



Eplerenone (Inspra[®])

Mechanism of Action: Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and non-epithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure; causes sodium and water reabsorption; causes magnesium and potassium losses; potentiates norepinephrine action; impairs baroreceptor and endothelial function; reduces vascular compliance; and stimulates vascular and cardiac fibrosis. However, its safety profile is improved over spironolactone because of reduced progesterone and androgen-receptor effects. It is labeled for treatment of hypertension, either alone or in combination. It has been studied in postmyocardial infarction (MI) patients with left ventricular dysfunction.

Metabolism: Eplerenone metabolism is primarily mediated via CYP450 3A4; no active metabolites have been identified in human plasma.

Elimination: 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.

Drug Interactions:

CYP450 3A4 Inhibitors (*ketoconazole, itraconazole, erythromycin, verapamil, saquinavir, fluconazole*) result in a 1.4 to 1.7-fold increase of C_{max} of eplerenone and a 2.0 to 5.4-fold increase in AUC. Results of co-administration with other CYP450 3A4 Inhibitors have not been reported

ACE inhibitors and angiotensin II receptor antagonists: addition of Inspra[®] to these drugs results in an increase in mean serum potassium and the frequency of hyperkalemia.³

Lithium: no studies have been conducted, but lithium toxicity has been reported with concomitant use of diuretics and ACE inhibitors.

Nonsteroidal anti-inflammatory drugs (NSAIDs): no studies have been conducted, but the administration of other potassium-sparing antihypertensives with NSAIDs has been shown to reduce the antihypertensive effect and result in severe hyperkalemia in patients with impaired renal function

Dosing/Administration: The recommended starting dose of Inspra[®] is 50 mg administered once daily. (**Ali's recommendation 25 mg PO QOD, after 2 weeks, 25 mg po QD**) The full therapeutic effect is apparent within 4 weeks. No adjustment of the starting dose is recommended for the elderly.

Inspra[®] is contraindicated in patients with renal impairment (serum creatinine >2.0 mg/dL in males or >1.8 mg/dL in females.)

Conclusion: Eplerenone is an effective agent for selective aldosterone blockade and subsequent reduction of hypertension. Its most prominent place in therapy may be as an add-on agent in hypertensive patients inadequately controlled on ACE inhibitor or ARB therapy alone. Eplerenone is the only compound on the market designed to selectively block aldosterone and its deleterious effects. The principal risk of eplerenone therapy is that of hyperkalemia, due to its potassium preserving effects; additionally, interactions with numerous CYP 450 3A4 inhibitors warrants caution in the co-administration of these drugs.

Price: A one-month supply of eplerenone will cost patients \$113. This price is significantly higher than the cost of spironolactone, which is approximately \$14 per month.

Efficacy:

Krum H, Nolly H, Workman D, He W, Roniker B, Krause S, Fakouhi K. Efficacy of eplerenone added to renin-angiotensin blockade in hypertensive patients.

Hypertension. 2002 Aug; 40(2):117-23.

This study assessed the safety, efficacy, and tolerability of eplerenone when used concurrently with preexisting ACE inhibitor therapy or angiotensin II receptor blocker (ARB) therapy. It lasted 8 weeks, and was conducted at multiple international sites as a randomized, double-blind, placebo-controlled, parallel-group study. The study showed that eplerenone with an ARB lowered diastolic blood pressure (BP) significantly from baseline when compared to placebo with an ARB. However, the effect of eplerenone and an ACE inhibitor on diastolic BP did not differ significantly from the placebo and ACE inhibitor combination. When added to either antihypertensive therapy eplerenone did significantly reduce systolic BP compared to placebo with either group. There was no significant difference in adverse events between eplerenone and placebo, and most events were not severe. A limitation of the study was its brief duration of 8 weeks, making it impossible to make assessments about long-term efficacy and safety. Eplerenone may be a useful addition in hypertensive patients who are insufficiently controlled on ACE inhibitor or ARB therapy alone.

Williams ES, Miller JM. Results from late-breaking clinical trial sessions at the American College of Cardiology 51st Annual Scientific Session: The 4E Study: eplerenone, enalapril, and eplerenone/enalapril combination therapy in patients with left ventricular hypertrophy. J Am Coll Cardiol. 2002 Jul 3; 40(1):1-18.

This study compared the efficacy and tolerability of eplerenone with enalapril (an ACE inhibitor) and with the two drugs used in combination. The objective of this double-blind, forced-titration study was to assess the change in left ventricular (LV) mass in hypertensive patients after nine months. There were 153 mild-to-moderate hypertensive patients assessed in the study. For the eplerenone-only group the mean decrease in LV mass from baseline was 14.5 g; for the enalapril-only group it was 19.7 g; and for the combination-therapy group it was 27.2 g. Although there was no significant difference in blood pressure reductions in the three groups, statistical significance occurred in the reduction of the urinary albumin-creatinine ratio between the combination group (-52.6%) compared with the eplerenone group (-24.9%, $p = 0.001$) and the enalapril group (-37.4%, $p = 0.038$). Cough was significantly more common in the enalapril group (14.1%, $p = 0.05$) than in the eplerenone group (3.1%), with 9.0% as the rate of cough in the combination group. This study was limited by the lack of placebo and the low number of participants, making it difficult to extrapolate the results to the larger population. Eplerenone used alone or in combination with ACE inhibitor therapy is effective for organ protection and BP control in patients with essential hypertension and LV hypertrophy.

Epstein M. Hypertensive Type 2 Diabetes Study.

This was a randomized, forced titration study that compared the effects of three antihypertensive regimens (eplerenone, enalapril, and eplerenone in combination with enalapril) on urinary albumin excretion levels, blood pressure, and tolerability in 257 Type 2 diabetic patients with hypertension and albuminuria. There was no statistical difference in blood pressure levels between the three groups. Eplerenone treatment resulted in a statistically significant reduction in proteinuria (-62%) as compared to enalapril (-45%). Combination therapy showed the greatest reduction (-74%). The adverse event profiles of both eplerenone and enalapril were generally similar. The number of patients who experienced potassium levels greater than or equal to 6.0 mEq/L when treated with eplerenone, enalapril, and their combination was 8.6%, 1.2%, and 6.9% respectively, while the frequency of hyperkalemia reported in the study was 16.1%, 6.0%, and 24.1% respectively. This study was limited by the lack of placebo and the low number of participants, making it difficult to extrapolate the results to the larger population. The results of this study show that in diabetic hypertensive patients, a significantly greater reduction in proteinuria is achieved with eplerenone compared to the ACE inhibitor enalapril.

Pitt B, et al. The EPHEsus Trial: eplerenone in patients with heart failure (HF) due to systolic dysfunction complicating acute myocardial infarction. NEJM 2003; The population randomized in EPHEsus averaged 64 years. Nearly three quarters were male, and the mean EF was 33%. There were no significant differences in baseline characteristics between the treatment groups. Study drug was initiated at 25 mg and then increased to 50 mg daily if tolerated; average dose received in the active group was 43 mg eplerenone per day. The primary endpoints of this event-driven study were all-cause mortality and combined cardiovascular (CV) mortality and CV hospitalization. EPHEsus Results Patients on "standard therapy" in the placebo arm experienced an overall mortality rate of 13.6% at 1 year. The addition of eplerenone resulted in a 15% reduction in all-cause mortality ($P = .008$) and a 17% reduction in CV mortality ($P = .005$). The combined primary endpoint of CV mortality and CV hospitalization was reduced by 13% ($P = .002$), and the beneficial effects of eplerenone were consistent across patient subgroups