### Emerging Drug List

#### Eplerenone for the Treatment of Hypertension

<table>
<thead>
<tr>
<th>Generic (Trade Name):</th>
<th>Eplerenone (Inspra&lt;sup&gt;TM&lt;/sup&gt;)&lt;sup&gt;1&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>Manufacturer:</td>
<td>Pharmacia (Pfizer)</td>
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<tr>
<td>Indication:</td>
<td>Eplerenone was approved by the US Food and Drug Administration (FDA) for the treatment of hypertension (either as single agent therapy or in combination with other antihypertensive agents).&lt;sup&gt;2&lt;/sup&gt; Eplerenone has also been evaluated for the treatment of congestive heart failure.&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Current Regulatory Status:</td>
<td>The US FDA approved Eplerenone on September 27, 2002.&lt;sup&gt;2&lt;/sup&gt; The only other country where it has been submitted for approval is in Japan. It has not been launched in the US.&lt;sup&gt;3&lt;/sup&gt;</td>
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<td>Description:</td>
<td>Eplerenone is structurally similar to spironolactone.&lt;sup&gt;1&lt;/sup&gt; Eplerenone is a selective aldosterone blocker, unlike spironolactone which is a non-selective aldosterone antagonist. Both eplerenone and spironolactone are a competitive antagonist of aldosterone at the mineralcorticoid receptors. Eplerenone therapy is initiated at a dose of 50 mg daily, which can be increased to 50 mg twice daily if response is inadequate after four weeks.&lt;sup&gt;1&lt;/sup&gt;</td>
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<td>Current Treatment:</td>
<td>Agents that are currently marketed in Canada for the treatment of hypertension include diuretics, beta-blockers, calcium channel blockers, alpha adrenergic blockers, vasodilators, centrally acting antiadrenergic agents, angiotensin converting enzyme inhibitors (ACEI), and angiotensin type 2 receptor blockers (ARB).</td>
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<tr>
<td>Cost:</td>
<td>No cost information is available for eplerenone.</td>
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</table>
| Evidence:            | The antihypertensive effects of eplerenone have been evaluated in at least four controlled trials involving over 1,400 subjects.<sup>4</sup> One trial compared eplerenone 50, 100 or 400 mg/day to spironolactone 50 mg bid or placebo in 417 hypertensive subjects over an eight week period.<sup>4</sup> Mean reductions in systolic blood pressure (SBP) ranged from 6.2 to 16.1 mmHg and in diastolic blood pressure (DBP) ranged from 4.1 to 9.0 mmHg (depending on the dose of eplerenone). Mean reductions in SBP and DBP with spironolactone were 15.8 and 8.7 mmHg, respectively. Another trial randomized 551 hypertensive patients to eplerenone 50 to 200 mg/day, losartan 50 to 100 mg/day, or placebo for 16 weeks (doses were initiated at the minimum range and increased at four week intervals).<sup>5</sup> At 16 weeks the mean decrease in DBP was 10.3, 6.9 and 5.3 mmHg for eplerenone, losartan, and placebo, respectively (p<0.001 for eplerenone vs. losartan or placebo). There was also a significant reduction in SBP (i.e. 12.8, 6.4 and 3.3 mmHg for eplerenone, losartan and placebo, p<0.001 eplerenone
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Eplerenone for the Treatment of Hypertension

vs. losartan or placebo). The number of patients who required dose escalation to 200 mg of eplerenone was not presented, hence the optimal dose of eplerenone cannot be determined from these results.

A third study evaluated the potential benefits of adding eplerenone (50 to 100 mg/day) or placebo to established, fixed dose ACEI or ARB therapy over eight weeks in 341 patients.6 In the ACEI group, the addition of eplerenone significantly reduced SBP compared to placebo (i.e. 13.4 vs. 7.5 mmHg, p=0.002), but no difference in DBP. In the ARB group, eplerenone significantly reduced in both SBP and DBP compared to placebo (i.e. 16.0 vs. 9.2 mmHg SBP p=0.001, and 12.7 vs. 9.3 mmHg DBP p=0.004).

A fourth study compared eplerenone 200 mg/day, enalapril 40 mg/day, a combination of eplerenone 200 mg/day with enalapril 10 mg/day or placebo in 153 hypertensive patients with left ventricular hypertrophy for nine months.7 The decrease in SBP was 24.7, 23.8 and 28.7 mmHg for eplerenone, enalapril, and the combination, respectively (p<0.05 for eplerenone vs. combination only). The mean reduction in left ventricular mass (based on magnetic resonance imaging) was 14.5, 19.7 and 27.2 for eplerenone, enalapril and the combination, respectively (p<0.05 for eplerenone vs. combination only).

The incidence of adverse effects and discontinuation due to adverse effects were similar between eplerenone and placebo. Adverse effects that were reported with eplerenone at a slightly higher incidence than placebo include diarrhea, abdominal pain, coughing, dizziness, fatigue, gynecomastia and flu influenza-like symptoms. Laboratory abnormalities reported with eplerenone include hypercholesterolemia, hypertriglyceridemia, albuminuria; and elevated potassium, liver function tests, and creatinine levels.

Initial data, available only in abstract form, indicate eplerenone is effective at reducing blood pressure and may reduce left ventricular mass in patients with left ventricular hypertrophy. Insufficient details of trial design and methodology are available to assess the validity of these studies. It should be noted that the dose of eplerenone in the hypertension studies was increased to a maximum of 200 to 400 mg/day, but the maximum FDA approved dose in the proposed monograph is only 100 mg/day.

Eplerenone has only been evaluated in mild to moderate hypertension and data from patients with severe hypertension are lacking. Nevertheless, the true value of any antihypertensive agent stems solely from its ability to reduce morbidity and mortality, not its effect on surrogate outcomes.8 Until these data are available, agents with proven effectiveness should remain the mainstay of therapy.

References:

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EPLERENONE FOR THE TREATMENT OF HYPERTENSION


This series highlights medical technologies that are not yet in widespread use in Canada and that may have a significant impact on health care. The contents are based on information from early experience with the technology; however, further evidence may become available in the future. These summaries are not intended to replace professional medical advice. They are compiled as an information service for those involved in planning and providing health care in Canada.

These summaries have not been externally peer reviewed.

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