

- Use of ACE inhibition alone initially reduces aldosterone levels, but a phenomenon of “aldosterone escape” occurs in long-term patients and aldosterone levels return to baseline⁸. It is not clear how this happens but it may be that angiotensin independent mechanisms of aldosterone production can occur⁸. One such mechanism occurs when potassium levels rise which subsequently stimulates aldosterone production⁸. Thus agents that specifically target aldosterone would appear to be of benefit in conditions where raised aldosterone levels can cause adverse cardiovascular effects⁷.

DOSING INFORMATION

- Doses of **eplerenone** should be administered with other standard therapies such as ACE inhibitors, angiotensin II antagonists and beta-blockers⁹.
- Treatment should be initiated at 25mg and then titrated up to the target dose of 50mg over 4 weeks as tolerated by the patient².
- It is not clear how quickly **eplerenone** should be initiated after an acute myocardial infarct but clinical trials initiated doses at between 3–14 days after myocardial infarct⁹.
- Doses are not affected by food and can be taken with or without food according to patient lifestyle².
- Peak blood levels are reached in 1.3 hours after dosing, the half-life is 4–6 hours and therapeutic levels are reached within 2 days of dosing².
- Kidney failure:
 - o No dosage adjustment is required in mild renal failure but in severe renal failure (creatinine clearance <30mL/min), blood levels increased by 24%¹. Thus, it is recommended that **eplerenone** not be administered to patients with moderate to severe renal failure (creatinine clearance<50mL/min)².
- Liver failure
 - o it is recommended that **eplerenone** not be administered to patients with severe liver failure².
- Elderly and paediatric populations
 - o There appeared to be no differences in the pharmacokinetics of **eplerenone** between children (2–16 years) and adults (18–65 years) when used for mild to moderate hypertension¹⁰.
- Serum potassium levels should be measured before **eplerenone** is started and then within 1 week and 1 month after starting therapy and then regularly after this time². Doses should be suspended if serum potassium is >=6.0mmol/L and restarted at a dose of 25mg every second day when levels fall below 5.5mmol/L². This is because aldosterone itself can increase potassium absorption and high potassium levels have been associated with fatal ventricular arrhythmias¹.

ADVERSE EFFECTS

- In the EPHEsus (**Eplerenone** Post-acute myocardial infarct Heart failure Efficacy and Survival Study) study of over 6000 patients, **eplerenone** was generally well-tolerated⁹. The study reported no significant difference between **eplerenone** and placebo in the proportion of patients experiencing 1 or more adverse effects (78.9% vs 79.5%)⁹.
- *Hyperkalaemia*
 - o Not unexpectedly, because of the role of aldosterone in excreting potassium, an aldosterone antagonist can increase potassium levels¹. Hyperkalaemia occurred more frequently than baseline if patients had a poorer kidney function⁹ In the EPHEsus trial, it was found that the hyperkalaemia that occurred with **eplerenone** was predictable, manageable and non-fatal⁹. It was found that patients with a creatinine clearance of 50ml/min or less (moderate to severe renal failure), the incidence of serious hyperkalaemia was 10.1% in the **eplerenone** group and 5.9% in the placebo group. Among patients with a creatinine clearance level of 50ml/min (mild renal failure) or more, the incidence of serious hyperkalaemia in the **eplerenone** group was 4.6% compared to the placebo group of 3.5%. Thus, **eplerenone** is contraindicated in patients with moderate to severe renal failure².
- *Gastrointestinal disorders*
 - o Gastrointestinal disorders (occurring at >1% in the EPHEsus trial) were more common with **eplerenone** than with placebo⁹. Diarrhoea and nausea were reported as occurring in 3% and 4% of patients respectively with other gastrointestinal effects of abdominal pain, constipation, dyspepsia and vomiting occurring much less frequently⁹.
- *Cardiovascular*
 - o Blood pressure in the **eplerenone** and placebo groups increased over the two years of the study but the blood pressure increase in the **eplerenone** group was significantly lower than the placebo group (5/3 mm Hg compared to 8/4 mm Hg)⁹. heart rate increase in the **eplerenone** group was also significantly lower than the placebo group (6 beats compared to 7 beats per minute)⁹. Thus, **eplerenone** appears to provide some protection in the deterioration of both blood pressure and heart rate.
- *Central nervous system*
 - o Patients were reported as having hypotension and dizziness (>1%)⁹. Patients should be warned that they could experience these effects and to be careful when rising from a sitting or lying position.

- *Endocrine and hormone abnormalities*
 - o Spironolactone, an inhibitor of aldosterone, was shown in the RALES trial that it improved the prognosis of severe heart failure patients when added to other therapies¹¹. Unfortunately, spironolactone can cause steroid related adverse effects such as breast enlargement, erectile dysfunction, and breast pain. Because of the selective nature of **eplerenone**, these effects were reported as not more than placebo⁹.

DRUG INTERACTIONS

- **Eplerenone** is significantly metabolised by the liver enzyme system CYP3A4¹. Thus drugs that inhibit this system can significantly raise blood levels of **eplerenone** and result in toxicity. Conversely drugs which can induce this enzyme system are likely to metabolise **eplerenone**, resulting in lower blood levels and loss of efficacy.

Drugs which inhibit CYP 3A4 enzymes (increased eplerenone blood levels and toxicity – hyperkalaemia, dizziness, hypotension, gastrointestinal disturbances)	Drugs which induce CYP 3A4 enzymes (decreased eplerenone blood levels and loss of efficacy)
CYP 3A4 inhibitors	CYP 3A4 inducers
Cimetidine (Tagamet)	Carbamazepine (Tegretol)
Ciprofloxacin (Ciproxin)	Phenytoin (Dilantin)
Clarithromycin (Klacid)	Pioglitazone (Actos)
Diltiazem (Cardizem)	St John's wort
Erythromycin (EES, Eryc)	
Fluconazole (Diflucan)	
Fluvoxamine (Luvox)	
Gestodene (in Diane, Brenda)	
Grapefruit juice	
Itraconazole (Sporanox)	
Ketoconazole (Nizoral)	
Nefazodone (Serzone)	
Norfloxacin (Noroxin)	
Norfluoxetine (Prozac)	

COMPARATIVE DATA

- Because **eplerenone** is the first drug in the group of aldosterone antagonists to be released there is no comparative data between **eplerenone** and other aldosterone antagonists for efficacy. Also, **eplerenone** was not used alone in the landmark EPHEsus trial but used in conjunction with other standard therapies.

- *Vs enalapril in measuring efficacy in regressing ventricle enlargement and blood pressure control*
 - o **Eplerenone** was as effective as enalapril in reducing the enlargement of the left ventricle and in controlling blood pressure (animal study)¹².
- *Vs enalapril in measuring efficacy in regressing ventricle enlargement and systolic blood pressure control*
 - o A combination of **eplerenone** and enalapril was more effective in reducing the enlargement of the left ventricle and in controlling systolic blood pressure than **eplerenone** alone (202 patients)¹³.
- *vs losartan in hypertension*
 - o **eplerenone** was more effective than losartan in reducing blood pressure in patients with low-renin hypertension (82 patients)¹⁴.

PLACE IN THERAPY

- Patients with acute MI who develop heart failure continue to have a worse outcome than those without heart failure¹. Even transient pulmonary congestion has been identified as an independent risk factor for death¹.
- Drugs that interrupt the renin-angiotensin-aldosterone system such as the ACE inhibitor and the All receptor antagonists have demonstrated beneficial effects in patients with post-myocardial infarct left ventricular systolic dysfunction and/or heart failure, as has the beta-blockers carvedilol, bisoprolol and sustained release metoprolol.
- In the VALiant (VALsartan In Acute myocardial iNfarction) study, no additional benefit was seen with the addition of valsartan to captopril in patients with post-myocardial infarct left ventricular systolic dysfunction and/or heart failure¹⁵. In contrast, the results of EPHEsus demonstrate that the outcome of these high-risk patients can be improved by the addition of the selective aldosterone blocker **eplerenone** to standard medical therapy⁹. **Eplerenone** significantly reduced all-cause mortality and the combined endpoint of cardiovascular mortality or first cardiovascular hospitalisation (primary endpoints) in patients with left ventricular systolic dysfunction and heart failure following acute myocardial infarct⁹. Amazingly the positive effect of **eplerenone** on all-cause mortality was seen within 30 days of starting treatment.
- A beneficial effect of **eplerenone** on secondary endpoints was also seen. In particular, the significant reduction in the secondary endpoint of cardiovascular mortality that occurred with **eplerenone** was attributed to a significant reduction in the risk of sudden death due to cardiac causes⁹.

CLINICAL TRIALS

- EPHESUS⁹
 - o In the EPHESUS trial (a randomised, double-blind, multi-centre study), patients who had experienced an acute myocardial infarct 3–14 days previously were randomised to either **eplerenone** 25mg (3319 patients) or placebo (3313 patients).
 - o At 4 weeks, patients could be increased to 50mg **eplerenone**. Patients were also receiving standard treatment which included ACE inhibitors, All receptor antagonists, beta-blockers, diuretics and statins.
 - o Compared to placebo, patients had a significant 15% reduction in all causes of mortality and a significant 13% reduction in a combined endpoint of cardiovascular mortality or hospitalisation for a cardiovascular event. The beneficial effects of **eplerenone** were seen within 30 days of initiation of therapy
 - o The reduction in cardiovascular mortality was largely due to a significantly lower incidence of sudden death from cardiac causes
 - o Significantly fewer **eplerenone** patients were hospitalised for heart failure compared to placebo and the mean length of hospital stay was considerably shorter
 - o **Eplerenone** had beneficial effects on mortality and morbidity in patients with a history of hypertension at baseline and in patients with diabetes with signs of heart failure.

WEB SITE

- A discussion of the landmark EPHESUS trial is available at:
<http://www.medscape.com/viewarticle/461245>
- Full prescribing information is available for Inspra at:
http://www.pfizer.com/pfizer/download/uspi_inspra.pdf

COMPILATION DATE

- 11th October 2005

REFERENCES

1. Keating GM, Plosker GL. **Eplerenone**: A review of its use in left ventricular systolic dysfunction and heart failure after acute myocardial infarction. *Drugs* 2004;64(23):2689–2707.
2. Inspra product information. Pfizer Australia Pty Ltd. West Ryde NSW. 20th June 2005.
3. Pfeffer MA, McMurray JV. Myocardial infarct: no one size fits all. *Circulation* 2002;105:2577–2579.
4. Vantrimpont P, Rouleau JL, Ciampi A et al. Two-year time course and significance of neurohormonal activation in the Survival and ventricular Enlargement (SAVE) study. *Eur Heart J* 1998;19:1552–1563.

5. Sica DA. Aldosterone receptor blockade: a therapy resurrected. *Heart Dis* 2003;5(2):85–88.
6. Moore TD, Nawarskas JJ, Anderson JR. **Eplerenone**: a selective aldosterone receptor antagonist for hypertension and heart failure. *Heart Dis* 2003; 5 (5): 354–63.
7. van de Wal RMA, Voors AA, Plokker HWM, van Gilst WH, van Veldhuisen DJ. New pharmacological strategies in heart failure. *Cardiovascular Drugs & Ther* 2004;18:491–501.
8. Stassen J, Lijnen P, Fagard R, et al. Rise in plasma concentration of aldosterone during long-term angiotensin II suppression. *J Endocrinol* 1981; 91: 457–65.
9. Pitt B, Remme W, Zannad F, et al. **Eplerenone**, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003 Apr 3; 348 (14): 1309–21.
10. Reid SE, Tolbert DS, Ferry J. The effect of age on the pharmacokinetic of **eplerenone**. *Pharmacotherapy* 2003; 23 (10): 1359.
11. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999 Sep 2; 341 (10): 709–17.
12. Fraccarollo D, Galuppo P, Schmidt I, Ertl G, Bauersachs J. Additive amelioration of left ventricular remodeling and molecular alterations by combined aldosterone and angiotensin receptor blockade after myocardial infarction. *Cardiovasc Res.* 2005;67(1): 97–105.
13. Pitt B, Reichek N, Willenbrock R, et al. Effects of **eplerenone**, enalapril, and **eplerenone**/enalapril in patients with essential hypertension and left ventricular hypertrophy: the 4E-left ventricular hypertrophy study. *Circulation.* 2003;108(15):1831–8.
14. Weinberger MH, White WB, Ruilope LM, et al. Effects of **eplerenone** versus losartan in patients with low-renin hypertension. *Am Heart J.* 2005;150(3):426–33.
15. Pfeffer MA, McMurray JJV, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; 349 (20): 1893–906.

National Prescribing Service believes that the New Drug Brief is a useful information source for pharmacists on new drugs. It provides valuable information that will help pharmacists critically assess the place of a new drug and ensure they are prepared to answer consumer questions about new drugs.

The New Drug Brief is an informational service provided by Gold Cross Products and Services Pty Ltd on behalf of the Pharmacy Guild of Australia. Tel 02 6270 1860 Fax 02 6273 8175 Web www.goldx.com.au

Gold Cross Products and Services Pty Ltd ('Gold Cross'), on behalf of the Pharmacy Guild of Australia ('Guild') has commissioned this Drug Brief (Drug Review) to provide information only for the benefit of health care professionals. While all care has been taken in compiling this Drug Brief, no responsibility is taken for the accuracy or correctness of the information. Should specific advice on any drug be required, specific enquiries should be made of the respective pharmaceutical manufacturer. To the full extent permitted by law, Gold Cross, the Guild and the author expressly disclaim all liability and responsibility to any person for any loss, damage, cost, expense or claim whatsoever arising directly or indirectly from the supply of, use of or reliance on, in whole or in part, this publication.

The New Drug Brief



Endorsed Supplier

Eplerenone (Inspra)

CLINICAL USE

- **Eplerenone** is the first release from a new class of drugs called selective aldosterone blockers which have been trialled in heart failure and hypertension¹.
- In heart failure and after a myocardial infarct, the renin-angiotensin-aldosterone system becomes activated and is associated with a cascade of events that can lead to cardiovascular death¹. These events include accumulation of collagen in non-infarcted heart muscle (reactive fibrosis), overgrowth of heart muscle and an increase in the size of the left ventricle¹. The beneficial effects of ACE inhibition on mortality in patients who have heart failure or who have suffered a heart attack are well established². Attention has now turned to discovering the benefits of inhibiting the aldosterone activation of the renin-angiotensin-aldosterone system by use of this new class of aldosterone antagonists.
- **Eplerenone** is used to reduce the risk of cardiovascular death in combination with standard treatments (such as ACE inhibitors, Angiotensin II blockers and beta-blockers) in patients who have evidence of heart failure within 3–14 days of an acute myocardial infarct³.

MECHANISM OF ACTION

- Elevated aldosterone levels have been linked to the development of heart failure post-myocardial infarct⁴. It had been thought that aldosterone action was wholly in the kidneys where it promoted sodium and water reabsorption and the excretion of potassium⁵. However, it is now known that there are aldosterone receptors in the heart, blood vessels and brain⁵. It is at these sites that aldosterone excess can cause adverse effects on the cardiovascular system including enlargement of the ventricle, fibrosis of heart muscle and activation of the sympathetic nervous system⁶. It is now well established that elevated aldosterone levels in patients with congestive heart failure is associated with increased mortality⁷.