

# NEW DRUG UPDATE

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## Inspra® (eplerenone)

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### Introduction

Inspra® [eplerenone (e-PLER-en-one)] was first approved by the FDA in September 2002. It is the first drug designed to selectively block the binding of aldosterone at the mineralocorticoid receptor site, while not binding to the glucocorticoid, progesterone, or androgen receptors. Aldosterone is a key component of the renin-angiotensin-aldosterone-system (RAAS). Eplerenone is currently indicated in hypertension treatment, as monotherapy or in combination with other anti-hypertensives, and to improve survival in patients with left ventricular dysfunction (ejection fraction = 40%) and heart failure symptoms following myocardial infarction.

### Therapeutic Recommendation

Eplerenone has been demonstrated to provide similar reductions in blood pressure to both amlodipine and enalapril. A comparison of eplerenone and amlodipine for 24 weeks revealed comparable results (-20.5/-4.5 mmHg for eplerenone and -20.1/-6.9 mmHg for am-

lodipine). A separate 12 month trial comparing eplerenone with enalapril yielded similar outcomes (-16.5/-13.3 mm Hg for eplerenone, -14.8/-14.1 mm Hg for enalapril). In both trials tolerability was similar. Interestingly, in those patients with baseline albuminuria, eplerenone reduced proteinuria more than the respective comparators in either trial. A clinical trial assessed the efficacy and tolerability of eplerenone when added to an existing anti-hypertensive regimen with an ACE-Inhibitor or an angiotensin II receptor blocker (ARB). Eplerenone decreased systolic blood pressure to a greater extent overall in both arms of the treatment groups when compared to placebo. A statistically significant decrease in diastolic blood pressure was demonstrated in the eplerenone/ARB arm, but not in the eplerenone/ACE arm. The coadministration of eplerenone with either an ACE or ARB appeared to be well tolerated when compared to placebo. Eplerenone was also examined in patients with left ventricular dysfunction after myocardial infarction. EPHEBUS was a double blind, placebo controlled trial that evaluated the effect of eplerenone on the morbidity and mortality in over 6,000 patients with an acute MI complicated by left ventricular dysfunction. Eplerenone was proven beneficial with patients already receiving optimal therapy (defined as

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an ACE-inhibitor or angiotensin receptor blocker, a beta-blocker, aspirin, a lipid lowering agent, and coronary reperfusion therapy). The direct mechanism by which eplerenone elicits myocardial protection in patients with an acute MI and LV dysfunction is not completely known, but eplerenone has shown to decrease coronary vascular inflammation, decrease oxidative stress, improve epithelial dysfunction, and improve ventricular remodeling. EPHEsus concluded that the estimated number of patients needed to treat is 50 to save one life in one year and the estimated number to treat is 33 to prevent one death from cardiovascular causes or one hospitalization for a cardiovascular event. The benefits of using eplerenone over other aldosterone inhibitors, such as spironolactone, are that the rates of gynecomastia and impotence are not greater than that of the placebo group. This is due to the greater selectivity of eplerenone for the aldosterone receptor. Other adverse effects, such as hyperkalemia, appear similar. It is questionable whether these benefits are worth the added costs for the majority of patients.

### Dosing and Administration

Eplerenone is available in 25 mg and 50 mg diamond shaped tablets for oral administration. The initial starting dose of eplerenone for treatment of hypertension is 50 mg once daily with the total therapeutic effect apparent within 4 weeks. If an adequate reduction in blood pressure is not

achieved on 50 mg once daily, the dose should be increased to 50 mg twice daily. Doses of eplerenone greater than 100 mg daily are not recommended because they are not associated with a greater decrease in blood pressure, but do have increased risk of hyperkalemia. Patients with mild-to-moderate hepatic impairment and elderly patients should not increase the dose to 50 mg twice daily. A starting dose of 25 mg daily should be used in patients that are concurrently taking a mild CYP 3A4 inhibitor such as saquinavir, erythromycin, verapamil or fluconazole. For treatment of heart failure post-MI, the recommended starting dose is 25 mg daily, titrating to 50 mg daily within four weeks as serum potassium levels permit. Doses should be reduced with potassium levels between 5.5 and 5.9, and held for potassium levels = 6.0.

### Cost Comparison

Medication/Dose	Cost <sup>^</sup>		
	CVS	Kroger	Rite Aid
spironolactone 50 mg	28.09	28.79	35.99
Inspra® (eplerenone) 50 mg	139.99	131.09	124.99

<sup>^</sup>Cost to patient for 30 tablets

### Contraindications

As a generality, eplerenone is contraindicated in patients with an underlying risk of hyperkalemia. Specifically, eplerenone is contraindicated in hypertension patients with the following characteristics: 1) serum potassium >5.5 mEq/L, 2) type II diabetes with microalbuminuria, 3) males with serum creatinine > 2.0 mg/dL, 4) females with serum creatinine > 1.8 mg/dL, or 5) a creatinine clearance of < 50 mL/min. In addition, patients who are receiving potassium supplements or potassium sparing diuretics, or strong inhibitors of CYP 3A4 (e.g. ketoconazole, itraconazole) are contraindicated for receiving eplerenone. In contrast to the above, the FDA has allowed use of eplerenone in heart failure patients with creatinine clearances >30 mL/min.

### Special Populations

**Pregnancy:** Eplerenone is Pregnancy Category B, based on favorable results in animal studies. There is not an adequate amount of evidence using eplerenone in pregnant women. It should only be used if the potential benefits outweigh the po-



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tential risks to the fetus.

**Lactation:** The concentration of eplerenone in human breast milk after oral administration is still unknown. Therefore, the risk of potential adverse effects in the infant should be considered when deciding to discontinue the drug or discontinue breast-feeding.

**Pediatrics:** Safety and efficacy of eplerenone in the pediatric population has not been evaluated.

**Geriatrics:** During clinical trials, there were no overall variances in safety and efficacy between older patients and younger patients. The hypothesis that a portion of elderly population may tend to be more sensitive to the antihypertensive effects of eplerenone cannot be neglected.

**Race:** African Americans had a decreased  $C_{max}$  and AUC at steady state. However, efficacy at reducing blood pressure does not appear to be diminished on a population basis.

**Renal Insufficiency:** Eplerenone is not recommended in hypertensive patients with a creatinine clearance of  $< 50$  mL/min, males with a serum creatinine of  $> 2$  mg/dL, or in women with a serum creatinine of  $> 1.8$  mg/dL. In contrast, in patients with heart failure, eplerenone is recommended with creatinine clearances down to 30 mL/min. Eplerenone is not removed by hemodialysis. Some have argued that these guidelines are too restrictive, in light of studies showing similar rates of hyperkalemia to spironolactone, which lacks such stringent guidelines, and that eplerenone can reduce proteinuria.

**Hepatic Insufficiency:** Patients with moderate (Child-Pugh Class B) hepatic dysfunction have an increased  $C_{max}$  and AUC at steady state. These patients should not have the original dose of eplerenone titrated to 50 mg twice daily.

### Drug Interactions

Eplerenone is metabolized by the CYP 3A4 enzyme pathway. Eplerenone is contraindicated in patients that are using potent inhibitors of CYP 3A4 such as ketoconazole and itraconazole because  $C_{max}$  and AUC are increased 1.7-fold and 5-fold respectively. Other CYP 3A4 inhibitors such as erythromycin, saquinavir, verapamil, and fluconazole can increase the concentration of eplerenone. The initial dose of eplerenone should be reduced to 25 mg daily with these drugs. Clinically relevant hyperkalemia was demonstrated in clinical trials when eplerenone was used concomi-

tantly with ACE-Inhibitors and angiotensin II antagonists. NSAIDs and eplerenone have not been evaluated specifically for a drug interaction, but patients receiving both should be closely monitored for desired blood pressure effects and hyperkalemia.

### Adverse Effects

In placebo-controlled trials adverse effects occurred at approximately the same rate regardless of age, sex, or race. Dizziness, headache, and angina were the most common reasons for discontinuation of eplerenone during clinical trials. Other adverse events that occurred at a rate of  $> 1\%$  during clinical trials were hyperkalemia, hypercholesterolemia, hypertriglyceridemia, diarrhea, abdominal pain, albuminuria, cough, fatigue, and flu-like symptoms. Gynecomastia, impotence, and abnormal vaginal bleeding were observed with eplerenone treatment, but were not statistically different from placebo ( $p$  value = 0.7 – 1.0). The rates of gynecomastia, impotence, and vaginal bleeding are much less that with treatment with spironolactone.

### Clinical Laboratory Tests

**Potassium:** There was a dose-related increase in potassium levels with eplerenone therapy. Patients with Type 2 diabetes or microalbuminuria were more likely to develop persistent hyperkalemia. As renal function in patients declined there was an increase in hyperkalemia.

**Triglycerides:** Eplerenone 50 mg daily demonstrated a dose-related increase of approximately 7.1 mg/dL in triglycerides during 8 to 12 week clinical trials.

**Cholesterol:** Eplerenone changed serum cholesterol levels in a dose-related method. Average changes reported a 0.4 mg/dL decrease with 50 mg and an increase with 400 mg daily.

**Liver Function Tests:** Serum alanine aminotransferase (ALT) and gamma glutamyl transpeptidase (GGT) are increased on a dose-related scale.

**BUN/Creatinine:** Serum creatinine and BUN are increased in a dose-related manner. Mean increases in serum creatinine were 0.1 mg/dL and 0.3 mg/dL for 50 mg and 400 mg of eplerenone respectively.

**Uric Acid:** Eplerenone produced increases in uric acid to greater than 9 mg/dL in approximately 0.3%

of the patients in the clinical trials.

### Pharmacology

**Mechanism of Action:** Eplerenone binds to the mineralocorticoid receptor and inhibits the binding of aldosterone. The binding of aldosterone to the mineralocorticoid receptor occurs in both the epithelial and non-epithelial tissues of the body, therefore affecting a variety of organs including the kidneys, heart, blood vessels, and brain. Aldosterone acts to increase blood pressure by inducing sodium reabsorption.

**Absorption/Distribution:** After oral administration of eplerenone, peak concentrations occurred 1.5 hours after dosing. Approximately 50% of eplerenone is plasma protein bound to alpha 1-acid glycoprotein. Steady state concentrations are achieved within 2 days and absorption is not affected by food. The bioavailability of eplerenone is currently unknown.

**Metabolism/Excretion:** Eplerenone is metabolized via the CYP450 3A4 pathway. No active metabolites are present in the human plasma. Less than 5% of the drug is excreted unchanged in the urine and feces. The elimination half-life is 4 to 6 hours and the apparent plasma clearance is 10 L/hour.

### Patient Information

1. Do not take potassium supplements or salt substitutes while taking eplerenone.
2. Always inform all your doctors of any medications (over-the-counter and prescription) that you are taking.
3. Do not take this medication if you are taking ketoconazole or itraconazole.
4. Eplerenone can be taken with or without food.
5. You may feel a little dizzy and fatigued when initiating the medication.

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## Fuzeon® (enfuvirtide)

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### Introduction

Fuzeon® [enfuvirtide (en-FEW-ver-tide)] is the first agent in a new class of antiretroviral drugs known as fusion inhibitors. It is the first approved HIV medicine that works by inhibiting entry of the HIV virus into the CD4 cell. Entry is a three-step process involving attachment, co-receptor binding and fusion inhibition. The FDA approved enfuvirtide (Fuzeon®) in March 2003 for the treatment of chronic HIV-1 infection. Enfuvirtide is a synthetic peptide chain of L-amino acids that works by inhibiting the fusion of viral and cell membranes.

### Therapeutic Recommendation

**Fuzeon® is currently approved for use in patients six years of age and older with advanced HIV-1 infection who have been on antiretroviral therapy. The drug has not been proven effective against HIV-2. The safety and efficacy of enfuvirtide have been studied only in antiretroviral-experienced persons. Preliminary data from two multicenter phase III clinical trials involving over 1,000 patients (T-20 versus Optimized Regimen Only (TORO-1 and TORO-2), suggest that the drug is safe and efficacious in heavily pretreated subjects through 24 weeks. In TORO-1, enfuvirtide decreased HIV-1 RNA levels by 1.696<sub>log10</sub> copies/ml and increased CD4<sup>+</sup> cells by 76 cells/mm<sup>3</sup> compared to a HIV-RNA 0.764<sub>log10</sub> reduction and a CD4<sup>+</sup> increase of 32 cells/mm<sup>3</sup> in the control group. It is currently recommended that patients be on at least two other antiretroviral agents to which the HIV virus is susceptible. Enfuvirtide is to be used as an adjunct agent in patients with advanced HIV-1 disease who have documented resistance to current drug therapy. Enfuvirtide should not be used as a first line agent or as a sole agent in treating HIV-1. Given the limitations regarding**

**complexity of production, mode of administration and cost, its use is unlikely to be widespread.**

### Dosing and Administration

The recommended dose of enfuvirtide is 90 mg subcutaneously twice a day for adults. For patients six to sixteen years of age, the dose is 2 mg/kg up to 90 mg twice a day. Enfuvirtide is only available as an injection that must be reconstituted by the patient prior to administration. It is available as a kit that contains everything needed for a 30 day supply of the drug. Enfuvirtide must be used within 24 hours of reconstitution. If not used immediately it must be refrigerated for up to 24 hours. The recommended injection sites are the abdomen, anterior thigh, or upper arm. The injection site should be rotated each time, due to local reactions.

### Cost Comparison

Enfuvirtide became available for dispensing through all major pharmacies nationwide in April 2004. Prior to that time it was only accessible through a central registry and central mail order pharmacy to ensure adequate supply for demand.

### Cost Comparison

Medication/Dose	Cost <sup>^</sup>		
	CVS	Drug Emporium	RiteAid
Combivir <sup>®</sup>	720.99	652.52	632.75
Epivir <sup>®</sup>	338.99	295.42	289.00
Zerit <sup>®</sup>	356.99	314.68	292.83
Kaletra <sup>®</sup>	738.99	708.90	698.58
Sustiva <sup>®</sup>	466.99	433.66	402.16
Viracept <sup>®</sup>	762.99	722.66	702.58
Fuzeon <sup>®</sup>	Not available	1,846.00	2,189.99

<sup>^</sup>Pricing information represents cost to patient for a 30-day supply

### Contraindications

Enfuvirtide is contraindicated in patients who have a hypersensitivity to enfuvirtide, mannitol, sodium carbonate, sodium hydroxide, or hydrochloric acid.

### Special populations

Pregnancy: Pregnancy category B. No studies

have been performed in humans. Animal studies in rats and rabbits have shown no harm to the fetus.

Lactation: Studies have not been conducted in humans on the transfer of enfuvirtide into breast milk. Breast-feeding is not recommended while on enfuvirtide.

Pediatrics: Enfuvirtide has been studied in those age six and older. Adverse events reported were similar to those in adults.

Geriatrics: Enfuvirtide has not been studied in those over 65 years of age.

Hepatic impairment: Specific studies have not been conducted. No dosage change is required.

Renal impairment: Specific studies have not been conducted. No dosage adjustment needed.

Gender: The clearance of enfuvirtide is approximately 20% greater in males than females. No dosage adjustment is recommended.

Weight: Clearance increases with increased body weight in males and females. No dosage adjustment is recommended.

### Drug Interactions

Like most drugs with peptide structures, enfuvirtide has not been found to affect the metabolism of other drugs or have its metabolism altered by other agents. Enfuvirtide is not metabolized by the CYP3A4 system. Specifically no interactions were found with ritonavir, saquinavir, or rifampin.

### Common Adverse Drug Reactions

The most common adverse events are injection site reactions. Up to 98% of patients experienced pain, induration, erythema, pruritis, and bruising upon injection. Common systemic reactions include: diarrhea, fatigue, nausea and vomiting, and headache.

### Pharmacology

Mechanism of Action: Enfuvirtide inhibits fusion of HIV-1 and cell membranes by binding to glycoprotein on the viral envelope. This prevents the change in conformation necessary for the HIV-1 protein to bind with the host cell membrane.

Absorption/Distribution: After a single injection the median time to peak plasma concentration was approximately 8 hours. With continued twice daily

dosing the median time to peak concentration was 4 hours. Absorption is similar from the upper arm, anterior thigh, or abdomen. The volume of distribution is 5.5 L and the drug is 92% bound to plasma proteins.

**Metabolism/Elimination:** Studies have not been performed in humans to determine the mechanism of elimination. It is expected that enfuvirtide is broken down into amino acids and recycled by the body. The half-life of the drug is 3.8 hours. The estimated rate of clearance is 25 ml/h/kg if administered alone. If administered with other antiretroviral agents the estimated clearance is 30 ml/h/kg.

### Patient Information

1. Enfuvirtide is an antiretroviral medication used to treat HIV infection.
2. Tell your doctor or pharmacist if you are pregnant or there is a chance you may become pregnant or are breast-feeding. Also, inform your healthcare provider of all your medical conditions and medications.
3. Fuzeon is given as an injection in the upper arm, thigh, or abdomen. Rotate your injection site each time you use the drug.
4. The most common side effects are pain,

warmth, and bruising at the injection site. You may also experience diarrhea, nausea, vomiting, fatigue, or headache.

5. If you miss a dose of enfuvirtide take it as soon as you remember. If it is close to the time of your next dose, skip it and take the scheduled dose. Do not take two doses of the drug at the same time.
6. After you mix your medication use it immediately. If you do not, you can store it in the refrigerator for up to 24 hours.

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