CDEC FINAL RECOMMENDATION

EPLERENONE
(Inspra — Pfizer Canada Inc.)
New indication: NYHA Class II Heart Failure

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that eplerenone not be listed at the submitted price for patients with New York Heart Association (NYHA) class II systolic chronic heart failure.

Reasons for the Recommendation:

1. Given the limitations identified with the manufacturer's pharmacoeconomic model, CDEC noted that the cost-effectiveness of eplerenone could not be properly assessed.
2. In one double-blind randomized controlled trial (RCT), eplerenone was shown to reduce the risk of death from cardiovascular (CV) causes and first hospitalization for heart failure compared with placebo in patients with NYHA class II systolic chronic heart failure.

Of Note:
Based on a review of the clinical evidence, CDEC noted that a reduced price would increase the likelihood of a recommendation to "list" or "list with clinical criteria and/or conditions."

Background:
Eplerenone has a Health Canada indication as an adjunct to standard therapy to reduce the risk of CV mortality and hospitalization for heart failure in patients with NYHA class II systolic chronic heart failure and left ventricular systolic dysfunction. Previously, eplerenone was granted an indication by Health Canada as an adjunct to standard therapy to reduce the risk of mortality and hospitalization for heart failure following myocardial infarction in clinically stable adult patients who have evidence of heart failure and left ventricular systolic dysfunction (ejection fraction ≤ 40%). Eplerenone is available as 25 mg and 50 mg tablets. The recommended starting dose is 25 mg once daily, titrated to a target dose of 50 mg once daily over four weeks, according to serum potassium level.

Submission History:
Eplerenone has been previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for reducing 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%) and received a recommendation of "do not list" (see Notice of CEDAC Final Recommendations, November 25, 2009).

Summary of CDEC Considerations

CDEC considered the following information prepared by Common Drug Review (CDR): a systematic review of RCTs of eplerenone, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Patient Input Information

The following is a summary of information provided by one patient group that responded to the CDR call for patient input:

- Heart failure is one of the leading causes of hospitalization and death for the elderly in Canada.
- In addition to a complex treatment regimen, heart failure is often associated with a range of comorbidities, frequent hospitalizations, and an unpredictable course of disease.
- Commitment and ability to actively manage the condition are integral for successful treatment.
- Caregiver involvement may be significant as some patients may be unable to handle common tasks that they once could perform such as shopping, housekeeping, bathing, or dressing. The support from caregivers may need to increase over time, often adversely impacting the caregiver's health (e.g., physical, psychiatric morbidities).
- Patients unable to care for themselves often have a lower quality of life.

Clinical Trials

The CDR systematic review included one event-driven, double-blind, placebo-controlled RCT (N = 2,737). The Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) randomized (1:1) participants to either eplerenone 25 mg once daily or placebo; after four weeks, the dose of eplerenone was increased to 50 mg once daily, if indicated by serum potassium level. Originally designed to run over approximately 48 months, the trial was stopped early (median of 21 months) due to meeting pre-specified stopping rules for the primary efficacy outcome.

Outcomes

Outcomes were defined a priori in the CDR systematic review protocol. Of these, CDEC discussed the following:

- CV mortality — defined as death due to heart failure, myocardial infarction, cardiac arrhythmia, stroke/cerebrovascular accident, or other cardiovascular cause.
- Heart failure hospitalization — defined as an overnight stay, or longer, in a hospital environment (emergency room, observation unit or in-patient care, or similar facility including admission to a day care-facility) with a discharge diagnosis that included a CV reason for hospitalization.
- Composite end point of CV mortality or first hospitalization for heart failure.
- All-cause mortality and all-cause hospitalization.
- Serious adverse events, total adverse events, withdrawals due to adverse events.

The primary efficacy outcome in EMPHASIS-HF was a composite of death from CV causes or first hospitalization for heart failure.

Efficacy

- The composite of CV death or first heart failure hospitalization occurred in 249 (18.3%) patients in the eplerenone group compared with 356 (25.9%) patients in the placebo group; this translated into a statistically significant difference in the time to the primary end point favouring eplerenone (hazard ratio [HR]: 0.63; 95% confidence interval [CI], 0.54 to 0.74).
- CV mortality occurred in 147 (10.8%) patients in the eplerenone group compared with 185 (13.5%) in the placebo group; the difference in time to event was statistically significant favouring eplerenone (HR: 0.76; 95% CI, 0.61 to 0.94).
- The product monograph indicates that a benefit on CV mortality was not observed in patients aged ≥ 75 years. In the trial, the results for this subgroup were reported as 51 (15.5%) CV deaths in the eplerenone group compared with 51 (15.6%) in the placebo group with an associated HR of 0.98 (95% CI, 0.67 to 1.45).
- Heart failure hospitalization occurred in 164 (12.0%) patients in the eplerenone group compared with 253 (18.4%) in the placebo group; the difference in time to event was statistically significant favouring eplerenone (HR: 0.58; 95% CI, 0.47 to 0.70).
- All-cause mortality occurred in 171 (12.5%) patients in the eplerenone group compared with 213 (15.5%) in the placebo group; the difference in time to event was statistically significant favouring eplerenone (HR: 0.76; 95% CI, 0.62 to 0.93).
- All-cause hospitalization occurred in 408 (29.9%) patients in the eplerenone group compared with 491 (35.8%) in the placebo group; the difference in time to event was statistically significant favouring eplerenone (HR: 0.77; 95% CI, 0.67 to 0.88).
- The following subgroups identified as being of interest in the systematic review protocol were examined in the trial: left ventricular ejection fraction (< 30% and ≥ 30%), age (< 75 years and ≥ 75 years), baseline estimated glomerular filtration rate, diabetes, and geographical region; results were consistent with those of the main trial findings in that eplerenone was favoured compared with placebo on the primary composite outcome.

Harms (Safety and Tolerability)

- Adverse events occurred with similar frequency in the eplerenone (72.0%) and placebo (73.6%) groups. Except for cardiac failure (eplerenone: 17.4% versus placebo: 21.8%) and hyperkalemia (eplerenone: 8.0% versus placebo: 3.7%), individual adverse events occurred at low frequencies in both groups without particular patterns of concentration.
- Serious adverse events — except cardiac failure (eplerenone: 13.8% versus placebo: 17.8%) — were infrequent and unremarkable in distribution, including the frequencies of renal impairment (eplerenone: 1.8% versus placebo: 1.3%), hyperkalemia (eplerenone: 1.2% versus placebo: 0.5%), and hypotension (eplerenone: 0.2% versus placebo: 0.4%).
- Withdrawals due to adverse events (WDAEs) occurred in 188 (13.8%) patients in the eplerenone group and 222 (16.2%) in the placebo group while temporary discontinuations or dose reductions due to adverse events occurred in 229 (16.8%) and 185 (13.5%) patients, respectively. The most commonly reported reason for WDAE was hyperkalemia (eplerenone: 1.1% versus placebo: 0.9%).

Cost and Cost-Effectiveness

The manufacturer stated that a cost-utility analysis was conducted in patients with NYHA class II chronic heart failure and left ventricular systolic dysfunction, using eplerenone once daily as an adjunct to standard optimal therapy (angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker, and a beta blocker) compared with standard optimal therapy alone, with the base case from the health-care system perspective. The analysis was stated to

have been conducted using a discrete event simulation (DES) to populate an excel model; however, CDR did not have access to the initial DES and, therefore, could not verify several inputs and the mechanics of the submitted pharmacoeconomic model. The manufacturer stated that patients could have the following events and remain in the model: CV hospitalization, heart failure hospitalization, atrial fibrillation, adverse events, and discontinuation. Patients were removed from the model due to CV mortality, non-CV mortality, and device implantation. Efficacy data were derived from patient-level data from the EMPHASIS-HF clinical trial. Utility values were obtained from a subpopulation of the earlier Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, which was conducted in patients with heart failure following myocardial infarction. The model was stated to have a lifetime time horizon. The manufacturer reported that eplerenone as an adjunct to standard optimal therapy was associated with an incremental cost per quality-adjusted life-year (QALY) of $7,347 compared with standard optimal therapy alone.

A key limitation with the manufacturer's pharmacoeconomic evaluation was the lack of transparency regarding the methods and how data were included in the model. The structure of the model limited the independent review and verification by CDR. In addition, the quality and appropriateness of the data used within the model, specifically the time to event estimates, were based on very small numbers of events which raised concern regarding the data analysis and interpretation. While other limitations were noted and assessed by CDR (such as movement among NYHA classes, how subsequent hospitalizations were modelled, capturing device implementation as an absorbing state; and, basing utility values on a subset of the EPHESUS trial population), the manufacturer's pharmacoeconomic model did not permit full assessment of the uncertainty of the manufacturer's submission. CDR reviewers attempted to obtain clarification from the manufacturer around the above limitations; however, the responses led to greater concerns with the model. Consequently, the likely cost-effectiveness of eplerenone could not be determined.

At the submitted price of $2.61 per tablet (25 mg or 50 mg), the annual cost of eplerenone is $955.

Other Discussion Points:

CDEC noted the following:

- CDEC felt that the clinical data reported in the EMPHASIS-HF trial was strong; however, because of the limitations noted with the manufacturer's pharmacoeconomic submission, CDR was unable to fully evaluate the cost-effectiveness of eplerenone and the committee could not be confident that eplerenone is cost-effective at the submitted price.
- Since the EMPHASIS-HF was stopped early for efficacy reasons, the risk of adverse events conferred by eplerenone in the population studied may be underestimated as a consequence of the shorter period during which patients were exposed to treatment.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- The EMPHASIS-HF did not assess the effect of eplerenone on the quality of life of patients with chronic heart failure.

- There are no well-designed comparative trials comparing spironolactone with eplerenone in patients with NYHA class II systolic chronic heart failure and left ventricular systolic dysfunction.

CDEC Members:
Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, and Dr. Adil Virani.

Regrets:
January 15, 2014: None
April 17, 2014: One CDEC member could not attend the meeting.

Conflicts of Interest:
None

About This Document:
CDEC provides formulary listing recommendations or advice to CDR participating drug plans. CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC deliberated on a review and made a recommendation or issued a record of advice. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

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

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