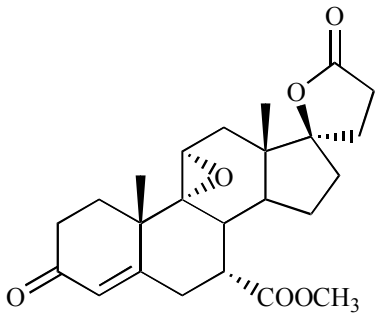
INSPRA ™

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, 50 mg, or 100 mg of eplerenone and the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl methylcellulose, 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 and 100 mg tablets).

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 effect of eplerenone on blood pressure.

Eplerenone has relative selectivity in binding to recombinant human mineralocorticoid receptors compared to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.

Pharmacokinetics

General

Eplerenone is cleared predominantly by CYP450 3A4 metabolism, with an elimination half-life of 4-6 hours. Steady state is reached within two days. Absorption is not affected by food. Inhibitors of

CYP450 3A4 (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 over 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 is primarily to alpha 1-acid glycoproteins. In healthy subjects and patients with hypertension, 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 cytochrome P450 3A4 (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 DOSAGE AND 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 WARNINGS, Hyperkalemia**)**.

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**).

Drug-Drug Interactions:

Also see PRECAUTIONS, Drug Interactions.

Drug-drug interactions 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 and DOSAGE AND ADMINISTRATION.)

Eplerenone is not an inhibitor of CYP1A2, CYP3A4, CYP2C19, CYP2C9 or CYP2D6. Eplerenone did not inhibit the metabolism of chloroxazone, diclofenac, methylphenidate, losartan, amiodarone, dexamethasone, mephobarbital, phenytoin, phenacetin, dextromethorphan, metoprolol, tolbutaminde, amlodipine, astemizole, cisapride, diazepam, 17α-ethinylestradiol, fluoxetine, lovastatin, methylprednisolone, midazolam, nifedipine, simvastatin, triazolam, verapamil, glyburide 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 or oral

contraceptives (norethindrone/ethinyl estradiol). St. Johns Wort (a CYP3A4 inducer) caused a small (about 30%) decrease in eplerenone AUC.

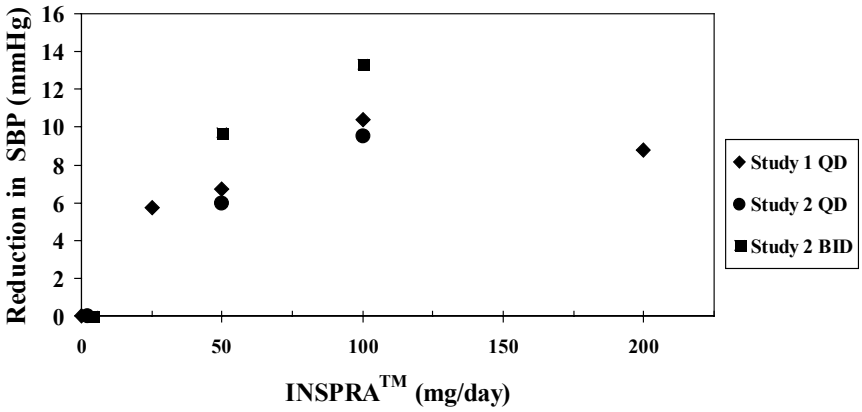
No significant changes in eplerenone pharmacokinetics were observed when eplerenone was administered with aluminum and magnesium-containing antacids.

CLINICAL STUDIES

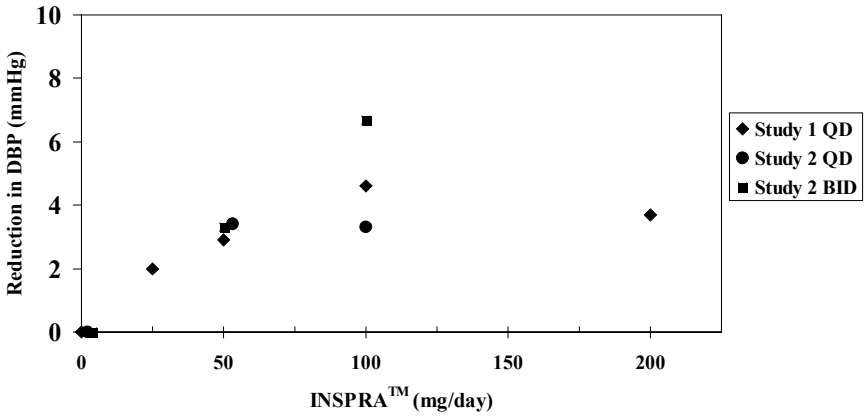
The safety and efficacy of INSPRA have been evaluated alone and in combination with other antihypertensive agents in clinical studies of 3,091 hypertensive patients. The studies included 46% women, 14% blacks, and 22% elderly (age≥65). The studies excluded patients with elevated baseline serum potassium (>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 the following figures.

INSPRA™ Dose Response - Trough Cuff SBP
Placebo-Subtracted Adjusted Mean Change from Baseline



INSPRA™ Dose Response - Trough Cuff DBP
Placebo-Subtracted Adjusted Mean Change from Baseline



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 8-24 weeks in six studies did not lead to adverse event rates in the week following INSPRA withdrawal greater than following placebo or active control withdrawal. Blood pressures in patients not taking other antihypertensives rose 1 week after INSPRA withdrawal by about 6/3 mm Hg, suggesting that INSPRA's antihypertensive effect was maintained through 8-24 weeks.

Blood pressure reductions in the two fixed-dose INSPRA 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

INSPRA is indicated for the treatment of hypertension. INSPRA may be used alone or in combination with other anti-hypertensive agents.

CONTRAINDICATIONS

INSPRA is contraindicated in patients with the following conditions:

- serum potassium > 5.5 meq/L
- 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

INSPRA is also contraindicated in patients treated concomitantly with the following medications:

- potassium supplements or potassium-sparing diuretics (amiloride, spironolactone, or triamterene)
- strong inhibitors of CYP450 3A4 (e.g., ketoconazole, itraconazole)

(See also **CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, Drug-Drug Interactions; **WARNINGS**, **Hyperkalemia**; **PRECAUTIONS**, **Drug-Drug Interactions**; and **ADVERSE REACTIONS**, **Clinical Laboratory Test Findings**, Potassium.)

WARNINGS

Hyperkalemia

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, Drug-Drug Interactions, and ADVERSE REACTIONS, Clinical Laboratory Test Findings.** 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. During the clinical trials serum potassium levels were monitored every 2 weeks for the first 1-2 months and then monthly thereafter.

PRECAUTIONS

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.

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**).

Drug Interactions

Inhibitors of CYP450 3A4: 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 strong inhibitors of CYP450 3A4 (e.g., ketoconazole, itraconazole). (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.**)

ACE inhibitors and angiotensin II receptor antagonists: The addition of INSPRA 50-100 mg to ACE inhibitors and angiontensin 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**). Because the concomitant use of another mineralocorticoid receptor blocker and ACE inhibitors or angiotensin II antagonists has led to clinically relevant hyperkalemia, caution should be used in administering INSPRA with these drugs.

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

Of the total number of subjects in clinical 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. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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

INSPRA has been evaluated for safety in 3,091 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 1.

Table 1. Rates (%) of Adverse Events Occurring in Placebo-Controlled 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

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

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

Table 2: Rates of Sex Hormone Related Adverse Events with INSPRA in 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

Serum Electrolytes

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

Table 3. Changes in Serum Potassium in the Placebo-Controlled, Fixed Dose 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 monotherapy 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 70-100 mL/min, and 2.6% of patients with baseline creatinine clearance of >100 mL/min.

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 patient.

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 15/2,259 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 5/2,259 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 in 1/2,259 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

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.)

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).

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
0025-1720-02	Hospital Unit Dose

INSPRA Tablets, 100 mg, are red diamond biconvex film-coated tablets. They are debossed with *PHA* on one side and 1730 on the other. They are supplied as follows:

NDC Number	Size
0025-1730-01	Bottle of 30 tablets
0025-1730-02	Bottle of 90 tablets
0025-1730-03	Hospital Unit Dose

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

Rx only

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

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Temple

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