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Inspra[®] Monograph¹⁻²

Brand Name: Inspra[®]

Generic Name: Eplerenone

Manufacturer: Pfizer, various

Year introduced: 2002

Mechanism of Action:

Eplerenone binds to the mineralocorticoid receptor and blocks the binding of aldosterone, a component of the renin-angiotensin system (RAAS).

FDA-Approved indications:

- Eplerenone is indicated to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction $\leq 40\%$) and clinical evidence of congestive heart failure after an acute myocardial infarction.
- Eplerenone is FDA-approved for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Contraindications:

- Serum potassium >5.5 mEq/L
- Creatinine clearance ≤ 30 mL/min
- Patients taking strong inhibitors of CYP450 3A4 (i.e., ketoconazole, itraconazole)
- Type 2 diabetes with microalbuminuria
- Patients taking potassium supplements or potassium-sparing diuretics (amiloride, spironolactone, or triamterene)
- Serum creatinine >2.0 mg/dL in males or >1.8 mg/dL in females
- Creatinine clearance <50 mL/min

Pharmacokinetics:

Eplerenone is rapidly absorbed following oral administration. Peak plasma concentrations are reached within approximately 1.5 hours. The absolute oral bioavailability is unknown. Volume of distribution is 43 to 90 L in healthy patients and those with hypertension. At therapeutic concentrations, 50% of eplerenone in plasma is bound, primarily to alpha 1-acid glycoproteins. Eplerenone is primarily metabolized via cytochrome P450 3A4. The half-life is approximately four to six hours. Eplerenone is excreted primarily in the urine (~67%) and to a

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lesser extent in the feces (~32%). Less than 5% is recovered as unchanged drug in the urine and feces.

Adverse Effects:

Clinical laboratory test findings demonstrated dose related increases in potassium, triglycerides, cholesterol, liver function tests, and blood urea nitrogen (BUN)/creatinine. Serum sodium decreased in a dose-related manner.

Adverse Events Occurring in Placebo-Controlled studies of Patients Treated with Inspra® (25 to 400 mg)

Adverse Reaction (%)	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

Sex-Related Adverse Events (%) with Inspra® in Clinical Studies

	All controlled studies	Controlled studies lasting ≥6 months	Open label, long term studies
Rates in Males			
Gynecomastia	0.5	0.7	1.0
Mastodynia	0.8	1.3	0.3
Either	1.0	1.6	1.0
Rates in Females			
Abnormal vaginal bleeding	0.6	0.8	2.1

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**Drug Interactions:**

Precipitant drug/ substance	Object drug/ substance		Description
Ketoconazole	Eplerenone	↑	Increased exposure to eplerenone approximately 5-fold
Erythromycin, saquinavir, verapamil, and fluconazole	Eplerenone	↑	Increased exposure to eplerenone approximately 2-fold
Grapefruit juice	Eplerenone	↑	Increased exposure by ~25%
Amiloride, spironolactone, triamterene, and ACEIs	Potassium	↑	Increased potassium levels when used concomitantly with eplerenone

Precaution/Warnings:**Hyperkalemia (patients treated for congestive heart failure post-myocardial infarction):**

Periodic monitoring is recommended in patients at risk for the development of hyperkalemia (including patients taking ACE inhibitors or angiotensin II receptor antagonists). In clinical trials serum potassium levels were monitored every two weeks for the first 1 to 2 months and then monthly thereafter.

Diabetic patients:

Patients with diabetes and proteinuria on the baseline urinalysis had increased rates of hyperkalemia.

Impaired hepatic function:

The use of eplerenone in patients with severe hepatic impairment has not been evaluated.

Impaired renal function:

Eplerenone is contraindicated in patients with type 2 diabetes and microalbuminuria, serum creatinine >2.0 mg/dL in males or >1.8 mg/dL in females and creatinine clearance <50 mL/min.

Pregnancy/Lactation:

- Pregnancy Category B: No adequate and well-controlled studies have been conducted in pregnant women. Eplerenone should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.
- Eplerenone and/or its metabolites were excreted in the milk of rats. Whether eplerenone is excreted in human milk is unknown. Caution should be exercised if eplerenone is administered to a nursing woman.



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Usual Dosage:

Eplerenone tablets are supplied in 25- and 50-mg strengths.

Congestive Heart Failure Post-Myocardial Infarction:

The recommended starting dose of eplerenone is 50 mg administered once daily for patients with congestive heart failure post-myocardial infarction. Treatment should be initiated at 25 mg once daily and titrated to the target dose of 50 mg once daily preferably within four weeks as tolerated by the patient. Eplerenone may be given with or without food.

Hypertension:

Eplerenone may be used alone or in combination with other antihypertensive agents. The recommended starting dose of eplerenone is 50 mg administered once daily for patients with hypertension. The starting dose must be reduced to 25 mg once daily for patients receiving weak CYP3A4 inhibitors, such as erythromycin, saquinavir, verapamil, and fluconazole. Use of eplerenone is contraindicated in patients taking strong inhibitors of CYP450 3A4. The full therapeutic effect of eplerenone is seen within four weeks. The dosage can be increased to 50 mg twice daily in patients with inadequate blood pressure response to the 50 mg once daily dosage. Doses higher than 100 mg are not recommended either because they have no greater effect on blood pressure or because they are associated with increased risk of hyperkalemia.

Clinical Studies:

Title & Author	Study design	Results
Efficacy of eplerenone added to renin-angiotensin blockade in hypertensive patients Krum H, et al. ³ (2002)	In a multicenter, randomized, double-blind, placebo-controlled study, 341 patients were assigned to receive 50 mg eplerenone (EPL, increased to 100 mg if required) once daily or placebo for 8 weeks. Eligible subjects were	<p style="text-align: center;">Primary endpoint:</p> <ul style="list-style-type: none"> • Comparison between mean change from baseline of trough cuff seated DBP and SBP at week 8 in patients who received either eplerenone or placebo <p style="text-align: center;">Secondary endpoints:</p> <ul style="list-style-type: none"> • Incidence of adverse events; mean change from baseline in hematology, biochemistry, and urinalysis parameters; and mean change from

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	<p>men or nonpregnant women between 18 and 85 years of age who were taking a fixed dose of an ACE inhibitor or an ARB and had a history of mild to moderate hypertension, or who were taking a fixed dose of one ACE inhibitor or one ARB alone and had current hypertension (diastolic BP ≥ 95 mm Hg and < 110 mmHg and systolic BP < 180 mmHg). In addition, eligible patients had an ECG without arrhythmia, no clinically significant abnormal clinical laboratory values and serum potassium level ≥ 3.0 mEq/L and ≤ 5.0 mEq/L.</p>	<p>baseline in plasma renin and serum aldosterone at week 8</p> <p>Efficacy: EPL/ARB > placebo/ARB, EPL/ACE = placebo/ACE</p> <ul style="list-style-type: none"> At week 8, 87.8% of eplerenone/ARB patients and 73.8% of placebo/ARB patients were responders ($p=0.003$). Responders was defined as patients who had a diastolic BP < 90 mm Hg or exhibited ≥ 10 mm Hg reduction from baseline. No significant difference in response rate was observed between eplerenone/ACE inhibitor recipients and placebo/ACE inhibitor patients throughout the entire course of the study. Eplerenone in combination with an ACE inhibitor or an ARB had no significant effect on heart rate. <p>Safety: EPL/ARB = EPL/ACE = PLACEBO</p> <ul style="list-style-type: none"> No significant differences were observed in total adverse events between the eplerenone/ACE inhibitor or ARB groups versus the placebo/ACE inhibitor or ARB groups. One patient in the eplerenone/ARB group, two patients in the eplerenone/ACE inhibitor group and two patients in the placebo/ACE inhibitor group withdrew due to adverse events No statistically significant differences were observed for selected laboratory values between the placebo/ACE inhibitor and eplerenone/ACE inhibitor groups. Statistically significant, but clinically unimportant, differences were observed between the placebo/ARB and eplerenone/ARB groups for a number of variables; all of the changes remained within normal ranges for each treatment group.
<p>Eplerenone, a selective aldosterone blocker, in mild to moderate hypertension</p> <p>Weinberger M, et al.⁴ (2002)</p>	<p>In this 8-week, multicenter, double-blind, placebo-controlled trial, 417 patients were randomized to eplerenone (EPL) 50, 100, or 400 mg once daily; eplerenone 25, 50, or 200 mg twice daily; spironolactone 50 mg twice daily; or placebo. The subjects included in the study were 21 to 80</p>	<p>Primary endpoint:</p> <ul style="list-style-type: none"> Adjusted mean change from baseline in seated and standing, cuff-assessed DBP, measured at trough compared to placebo <p>Secondary endpoints:</p> <ul style="list-style-type: none"> Adjusted mean change from baseline in seated, cuff-assessed systolic blood pressure; 24-h ABPM and mean SBP and DBP; total and active plasma rennin levels; and serum aldosterone levels <p>Efficacy: EPL > spironolactone > placebo</p> <ul style="list-style-type: none"> When EPL was compared to placebo all groups had mean significant reductions in seated and standing SBP and DBP from baseline to final visit

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	<p>years of age and had both seated, cuff-assessed DBP ≥ 95 mmHg and < 114 mmHg and a 24-h mean DBP ≥ 85 mm Hg determined by a 24-h ambulatory BP monitoring device.</p>	<p>($P < 0.041$) except the 100mg EPL group. In the 100mg group, there was not a significant reduction in standing DBP.</p> <ul style="list-style-type: none"> Greater reductions occurred for seated and standing DBP in the twice-daily 50-mg EPL group compared to the daily 100mg EPL group ($p = 0.036$ seated, $p = 0.012$ standing). Reductions compared to placebo were observed across all but two eplerenone groups in mean change from baseline to final visit in trough ABPM DBP measurements. In general, adjusted mean changes from baseline to final visit in SBP and DBP for twice daily 50mg and daily 100mg of eplerenone dosing were approximately 50% to 75% of those observed with the twice-daily 50mg groups. Spironolactone caused reductions ($p \leq 0.001$) in SBP and DBP compared to placebo. <p>Safety: EPL = spironolactone \leq placebo</p> <ul style="list-style-type: none"> Increases in serum aldosterone levels were observed in all EPL groups, but were significant in the twice-daily 50 and 200mg groups ($p \leq 0.05$). Aldosterone levels were increased in the spironolactone group as compared to the placebo group ($p < 0.001$). Increases in aldosterone levels in the twice daily 25 and 50mg eplerenone groups were less than those observed in the twice daily 50mg spironolactone group. The incidence of adverse events in EPL-treated patients was similar to placebo. Mean change in serum potassium levels from baseline was significant ($p < 0.05$) in the daily 400mg EPL group, the twice-daily 25, 50, and 100mg EPL groups, and the spironolactone group. An increase ($P \leq 0.05$) in mean TSH was observed in the daily 400mg EPL group.
<p>Efficacy and tolerability of eplerenone and losartan in hypertensive black patients and white patients Pratt JH, et al.⁵</p>	<p>In this 16-week, double-blind, randomized study, 551 patients were randomized to receive eplerenone (EPL) 50 mg QD, losartan (LOS) 50 mg QD or placebo (PBO). Eligible patients had mild-to-moderate</p>	<p>Primary endpoint:</p> <ul style="list-style-type: none"> Change from baseline to week 16 in SBP/DBP Active renin levels <p>Efficacy: EPL \geq LOS $>$ PBO</p> <ul style="list-style-type: none"> Significant reductions in SBP/DBP occurred in black patients (EPL vs. PBO, $p = 0.001$; EPL vs. LOS, $p = 0.001$). Significant reductions in SBP/DBP occurred in

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<p>(2002)</p>	<p>hypertension (DBP \geq95 mmHg and <110 mmHg).</p>	<p>white patients when EPL was compared to PBO ($p=0.001$) but not to LOS ($p=0.126$, SBP; $p=0.068$, DBP).</p> <ul style="list-style-type: none"> Overall, all patients had significant reductions in blood pressure. Active renin increased significantly in both groups. <p>Safety: EPL= LOS = PBO</p> <ul style="list-style-type: none"> No significant difference occurred in the number of AEs. Both drugs decreased microalbuminuria, a prognostic predictor of end-organ damage and cardiovascular damage.
<p>Antihypertensive effects of eplerenone and enalapril in patients with essential hypertension</p> <p>Burgess E, et al.⁶ (2002)</p>	<p>In this 12-month, double-blind, titration to effect study, 499 patients were randomized to receive initially EPL 50 mg QD or enalapril (ENAL) 10 mg QD. If DBP \geq90 mmHg, EPL was titrated to 100 mg and 200 mg QD, or ENAL 20 mg and 40 mg QD.</p>	<p>Primary endpoint:</p> <ul style="list-style-type: none"> CHANGE IN BP FROM BASELINE Change in microalbuminuria was measured using the urinary albumin-to-creatinine ratio (UACR) <p>Efficacy: EPL \geq ENAL</p> <ul style="list-style-type: none"> Both drugs at Week 24 (EPL $-14.5/-11.2$ mmHg, ENAL $-12.7/-11.3$) and 12 months (EPL $-16.5/-13.3$ mmHg, ENAL $-14.8/-14.1$) comparably reduced blood pressures. At week 24, a significant reduction in UACR was observed with EPL compared to ENAL (-61.5% vs. -25.7%, $p=0.01$). <p>Safety: EPL > ENAL</p> <ul style="list-style-type: none"> Greater numbers of ENAL patients experienced coughing (6.5% vs 2.4%, $p=0.029$), hyperglycemia (2.8% vs. 0%, $p=0.007$), and UTI (2.8% vs. 0.4%, $p=0.035$).
<p>Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction</p> <p>Pitt B, et al.⁷ (EPHESUS) (2003)</p> <p>(Supported by a grant from Pharmacia)</p>	<p>In this multicenter, international, randomized, double-blind, placebo-controlled trial, 6642 patients were randomly assigned to receive eplerenone (EPL) 25 mg per day or matching placebo (PBO) for 4 weeks, followed by a dose increase to 50 mg daily. Eligible patients had an acute myocardial infarction as documented according to standard criteria, left ventricular dysfunction</p>	<p>Primary endpoint:</p> <ul style="list-style-type: none"> Time to death from any cause, time to death from cardiovascular causes, or time to occurrence of first hospitalization for a cardiovascular event, including heart failure, recurrent acute myocardial infarction, stroke, or ventricular arrhythmia <p>Secondary endpoint:</p> <ul style="list-style-type: none"> Death from cardiovascular causes and death from any cause or any hospitalization <p>Efficacy: EPL > PBO</p> <ul style="list-style-type: none"> 478 patients in the eplerenone group (14.4%) and 554 patients in the placebo group (16.7%) died (RR, 0.85; $p=0.008$). Death from cardiovascular events or hospitalization occurred in 885 patients in the eplerenone group (26.7%) and 993 patients in the placebo group (30%) (RR, 0.87; $p=0.002$).

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	<p>as documented by a left ventricular ejection fraction of 40 percent or lower on echocardiography, radionuclide angiography, or angiography of the left ventricle after the index acute myocardial infarction and before randomization, and heart failure as documented by the presence of pulmonary rales, chest radiography showing pulmonary venous congestion, or the presence of a third heart sound.</p>	<ul style="list-style-type: none"> • There was a relative risk reduction of 15% in the risk of hospitalization for heart failure with eplerenone (RR, 0.85; p=0.03), and there were 23% fewer episodes of hospitalization for heart failure in the eplerenone group than in the placebo group (RR, 0.77; p=0.002). • Rate of death from any cause or any hospitalization was 8% lower in the eplerenone group than in the placebo group (RR, 0.92; p=0.02). <p style="text-align: center;">Safety: EPL ≤ PBO</p> <ul style="list-style-type: none"> • Serum creatinine had increased by 0.02 mg per deciliter in the placebo group and by 0.06 mg per deciliter in the eplerenone group (P<0.001) at one year. • There were no significant differences between the treatment groups in the number of patients with changes in laboratory variables that met prespecified criteria for abnormally low or high values.
<p>Effects of eplerenone, enalapril, and eplerenone/enalapril in patients with essential hypertension and left ventricular hypertrophy (LVH). The 4E-left ventricular hypertrophy study.</p> <p>Pitt B, et al.⁸ (2003)</p> <p>(Supported by funding from Pharmacia)</p>	<p>In this 9-month, placebo run-in, randomized, double-blind, active-controlled, parallel-group study, 202 patients were randomly assigned to receive eplerenone (EPL) 200 mg per day, enalapril 40 mg daily plus a placebo tablet (ENAL + PBO) or eplerenone 200 mg and enalapril 10 mg daily (EPL + ENAL). At week 8, hydrochlorothiazide 12.5 to 25 mg and/or amlodipine 10 mg was added if diastolic blood pressure was >90 mmHg. Eligible patients were male and nonpregnant females who were predominantly in sinus rhythm with LVH diagnosed by either ECG or echocardiogram and history of hypertension.</p>	<p style="text-align: center;">Primary endpoint:</p> <ul style="list-style-type: none"> • Change from baseline in LV mass among patients who had a baseline MRI, and an end point MRI at month 9 or at the time of study discontinuation (MRI studies were not performed if treatment had been administered for less than 3 months). <p style="text-align: center;">Secondary endpoint:</p> <ul style="list-style-type: none"> • Change from baseline in blood pressure, urinary albumin excretion, and RAAS hormone <p style="text-align: center;">Efficacy: EPL + ENAL ≥ EPL = ENAL</p> <ul style="list-style-type: none"> • At month 9, treatment with EPL resulted in an adjusted mean change of -14.5 ± 3.36 g (p<0.0001 versus baseline) in LV mass, ENAL, -19.7 ± 3.20 g (p<0.001 versus baseline) and EPL + ENAL, -27.2 ± 3.39 g (p<0.001 versus baseline). The LV mass regression caused by EPL was not statistically different from that caused by ENAL (p=0.258). However, the regression caused by EPL + ENAL was significantly greater than that observed with the EPL monotherapy group (p=0.007 for EPL + ENAL versus EPL; p=0.107 for EPL + ENAL versus ENAL). • SBP was reduced significantly more with EPL + ENAL (-28.7 ± 1.8) than with EPL (-23.8 ± 1.8) (p=0.048). • Only 22 of 54 (40.7%) patients achieved BP

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		<p>control with ENAL, whereas 35 of 50 (70.0%) and 39 of 49 (79.6%) achieved control with EPL and EPL + ENAL (p=0.003 for ENAL vs. EPL and p=0.001 for ENAL vs. EPL + ENAL).</p> <ul style="list-style-type: none"> • Treatment with EPL significantly decreased 24-hour UACR (-24.9%) from baseline, as did ENAL (-37.4%) and EPL + ENAL (-52.6%). Differences between improvements in the 3 groups were significant (EPL + ENAL vs. EPL, p=0.001; EPL + ENAL vs. ENAL, p=0.038). <p>Safety: EPL = ENAL + EPL = ENAL</p> <ul style="list-style-type: none"> • Adverse events were reported with similar incidence among treatment groups; treatment emergent adverse events (events reported after at least 1 dose of study medication) were reported by 65.6% of EPL, 70.4% of ENAL, and 55.2% of EPL + ENAL patients. • A significantly greater number of ENAL patients than EPL patients experienced cough (p=0.033). Two ENAL patients discontinued due to cough. • Seven EPL (10.9%), 2 ENAL (2.8%), and 3 EPL + ENAL patients (4.5%) had serious hyperkalemia (maximum potassium level ≥ 6.0 mmol/L on 1 occasion).
<p>Efficacy of eplerenone versus enalapril as monotherapy in systemic hypertension</p> <p>Williams HG et al.⁹ (2004)</p> <p>(Supported by a grant from Pharmacia)</p>	<p>In this multicenter, randomized, double-blind, active controlled, parallel-group design, 499 patients were randomly assigned initial doses of eplerenone (EPL) 50 mg or enalapril (ENAL) 10 mg. These were up-titrated at 4, 8, or 12 weeks if the seated DBP was not <90 mmHg. The second dose titration was 100 mg of EPL or 20 mg ENAL, and the third dose was 200 mg EPL or 40 mg of ENAL. Eligible patients were men and nonpregnant women aged ≥ 18 years, who were newly diagnosed with or had a</p>	<p>Primary Endpoint:</p> <ul style="list-style-type: none"> • Comparison of long-term safety and antihypertensive efficacy of eplerenone versus enalapril using titration-to-effect dosing by measuring seated-trough DBP <p>Secondary Endpoints:</p> <ul style="list-style-type: none"> • Reduction in seated-trough SBP, effect on sex hormones, changes in albuminuria from baseline <p>Efficacy: EPL = ENAL</p> <ul style="list-style-type: none"> • Similar (-11.2 versus -11.3 mmHg) reductions in DBP were seen (p=0.91). Noninferiority of EPL compared with ENAL was established (p<0.001). • EPL produced a slightly greater reduction in SBP than ENAL, but this did not reach statistical significance (p=0.20). • At the month 12 end point, the adjusted mean decrease from baseline of seated DBP was -13.3 mmHg in the EPL group (n=161) and -14.1 mmHg in the ENAL group (n=153) (p=0.33). Similar findings were obtained for seated SBP with -16.5 mmHg in the EPL group and -14.8 mmHg in the ENAL group (p=0.25).

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	<p>history of stage 1 or 2 hypertension, defined as seated DBP \geq90 mmHg but $<$110 MMHG, and seated SBP $<$190 mmHg.</p>	<ul style="list-style-type: none"> • In patients who had a normal UACR level, there was little change in either treatment group. In patients with baseline microalbuminuria (n=34 for EPL; n=30 for ENAL), both treatments significantly reduced the level of UACR, and the response to EPL was significantly greater than the response to ENAL (p=0.01). <p style="text-align: center;">Safety: EPL = ENAL</p> <ul style="list-style-type: none"> • The most frequent treatment-emergent adverse effects of EPL were headache, upper respiratory tract infection, influenza-like symptoms, backache, and bronchitis. • The most frequent treatment-emergent adverse effects of EPL were headache, upper respiratory tract infection, influenza-like symptoms, and cough • Total testosterone, leuteinizing hormone, and total estradiol levels by gender and in women by age ($<$55 and \geq55 years) showed no clinically significant changes within or between groups. • One male EPL-treated and 2 ENAL-treated patients experienced mild to moderate impotency, and 2 EPL-treated patients experienced gynecomastia.
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Key: DBP=diastolic blood pressure, SBP=systolic blood pressure, ARB=angiotensin receptor blocker, ACE=angiotensin converting enzyme, TSH=thyroid stimulating hormone, ABPM=ambulatory blood pressure monitor, ECG=electrocardiogram, MRI=magnetic resonance imaging, UACR=urinary albumin creatinine ratio

Conclusion:

Eplerenone is an aldosterone receptor antagonist with fewer progestational and anti-androgenic adverse reactions than spironolactone. It is effective in reducing blood pressure, and the findings of the EPHEBUS trial demonstrate that eplerenone reduces morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure. Because spironolactone is inexpensive and well studied, it remains the aldosterone receptor blocker of choice. Men who experience gynecomastia or breast tenderness on spironolactone may benefit from a change of therapy to eplerenone.

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