CEDAC FINAL RECOMMENDATION

EPLERENONE
(Inspra – Pfizer Canada Inc.)
Indication: Heart Failure Post Myocardial Infarction

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that eplerenone not be listed.

Reason for the Recommendation:
The Committee felt that the most appropriate comparator for eplerenone was spironolactone because both are aldosterone antagonists and they have the same mechanism of action. There are no double blind randomized controlled trials comparing spironolactone with eplerenone in patients with heart failure post myocardial infarction. The cost-effectiveness of eplerenone compared with spironolactone is unknown.

Background:
Eplerenone has a Health Canada indication to reduce the risk of mortality following myocardial infarction, as an adjunct to standard therapy in clinically stable patients who have evidence of heart failure and left ventricular systolic dysfunction (ejection fraction ≤ 40 %). It is an aldosterone antagonist and is available as 25 mg and 50 mg tablets. The recommended starting dose of eplerenone is 25 mg once daily, which can be increased to a maximum dose of 50 mg once daily. Eplerenone should not be initiated if initial serum postassium is > 5 mmol/L and dose adjustments are recommended based on monitoring of serum potassium levels.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review: a systematic review of double-blind randomized controlled trials of eplerenone and a critique of the manufacturer's pharmacoeconomic evaluation.

Clinical Trials
The CDR systematic review included one large manufacturer-sponsored, double-blind, randomized, placebo-controlled trial (EPHESUS) of 6,632 patients. The trial included patients

who had experienced a myocardial infarction within the past three to 14 days, had a left ventricular ejection fraction (LVEF) of ≤ 40%, and had either diabetes or symptoms of heart failure. Eplerenone was initiated at a dose of 25 mg once daily for four weeks, and was increased to 50 mg once daily if the serum potassium was below 5 mmol/L. The dose was adjusted based on serum potassium levels thereafter. Optimal medical therapy was continued (87% taking angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, 82% taking beta-blockers, 65% taking loop diuretics), however, potassium-sparing diuretics including spironolactone were prohibited during the trial. Patients with serum creatinine > 2.5 mg/dL were excluded as were patients with serum potassium concentration > 5.0 mmol/L. Approximately 70% of patients were male.

The trial was designed to continue until there were 1,012 deaths, at which point the efficacy of eplerenone would be evaluated. At the time this point was reached, the majority of patients in each treatment group had participated in the study for at least 451 days. Approximately 15% of patients withdrew during the trial. Withdrawals and withdrawals due to adverse events were similar between eplerenone and placebo. There were very few patients, approximately 1%, lost to follow-up.

No studies evaluating active comparators such as spironolactone were identified that met the inclusion criteria for the systematic review.

Outcomes

The co-primary endpoints of EPHESUS were time to death from any cause and the composite of time to death from cardiovascular causes or first hospitalization for a cardiovascular event.

In addition, the Committee discussed the following outcomes included in the CDR systematic review: all-cause hospitalizations, change in electrolytes, change in renal function, quality of life and adverse events.

Results

Efficacy or Effectiveness

- There was a statistically and clinically significant reduction in all-cause mortality with eplerenone compared with placebo (absolute risk reduction 3%, relative risk reduction 15%, P = 0.009).
- Eplerenone significantly increased time to death from any cause (hazard ratio [HR]: 0.85, 95% confidence interval [CI]: 0.75 to 0.96, P = 0.008) and time to death from cardiovascular causes or hospitalization for first cardiovascular event (HR: 0.87, 95% CI: 0.79 to 0.95, P = 0.002) compared with placebo. The majority of the clinical effect was observed within the first 30 days of treatment.
- Eplerenone significantly reduced deaths due to cardiovascular causes compared to placebo (12% versus 15%, P = 0.003, relative risk reduction of 17%, P = 0.005).
- There were no statistically significant differences between eplerenone and placebo in all-cause hospitalizations or cardiovascular-related hospitalizations.
- There were no clear differences in quality of life between eplerenone and placebo. Interpretation of these results is limited as this outcome was assessed in only one-third of patients and data are too incomplete to draw conclusions.

Harms (Safety and Tolerability)

- There was a statistically significant increase from baseline in serum creatinine for eplerenone compared with placebo (6.9 umol/L versus 3.9 umol/L, P < 0.001).
- Significantly more eplerenone-treated patients experienced serious hyperkalemia, defined as a serum potassium ≥ 6 mmol/L (5% versus 4%, P = 0.002), compared with placebo.
- The incidence of gynecomastia was similar between eplerenone and placebo groups (< 1% each). Two eplerenone patients and one placebo patient withdrew due to gynecomastia.

Cost and Cost-Effectiveness

At recommended doses, the daily cost of eplerenone (25 mg or 50 mg, $2.49) is greater than spironolactone (25 mg, $0.07).

The manufacturer submitted a cost utility analysis of eplerenone plus standard therapy (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, diuretics, statins, coronary reperfusion therapy) compared to standard therapy alone over a patient lifetime time horizon. The duration of treatment with eplerenone was assumed to be three years, which was consistent with the duration of the EPHESUS trial, while benefits in survival were extrapolated over a patient's lifetime. Resource utilization (hospitalizations, major outpatient diagnostic procedures and tests, emergency room visits, concomitant medication, use of eplerenone) and utility values were obtained from the EPHESUS trial, while life expectancy was predicted based on a model developed using a provincial health database from Saskatchewan. The manufacturer reported that eplerenone plus standard therapy versus standard therapy alone, was associated with an incremental cost per life year of $13,431 and an incremental cost per quality-adjusted life year (QALY) of $19,902. The economic model was robust to changes in most input parameters. The duration of eplerenone therapy over a longer period of time, and similar time horizons for costs and benefits, could not be evaluated using the manufacturer's model.

The Committee felt that the most relevant comparator for this analysis was spironolactone, which was not considered by the manufacturer. Consequently, they felt that the cost effectiveness of eplerenone compared with spironolactone is unknown.

Other Discussion Points:

- There are no well designed randomized controlled trials comparing eplerenone with spironolactone. The Committee discussed the results of the RALES study, a large randomized controlled trial that compared spironolactone with placebo in patients with heart failure. Patients included in RALES had more advanced heart failure than the patients in EPHESUS (baseline LVEF 25% versus 33%, respectively) and their heart failure was not required to be post-myocardial infarction. Results of the RALES study demonstrated that compared with placebo, spironolactone improved mortality. Incidence of gynecomastia was increased with spironolactone compared with placebo but discontinuation because of gynecomastia was low. The incidence of serious hyperkalemia was similar between the two groups.
- The Committee noted that the inclusion criteria of the RALES trial did not exclude patients who could have also met the inclusion criteria for EPHESUS. The Committee discussed that they would be interested in being able to identify patients included in RALES who had a LVEF < 40% and who had a myocardial infarction 14 days prior to enrolment.

- Both eplerenone and spironolactone are aldosterone antagonists that inhibit binding of endogenous aldosterone to mineralocorticoid receptors and it is this mechanism of action that is thought to be responsible for the survival benefit observed with both eplerenone and spironolactone.
- Eplerenone has lower affinity for androgen and progesterone receptors compared with spironolactone, which may reduce the incidence of gynecomastia but this difference would not be expected to influence the survival benefit.
- The Committee noted that the risk of serious hyperkalemia is likely higher in actual practice than what was observed in EPHESUS, given that patients in EPHESUS had to have normal renal function and potassium levels at baseline.

CEDAC Members Participating:
September 16th, 2009: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Michael Evans, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

November 18th, 2009: Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Ken Bassett, Dr. Bruce Carleton, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:
September 16th, 2009: None.

November 18th, 2009: Dr. Michael Allan, Dr. Lindsay Nicolle.

Conflicts of Interest:
One CEDAC member reported receiving institutional funding through Pfizer but no direct payments were received and funding was not related to eplerenone, therefore, this did not preclude participation in the discussion and voting.

One CEDAC member reported a conflict of interest and did not participate in the vote.

About This Document:
CEDAC provides formulary listing recommendations to publicly funded drug plans.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CEDAC made its recommendation. An overview of these reviews, as well as a plain language version of this document are posted on the CADTH website when available.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the CDR Confidentiality Guidelines.

The CEDAC Final Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

CADTH is not legally responsible for any damages arising from the use or misuse of any information contained in or implied by the contents of this document. The statements, conclusions, and views expressed herein do not necessarily represent the view of Health Canada or any provincial, territorial, or federal government or the manufacturer.