methylphenidate,
122 losartan, amiodarone, dexamethasone, mephobarbital, phenytoin, phenacetin, dextromethorphan,

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

127
128 No clinically significant drug-drug pharmacokinetic interactions were observed when eplerenone
129 was administered with digoxin, warfarin, midazolam, cisapride, cyclosporine, simvastatin,
130 glyburide, or oral contraceptives (norethindrone/ethinyl estradiol). St. Johns Wort (a CYP3A4
131 inducer) caused a small (about 30%) decrease in eplerenone AUC.

132
133 No significant changes in eplerenone pharmacokinetics were observed when eplerenone was
134 administered with aluminum and magnesium-containing antacids.

135
136

137 **CLINICAL STUDIES**

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

139 The eplerenone post-acute myocardial infarction heart failure efficacy and survival study
140 (EPHESUS) was a multinational, multicenter, double-blind, randomized, placebo-controlled study in
141 patients clinically stable 3-14 days after an acute myocardial infarction (MI) with left ventricular
142 dysfunction (as measured by left ventricular ejection fraction [LVEF] \leq 40%) and either diabetes or
143 clinical evidence of congestive heart failure (CHF) (pulmonary congestion by exam or chest x-ray or
144 S₃). Patients with CHF of valvular or congenital etiology, patients with unstable post-infarct angina,
145 and patients with serum potassium $>$ 5.0 mEq/L or serum creatinine $>$ 2.5 mg/dL were to be excluded.
146 Patients were allowed to receive standard post-MI drug therapy and to undergo revascularization by
147 angioplasty or coronary artery bypass graft surgery.

148
149 Patients randomized to INSPRA were given an initial dose of 25 mg once daily and titrated to the
150 target dose of 50 mg once daily after 4 weeks if serum potassium was $<$ 5.0 mEq/L. Dosage was
151 reduced or suspended anytime during the study if serum potassium levels were \geq 5.5 mEq/L. (See
152 **DOSAGE AND ADMINISTRATION, Congestive Heart Failure Post-Myocardial Infarction.**)

153
154 EPHESUS randomized 6,632 patients (9.3% U.S.) at 671 centers in 27 countries. The study
155 population was primarily white (90%, with 1% black, 1% Asian, 6% Hispanic, 2% other) and male
156 (71%). The mean age was 64 years (range, 22-94 years). The majority of patients had pulmonary
157 congestion (75%) by exam or x-ray and were Killip Class II (64%). The mean ejection fraction was
158 33%. The average time to enrollment was 7 days post-MI. Medical histories prior to the index MI
159 included hypertension (60%), coronary artery disease (62%), dyslipidemia (48%), angina (41%),
160 type 2 diabetes (30%), previous MI (27%), and HF (15%).

161
162 The mean dose of INSPRA was 43 mg/day. Patients also received standard care including aspirin
163 (92%), ACE inhibitors (90%), β -blockers (83%), nitrates (72%), loop diuretics (66%), or HMG-CoA
164 reductase inhibitors (60%).

165
166 Patients were followed for an average of 16 months (range, 0-33 months). The ascertainment rate
167 for vital status was 99.7%.

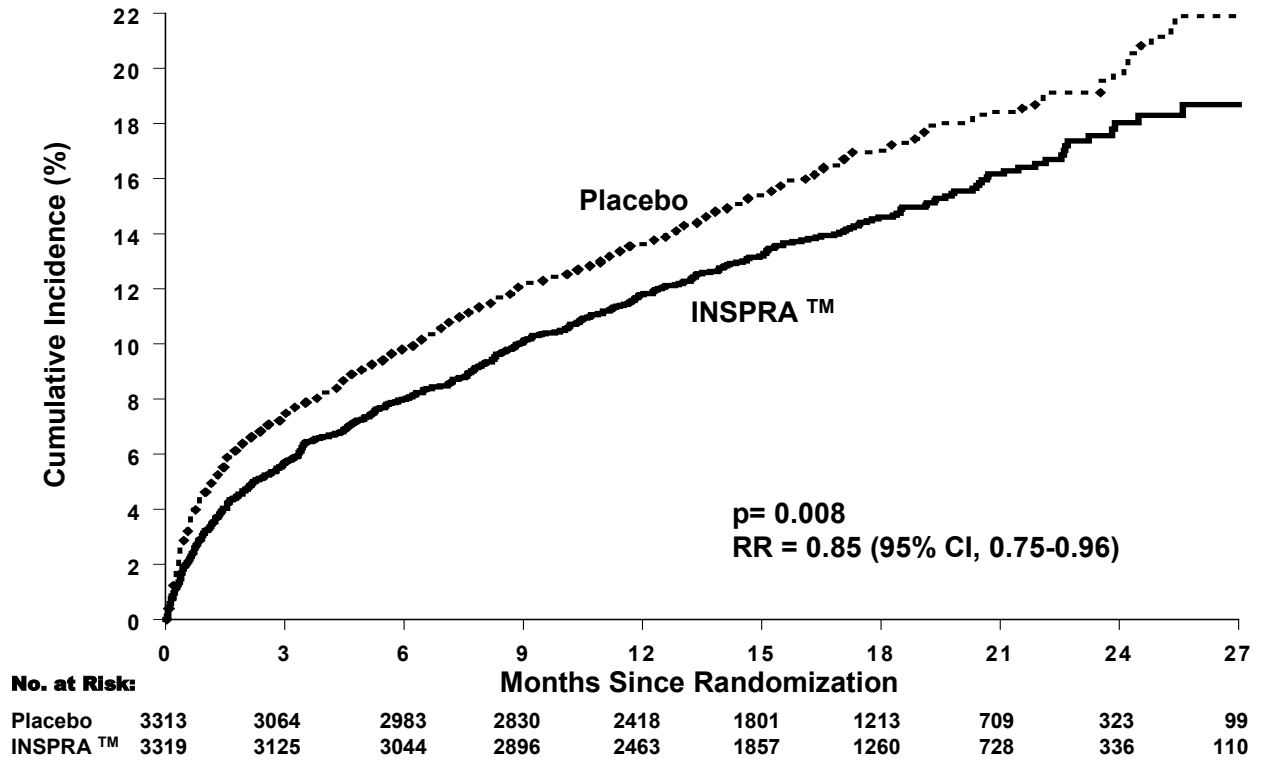
168
169 The co-primary endpoints for EPHESUS were (1) the time to death from any cause, and (2) the
170 time to first occurrence of either cardiovascular (CV) mortality [defined as sudden cardiac death
171 or death due to progression of congestive heart failure (CHF), stroke, or other CV causes] or CV
172 hospitalization (defined as hospitalization for progression of CHF, ventricular arrhythmias, acute
173 myocardial infarction, or stroke). For the co-primary endpoint for death from any cause, there
174 were 478 deaths in the INSPRA group (14.4%) and 554 deaths in the placebo group (16.7%).
175 The risk of death with INSPRA was reduced by 15% [hazard ratio equal to 0.85 (95%
176 confidence interval 0.75 to 0.96; $p = 0.008$ by log rank test)]. Kaplan-Meier estimates of all-
177 cause mortality are shown in Figure 1 and the components of mortality are provided in Table 1.

178

179

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

180



181

182

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)		

183

184 Most CV deaths were attributed to sudden death, acute MI, and CHF.

185

186 The time to first event for the co-primary endpoint of CV death or hospitalization as defined above,
 187 was longer in the INSPRA group (hazard ratio 0.87, 95% confidence interval 0.79 to 0.95, p =
 188 0.002). An analysis that included the time to first occurrence of CV mortality and all CV
 189 hospitalizations (atrial arrhythmia, angina, CV procedures, progression of CHF, MI, stroke,
 190 ventricular arrhythmia, or other CV causes) showed a smaller effect with a hazard ratio of 0.92 (95%
 191 confidence interval 0.86 to 0.99; p = 0.028). The combined endpoints, including combined all-cause
 192 hospitalization and mortality were driven primarily by CV mortality. The combined endpoints in
 193 EPHESUS, including all-cause hospitalization and all-cause mortality, are presented in Table 2.

194

195

Table 2. Rates of Death or Hospitalization in EPHEBUS

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)

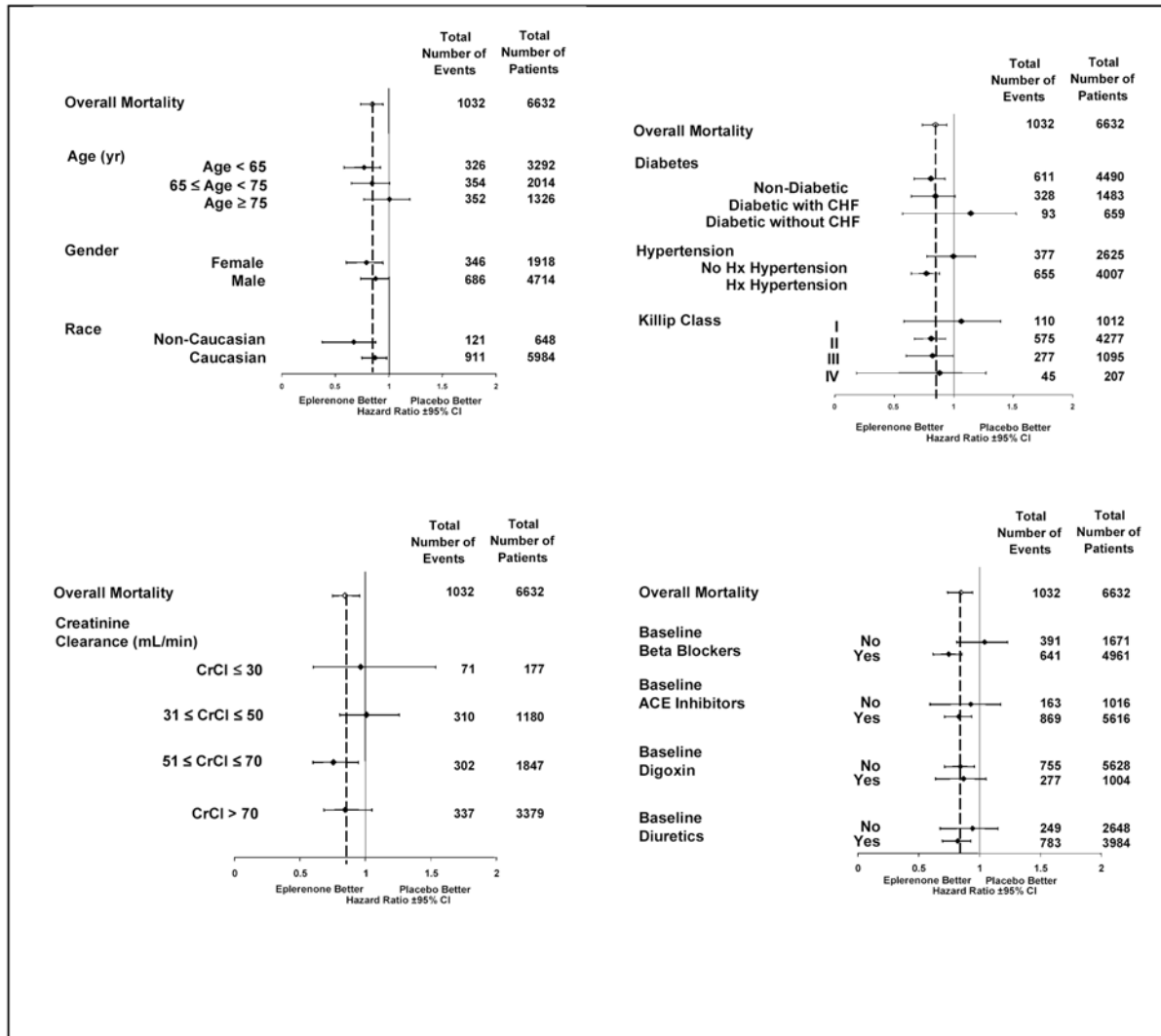
196 ¹ Co-Primary Endpoint.

197

198 Mortality hazard ratios varied for some subgroups as shown in Figure 2. Mortality hazard ratios
199 appeared favorable for INSPRA for both genders and for all races or ethnic groups, although the
200 numbers of non-caucasians were low (648, 10%). Patients with diabetes without clinical
201 evidence of CHF and patients greater than 75 years did not appear to benefit from the use of
202 INSPRA. Such subgroup analyses must be interpreted cautiously.

203

Figure 2. Hazard Ratios of All-Cause Mortality by Subgroups



204
205
206
207
208
209
210

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

Hypertension

212 The safety and efficacy of INSPRA have been evaluated alone and in combination with other
213 antihypertensive agents in clinical studies of 3091 hypertensive patients. The studies included
214 46% women, 14% blacks, and 22% elderly (age ≥65). The studies excluded patients with

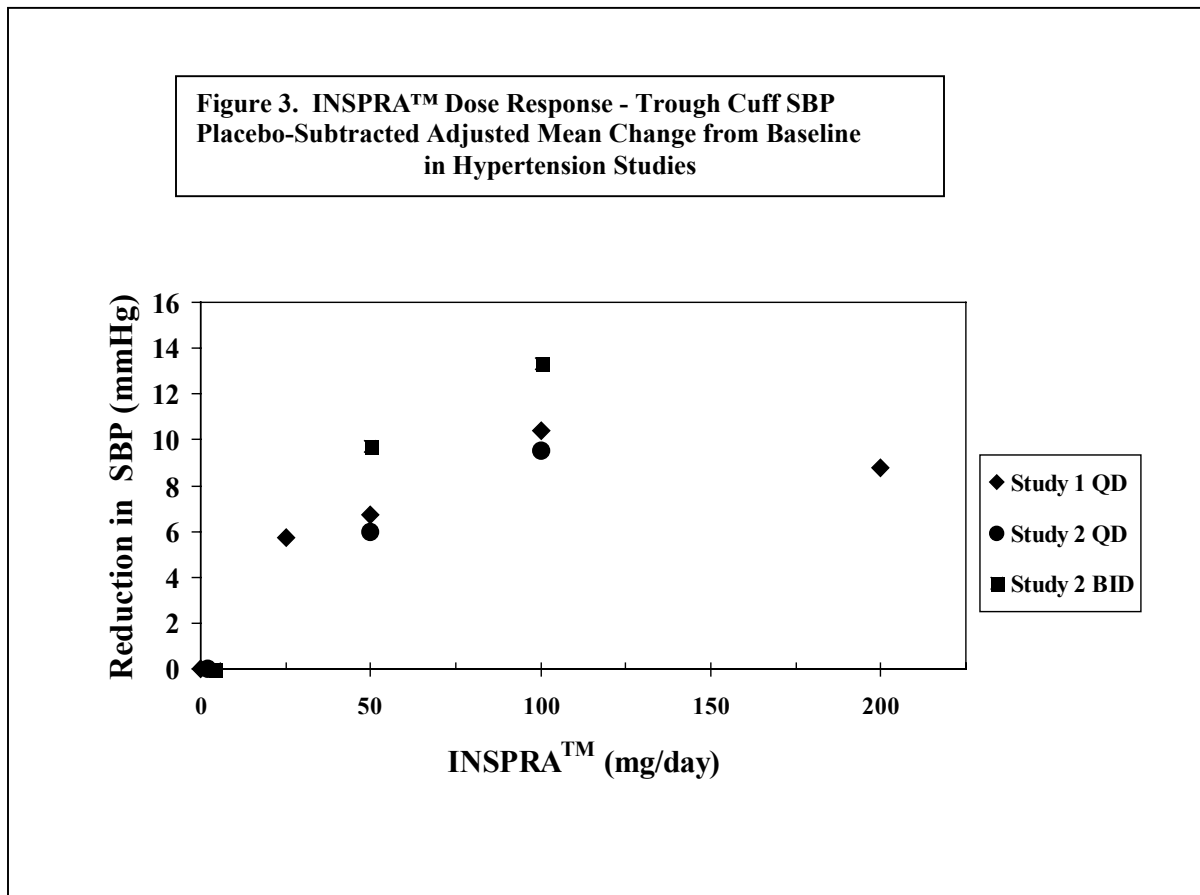
215 elevated baseline serum potassium (>5.0 mEq/L) and elevated baseline serum creatinine
216 (generally >1.5 mg/dL in males and >1.3 mg/dL in females).

217

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

225

226

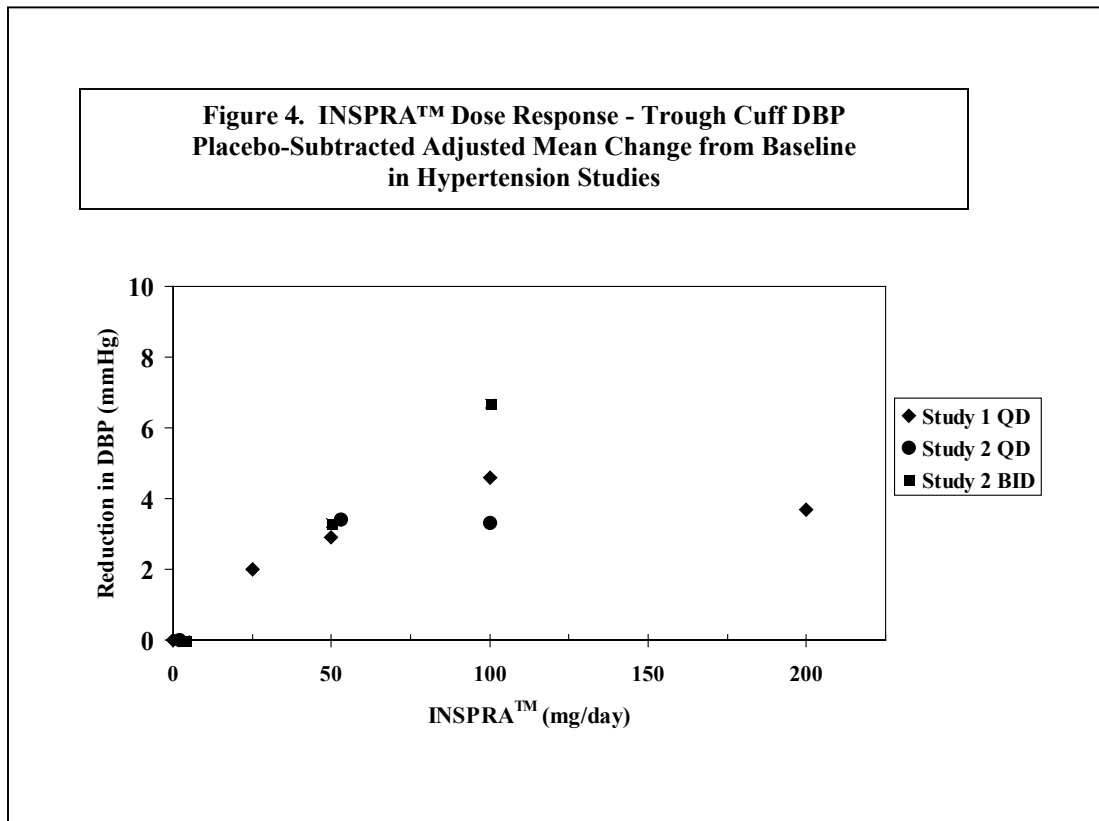


227

228

229

230



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

239

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

247

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

253

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

258

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

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

263

264

265 **INDICATIONS AND USAGE**

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

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

271

272 **Hypertension**

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

275

276 **CONTRAINDICATIONS**

277 INSPRA is contraindicated in all patients with the following:

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

287

288 **Hypertension**

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

- 290 • type 2 diabetes with microalbuminuria

- 291 • serum creatinine >2.0 mg/dL in males or >1.8 mg/dL in females
 - 292 • creatinine clearance <50 mL/min
 - 293 • concomitant use of potassium supplements or potassium-sparing diuretics (amiloride,
 - 294 spironolactone, or triamterene)
- 295 (See **CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions;**
296 **WARNINGS, Hyperkalemia in Patients Treated for Hypertension; PRECAUTIONS,**
297 **Congestive Heart Failure Post-Myocardial Infarction and Hypertension, Drug**
298 **Interactions; and ADVERSE REACTIONS, Clinical Laboratory Test Findings,**
299 **Hypertension, Potassium.**)

300

301

302 **WARNINGS**

303 **Hyperkalemia in Patients Treated for Hypertension**

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

316

317

318 **PRECAUTIONS**319 **Hyperkalemia in Patients Treated for Congestive Heart Failure Post-**
320 **Myocardial Infarction**

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

332
333 Patients with CHF post MI who have serum creatinine levels >2.0 mg/dL (males) or >1.8 mg/dL
334 (females) or creatinine clearance ≤50mL/min should be treated with caution. The rates of
335 hyperkalemia increased with declining renal function. (See **ADVERSE REACTIONS, Clinical**
336 **Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction,**
337 **Potassium.**)

338
339 Diabetic patients with CHF post-MI, including those with proteinuria, should also be treated with
340 caution. The subset of patients in EPHESUS with both diabetes and proteinuria on the baseline
341 urinalysis had increased rates of hyperkalemia. (See **ADVERSE REACTIONS, Clinical**
342 **Laboratory Test Findings, Congestive Heart Failure Post-Myocardial Infarction,**
343 **Potassium.**)

344
345 **Congestive Heart Failure Post-Myocardial Infarction and Hypertension**

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

348 observed. The mean increase in serum potassium was 0.12 mEq/L in patients with hepatic
349 impairment and 0.13 mEq/L in normal controls. The use of INSPRA in patients with severe
350 hepatic impairment has not been evaluated. (See **DOSAGE AND ADMINISTRATION** and
351 **CLINICAL PHARMACOLOGY, Special Populations.**)

352

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

355

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

360

361 ***Drug Interactions:***

362 ***Inhibitors of CYP3A4-*** Eplerenone metabolism is predominantly mediated via CYP3A4. A
363 pharmacokinetic study evaluating the administration of a single dose of INSPRA 100 mg with
364 ketoconazole 200 mg BID, a potent inhibitor of the CYP3A4 pathway, showed a 1.7-fold
365 increase in C_{max} of eplerenone and a 5.4-fold increase in AUC of eplerenone. INSPRA should
366 not be used with drugs described as strong inhibitors of CYP3A4 in their labeling. (See
367 **CONTRAINDICATIONS.**)

368

369 Administration of eplerenone with other CYP3A4 inhibitors (e.g., erythromycin 500 mg BID,
370 verapamil 240 mg QD, saquinavir 1200 mg TID, fluconazole 200 mg QD) resulted in increases
371 in C_{max} of eplerenone ranging from 1.4- to 1.6-fold and AUC from 2.0- to 2.9-fold. (See
372 **CLINICAL PHARMACOLOGY, Pharmacokinetics, Drug-Drug Interactions** and
373 **DOSAGE AND ADMINISTRATION, Hypertension.**)

374

375 ***ACE Inhibitors and Angiotensin II Receptor Antagonists (Congestive Heart Failure Post-***
376 ***Myocardial Infarction)-*** In EPHEBUS, 3020 (91%) patients receiving INSPRA 25 to 50 mg also
377 received ACE inhibitors or angiotensin II receptor antagonists (ACEI/ARB). Rates of patients
378 with maximum potassium levels >5.5 mEq/L were similar regardless of the use of ACEI/ARB.

379

380 **ACE Inhibitors and Angiotensin II Receptor Antagonists (Hypertension)-** In clinical studies of
381 patients with hypertension, the addition of INSPRA 50 to 100 mg to ACE inhibitors and
382 angiotensin II receptor antagonists increased mean serum potassium slightly (about 0.09-0.13
383 mEq/L). In a study in diabetics with microalbuminuria INSPRA 200 mg combined with the
384 ACE inhibitor enalapril 10 mg increased the frequency of hyperkalemia (serum potassium >5.5
385 mEq/L) from 17% on enalapril alone to 38%. (See **CONTRAINDICATIONS.**)

386

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

391

392 **Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)-** A drug interaction study of eplerenone with an
393 NSAID has not been conducted. The administration of other potassium-sparing
394 antihypertensives with NSAIDs has been shown to reduce the antihypertensive effect in some
395 patients and result in severe hyperkalemia in patients with impaired renal function. Therefore,
396 when INSPRA and NSAIDs are used concomitantly, patients should be observed to determine
397 whether the desired effect on blood pressure is obtained.

398

399 ***Pregnancy:***

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

403

404 **Teratogenic Effects-** Embryo-fetal development studies were conducted with doses up to 1000
405 mg/kg/day in rats and 300 mg/kg/day in rabbits (exposures up to 32 and 31 times the human
406 AUC for the 100-mg/day therapeutic dose, respectively). No teratogenic effects were seen in
407 rats or rabbits, although decreased body weight in maternal rabbits and increased rabbit fetal
408 resorptions and post-implantation loss were observed at the highest administered dosage.

409 Because animal reproduction studies are not always predictive of human response, INSPRA
410 should be used during pregnancy only if clearly needed.

411
412 ***Nursing Mothers:*** The concentration of eplerenone in human breast milk after oral
413 administration is unknown. However preclinical data show that eplerenone and/or metabolites
414 are present in rat breast milk (0.85:1 [milk:plasma] AUC ratio) obtained after a single oral dose.
415 Peak concentrations in plasma and milk were obtained from 0.5 to 1 hour after dosing. Rat pups
416 exposed by this route developed normally. Because many drugs are excreted in human milk
417 and because of the unknown potential for adverse effects on the nursing infant, a decision
418 should be made whether to discontinue nursing or discontinue the drug, taking into account the
419 importance of the drug to the mother.

420
421 ***Pediatric Use:*** The safety and effectiveness of INSPRA has not been established in pediatric
422 patients.

423
424 ***Geriatric Use:***
425 **Congestive Heart Failure Post-Myocardial Infarction-** Of the total number of patients in
426 EPHESUS, 3340 (50%) were 65 and over, while 1326 (20%) were 75 and over. Patients greater
427 than 75 years did not appear to benefit from the use of INSPRA. (See **CLINICAL STUDIES,**
428 **Congestive Heart Failure Post-Myocardial Infarction.**) No differences in overall incidence of
429 adverse events were observed between elderly and younger patients. However, due to age-
430 related decreases in creatinine clearance, the incidence of laboratory-documented hyperkalemia
431 was increased in patients 65 and older. (See **PRECAUTIONS, Hyperkalemia in Patients**
432 **Treated for Congestive Heart Failure.**)

433
434 **Hypertension-** Of the total number of subjects in clinical hypertension studies of INSPRA, 1123
435 (23%) were 65 and over, while 212 (4%) were 75 and over. No overall differences in safety or
436 effectiveness were observed between elderly subjects and younger subjects.

437
438 ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Eplerenone was non-genotoxic in a
439 battery of assays including in vitro bacterial mutagenesis (Ames test in *Salmonella* spp. and *E.*

440 *Coli*), in vitro mammalian cell mutagenesis (mouse lymphoma cells), in vitro chromosomal
441 aberration (Chinese hamster ovary cells), in vivo rat bone marrow micronucleus formation, and
442 in vivo/ex vivo unscheduled DNA synthesis in rat liver.

443
444 There was no drug-related tumor response in heterozygous P53 deficient mice when tested for 6
445 months at dosages up to 1000 mg/kg/day (systemic AUC exposures up to 9 times the exposure in
446 humans receiving the 100-mg/day therapeutic dose). Statistically significant increases in benign
447 thyroid tumors were observed after 2 years in both male and female rats when administered
448 eplerenone 250 mg/kg/day (highest dose tested) and in male rats only at 75 mg/kg/day. These
449 dosages provided systemic AUC exposures approximately 2 to 12 times higher than the average
450 human therapeutic exposure at 100 mg/day. Repeat dose administration of eplerenone to rats
451 increases the hepatic conjugation and clearance of thyroxin, which results in increased levels of
452 TSH by a compensatory mechanism. Drugs that have produced thyroid tumors by this rodent-
453 specific mechanism have not shown a similar effect in humans.

454
455 Male rats treated with eplerenone at 1000 mg/kg/day for 10 weeks (AUC 17 times that at the
456 100-mg/day human therapeutic dose) had decreased weights of seminal vesicles and
457 epididymides and slightly decreased fertility. Dogs administered eplerenone at dosages of 15
458 mg/kg/day and higher (AUC 5 times that at the 100-mg/day human therapeutic dose) had dose-
459 related prostate atrophy. The prostate atrophy was reversible after daily treatment for 1 year at
460 100 mg/kg/day. Dogs with prostate atrophy showed no decline in libido, sexual performance, or
461 semen quality. Testicular weight and histology were not affected by eplerenone in any test
462 animal species at any dosage.

463

464

465 **ADVERSE REACTIONS**

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

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

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

472
473 Adverse events that occurred more frequently in patients treated with INSPRA than placebo
474 were hyperkalemia (3.4% vs 2.0%) and increased creatinine (2.4% vs 1.5%). Discontinuations
475 due to hyperkalemia or abnormal renal function were less than 1.0% in both groups.

476 Hypokalemia occurred less frequently in patients treated with INSPRA (0.6% vs. 1.6%).

477
478 The rates of sex hormone related adverse events are shown in Table 3.

479
480 **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%

481
482 **Hypertension**

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

485
486 In placebo-controlled studies, the overall rates of adverse events were 47% with INSPRA and
487 45% with placebo. Adverse events occurred at a similar rate regardless of age, gender, or race.
488 Therapy was discontinued due to an adverse event in 3% of patients treated with INSPRA and
489 3% of patients given placebo. The most common reasons for discontinuation of INSPRA were
490 headache, dizziness, angina pectoris/myocardial infarction, and increased GGT. The adverse
491 events that were reported at a rate of at least 1% of patients and at a higher rate in patients treated
492 with INSPRA in daily doses of 25 to 400 mg versus placebo are shown in Table 4.

493

494

Table 4. Rates (%) of Adverse Events Occurring in Placebo-Controlled Hypertension Studies in $\geq 1\%$ 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.

503

504

505

506

507

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%

508

509 **Clinical Laboratory Test Findings**

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

511 **Creatinine-** Increases of more than 0.5 mg/dL were reported for 6.5% of patients administered
512 INSPRA and for 4.9% of placebo-treated patients.

513

514 **Potassium-** In EPHEBUS, the frequency of patients with changes in potassium (<3.5 mEq/L or
515 >5.5 mEq/L or ≥6.0 mEq/L) receiving INSPRA compared with placebo are displayed in Table 6.

516

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

517

518

519

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)

520

521

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

524
525
526

**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%

527
528

* Estimated using the Cockcroft-Gault formula.

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

533
534
535
536

**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%

537
538
539
540

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

541 ***Hypertension:***

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

544

545

546

547

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

548

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

553

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

559

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

563

564 **Triglycerides-** Serum triglycerides increased in a dose-related manner. Mean increases ranged
 565 from 7.1 mg/dL at 50 mg daily to 26.6 mg/dL at 400 mg daily. Increases in triglycerides (above
 566 252 mg/dL) were reported for 15% of patients administered INSPRA and 12% of placebo-treated
 567 patients.

568

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

573
574 **Liver Function Tests-** Serum alanine aminotransferase (ALT) and gamma glutamyl
575 transpeptidase (GGT) increased in a dose-related manner. Mean increases ranged from 0.8 U/L
576 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
577 mg daily for GGT. Increases in ALT levels greater than 120 U/L (3 times upper limit of normal)
578 were reported for 15/2259 patients administered INSPRA and 1/351 placebo-treated patients.
579 Increases in ALT levels greater than 200 U/L (5 times upper limit of normal) were reported for
580 5/2259 of patients administered INSPRA and 1/351 placebo-treated patients. Increases of ALT
581 greater than 120 U/L and bilirubin greater than 1.2 mg/dL were reported 1/2259 patients
582 administered INSPRA and 0/351 placebo-treated patients. Hepatic failure was not reported in
583 patients receiving INSPRA.

584
585 **BUN/Creatinine-** Serum creatinine increased in a dose-related manner. Mean increases ranged
586 from 0.01 mg/dL at 50 mg daily to 0.03 mg/dL at 400 mg daily. Increases in blood urea nitrogen
587 to greater than 30 mg/dL and serum creatinine to greater than 2 mg/dL were reported for 0.5%
588 and 0.2%, respectively, of patients administered INSPRA and 0% of placebo-treated patients.

589
590 **Uric Acid-** Increases in uric acid to greater than 9 mg/dL were reported in 0.3% of patients
591 administered INSPRA and 0% of placebo-treated patients.

592

593

594 **OVERDOSAGE**

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

600

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

605

606

607 **DOSAGE AND ADMINISTRATION**

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

609 The recommended dose of INSPRA is 50 mg once daily. Treatment should be initiated at 25 mg
610 once daily and titrated to the target dose of 50 mg once daily preferably within 4 weeks as
611 tolerated by the patient. INSPRA may be administered with or without food.

612

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

622

623

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	

624

625 Following withholding INSPRA due to serum potassium ≥6.0 mEq/L, INSPRA can be restarted

626 at a dose of 25 mg QOD when serum potassium levels have fallen below 5.5 mEq/L.

627

Hypertension

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

636

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

642

643

644 **HOW SUPPLIED**

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

647

648	NDC Number	Size
649	0025-1710-01	Bottle of 30 tablets
650	0025-1710-02	Bottle of 90 tablets
651	0025-1710-03	Hospital Unit Dose

652

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

655

656	NDC Number	Size
657	0025-1720-03	Bottle of 30 tablets
658	0025-1720-01	Bottle of 90 tablets

659

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

662

663 Rx only Revised: Date

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

665 INSPRA Tablets are manufactured for:

666 G.D. Searle LLC

667 A subsidiary of Pharmacia Corporation

668 Chicago, IL 60680, USA.

669

670 Date Copy Code

671 **October 7, 2003**

672

673

674