Common Drug Review

Pharmacoeconomic Review Report

October 2014

Drug	Eplerenone (Inspra) (25 mg tablet and 50 mg tablet)
Indication	As an adjunct to standard therapy to reduce the risk of cardiovascular mortality and hospitalization for heart failure in patients with NYHA class II systolic chronic heart failure and left ventricular systolic dysfunction
Listing request	As per indication
Manufacturer	Pfizer Canada Inc.

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The report contains an evidence-based clinical and/or pharmacoeconomic drug review, based on published and unpublished material, including manufacturer submissions; studies identified through independent, systematic literature searches; and patient-group submissions. In accordance with *CDR Update — Issue 87*, manufacturers may request that confidential information be redacted from the CDR Clinical and Pharmacoeconomic Review Reports.

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ABBREVIATIONS

ACE	angiotensin-converting enzyme
AE	adverse event
AF	atrial fibrillation
ARB	angiotensin receptor blockers
AWMSG	All Wales Medicines Strategy Group
BB	beta blocker
CADTH	Canadian Agency for Drugs and Technologies in Health
CEDAC	Canadian Expert Drug Advisory Committee
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CDR	Common Drug Review
CRT	cardiac resynchronization therapy
CUA	cost-utility analysis
CV	cardiovascular
EF	ejection fraction
eGFR	epidermal growth factor receptor
EMPHASIS-HF	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
EPHESUS	Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study
HF	heart failure
HTA	health technology assessment
ICD	implantable cardioverter-defibrillator
ICER	incremental cost-effectiveness ratio
ICUR	incremental cost-utility ratio
INESSS	L'Institut National d'Excellence en Santé et en Services Sociaux
LVEF	left ventricular ejection fraction
LY	life-year
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
QALY	quality-adjusted life-year
PE	pharmacoeconomic
RAMQ	Régie de l'assurance maladie du Québec
SE	standard error
SMC	Scottish Medicines Consortium

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Eplerenone (Inspra)
Study Question	In this evaluation, eplerenone as an adjunct treatment to standard optimal therapy is compared with standard optimal therapy alone, which includes an ACE inhibitor (and/or an ARB) and a BB in order to reduce the risk of hospitalization and mortality in adult patients with NYHA class II (mild symptoms) chronic heart failure and left ventricular systolic dysfunction.
Type of Economic Evaluation	Cost-utility analysis Cost-effectiveness analysis
Target Population	Adult patients with NYHA class II (mild symptoms) chronic heart failure and left ventricular systolic dysfunction
Treatment	Eplerenone plus standard optimal therapy
Outcome(s)	QALYs LYs
Comparators	Standard optimal therapy alone, comprising an ACE inhibitor (and/or an ARB) and a BB
Perspective	Ministry of Health perspective
Time Horizon	Lifetime (undefined)
Manufacturer's Results (Base Case)[a]	$7,347 per QALY gained $5,490 per LY gained
Key Limitations and CDR Estimate(s)	• A key limitation with the manufacturer's economic evaluation was the lack of transparency regarding the methods and how data were included in the model. • Another major limitation relates to the quality and appropriateness of the data used within the model. Specifically, time to event estimates were based on very small numbers of events, which raises concern regarding the data analysis. • CDR also queried a number of the assumptions that were stated in the manufacturer's PE Review Report. ▪ Continued treatment effect beyond second hospitalization ▪ Patients can receive only one implantable device ▪ Appropriateness of the utility values ▪ The use of eplerenone in patients who have progressed to NYHA class III and IV disease appears to have occurred, which is outside the indication. • Given that CDR could not verify the mechanics of the model and was limited in the ability to conduct reanalyses (e.g., independent review and verification, ability to make alterations to the model structure base upon clinical feedback), the cost-effectiveness of eplerenone under these scenarios could not be assessed.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BB = beta blocker; CDR = Common Drug Review; LY = life-year; NYHA = New York Heart Association; PE = pharmacoeconomic; QALY = quality-adjusted life-year.
[a]Results presented in the manufacturer's PE evaluation report. Neither CDR nor the manufacturer could reproduce these results. The manufacturer indicated that this was due to new data in the patient input sheet of the model.

EXECUTIVE SUMMARY OF THE PHARMACOECONOMIC SUBMISSION

Background

Eplerenone is indicated as adjunct to standard optimal therapy in patients with New York Heart Association (NYHA) class II systolic chronic heart failure (HF) and left ventricular systolic dysfunction. Eplerenone is an oral tablet administered 25 mg daily for the first four weeks, then increasing to the recommended dose of 50 mg daily. The manufacturer submitted a price of $2.6137 per tablet (either 25 mg or 50 mg), or $2.61 daily.

Eplerenone was previously reviewed by the Common Drug Review (CDR) in 2009 for use in clinically stable adult patients who have evidence of HF and left ventricular systolic dysfunction (ejection fraction [EF] ≤ 40%) following myocardial infarction. At this time, the Canadian Expert Drug Advisory Committee (CEDAC) recommended that eplerenone not be listed.[1]

Summary of economic analysis

The manufacturer stated that a cost-utility analysis was conducted using a discrete event simulation, which was then used to populate an Excel workbook.[2] The target population was the Health Canada indication. Given the lack of transparency of the submitted model (CDR reviewers were not able to view the source discrete simulation model and test various assumptions within the model), the model could not be effectively assessed by CDR. The manufacturer indicated that on entry to the model, patients could have events that allowed the patient to remain in the model (cardiovascular [CV] hospitalization, HF hospitalization, atrial fibrillation, adverse events, discontinuation), or events that removed them from the model (CV mortality, non-CV mortality, device implantation). The manufacturer stated that patient-level data from the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial were used to determine risk equations for events by fitting a distribution to the time to each event, with these distributions providing a basis for the simulated model cohort. Cost elements included in the study were drug costs, hospitalization, adverse events and device implantation costs, and disease management and monitoring costs. Primary utility values were obtained from a subpopulation of the earlier Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial, with various alterations to these values as well as disutility values (from a variety of sources) stated to have been used to determine overall utility values for each patient throughout the model. The time horizon for the analysis was set at the patient lifetime; however the expected life expectancy of these patients has not been presented.

Results of manufacturer's analysis

The results of the manufacturer's economic evaluation indicated that eplerenone plus standard optimal therapy was more costly than standard optimal therapy alone ($51,378 versus $44,576), but led to more quality-adjusted life-years (QALYs; 5.29 versus 4.36), resulting in an incremental cost-utility ratio of $7,347 per QALY gained.

Interpretations and key limitations

The key limitations with the manufacturer's economic evaluation are:

- **Lack of transparency with the model:** The lack of transparency and the ability of CDR to independently assess the model logic did not allow CDR to verify the model nor conduct reanalyses. CDR listed a number of limitations in the report, as it is unclear whether these were appropriately included in the model by the manufacturer.

- **Patients included in the modelled population:** The manufacturer did not specify what happens to patients once they move out of NYHA class II disease within the model. Although the manufacturer acknowledged that patients did move between classes throughout the trial, this was not included in the model. Based on CDR clinical feedback, it was suggested that NYHA classes are subjective and transient states, and thus modelling other NYHA classes and including spironolactone would have been an appropriate scenario analysis. The CDR Clinical Review Report found uncertainty regarding the extent to which the studied patients are reflective of the typical NYHA class II HF patient population seen in clinical practice.
- **Modelling and assumptions for subsequent hospitalizations:** Given the lack of transparency with the submitted model, it is unclear what approach was used to model subsequent events (hospitalizations and adverse events). The validity of assuming treatment effects beyond two hospitalizations, given the small number of events in the clinical trial, especially as subsequent hospitalizations were not an established end point, was also questioned. The inclusion of patients with multiple subsequent hospitalizations may reflect patients who are no longer in class II and may have various comorbidities, potentially overestimating the benefit of eplerenone.

Other limitations are presented in the Discussion section.

Results of Common Drug Review analysis

CDR analyses were not conducted, given the issues with transparency and the ability to run analyses of interest independently.

Conclusions

Although CDR was unable to assess the manufacturer's economic evaluation to determine the cost-effectiveness of eplerenone, the CDR Clinical Report indicates that eplerenone appears to reduce the number of initial hospitalizations for patients with NYHA class II HF and left ventricular ejection fraction ≤ 35%. At the submitted price, eplerenone costs $2.61 daily (25 mg and 50 mg), or approximately $955 annually.

REVIEW OF THE PHARMACOECONOMIC SUBMISSION

1. INTRODUCTION

1.1 Study question

"… to assess the cost-effectiveness of eplerenone (Inspra) as an adjunct to standard therapy to reduce the risk of cardiovascular mortality and hospitalization for heart failure in patients with NYHA class II systolic chronic heart failure and left ventricular systolic dysfunction … Eplerenone is assessed as an adjunct to standard optimal therapy and compared to standard optimal therapy alone, which includes an ACE inhibitor (and/or an ARB) and a beta blocker."

(Manufacturer's Pharmacoeconomic Submission, page 16.)[2]

1.2 Treatment

Eplerenone as an adjunct to standard optimal therapy. The recommended dosage for eplerenone is 25 mg daily, subsequently increased to a maximum of 50 mg daily after four weeks, based on patient tolerance.

1.3 Comparators

The submitted comparator was standard optimal therapy alone, which includes an angiotensin-converting enzyme (ACE) inhibitor (and/or an angiotensin receptor blocker [ARB]) and a beta blocker. The clinical review team indicated that spironolactone may also be an appropriate comparator, given its common use in this indication in clinical practice and the transient nature of heart failure (HF) between New York Heart Association (NYHA) classes.

1.4 Type of economic evaluation

The manufacturer undertook both a cost-utility analysis and cost-effectiveness analysis. Both types of evaluations are appropriate as per CADTH *Guidelines for Economic Evaluations of Health Technologies: Canada*.

The analysis takes a Ministry of Health perspective. This is appropriate as per CADTH guidelines.

1.5 Population

The target population is patients with chronic systolic HF with NYHA class II symptoms and left ventricular ejection fraction (LVEF) ≤ 30% (or, if LVEF is between 30% and 35%, a QRS duration of greater than 130 ms on electrocardiography), in line with the patient population in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial: age > 55 years; NYHA class II symptoms; LVEF ≤ 30%; treatment with an ACE inhibitor, and/or an ARB, and a beta blocker (unless contraindicated) at the recommended dose or maximal tolerated dose; and hospitalization for a cardiovascular (CV) reason within the last six months or a B-type natriuretic peptide plasma level of at least 250 pg/mL or a plasma level of amino terminal pro-brain natriuretic peptide (NT-p-BNP) of at least 500 pg/mL in men and 750 pg/mL in women. This is in line with the Health Canada indication.

2. METHODS

The manufacturer stated that the analysis was conducted through the use of discrete event simulation, indicating that patient-level data from the EMPHASIS-HF trial were used to determine risk equations for each event by fitting a distribution to the time to each event. These distributions were stated as having been used as the basis for the modelled cohort of 25,000 patients. Given the type of model submitted, the Common Drug Review (CDR) could not verify the functioning of the model. The manufacturer stated that at the start of the model, a person has an event from which they are either removed from the model or cycle back into the model. The events simulated within the model are listed below, along with whether these are single-occurrence events or multiple-occurrence events.

Events for which persons are removed from the model (absorbing states) include CV mortality, non-CV mortality, and device implantation. Events that will allow the person to remain in the model include CV hospitalization, hospitalization for HF, atrial fibrillation, adverse events, and discontinuations. Certain events were also deemed to affect the time to future events. These include HF hospitalization (increases the likelihood of CV mortality and increases the likelihood of future HF hospitalizations); other CV hospitalization (increases the likelihood of CV mortality and increases the likelihood of future CV hospitalizations); and adverse events (increases the likelihood of future adverse events).

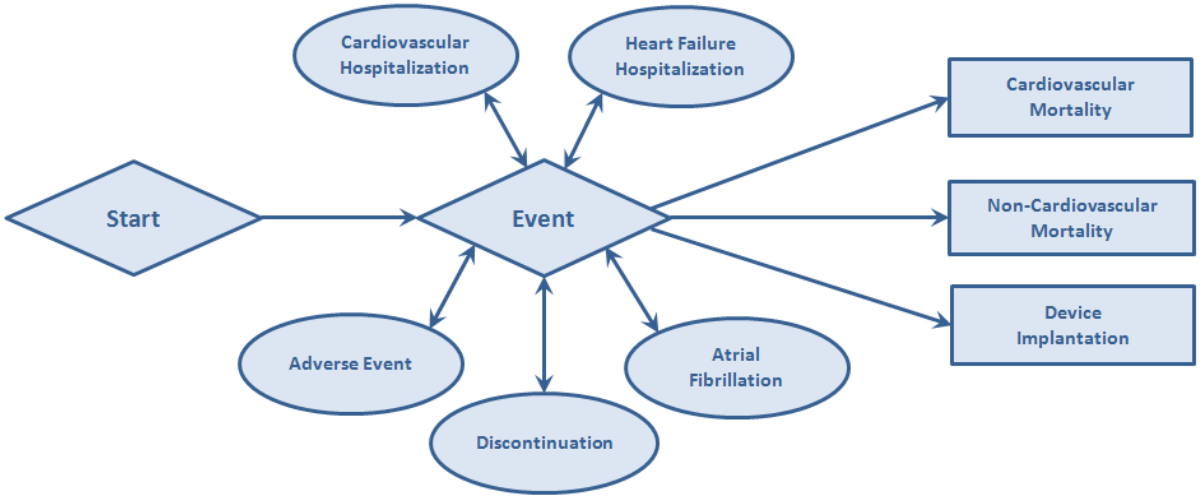
The manufacturer stated that the assumption that persons who discontinue treatment return to receiving standard optimal therapy was incorporated into the model.

See Table 5 for a summary of the key limitations.

2.1 Model structure

The manufacturer submitted a discrete event simulation that models the time to clinically and economically meaningful events to an individually simulated patient basis. Patient-level data from EMPHASIS-HF were used to determine risk equations for each event for fitting a distribution to the time to each event.

FIGURE 1: EPLERENONE COST-EFFECTIVENESS MODEL STRUCTURE



Source: Manufacturer's Pharmacoeconomic Evaluation Report.[2]

The manufacturer indicated that a discrete event simulation is ideal for this condition, as a Markov model cannot consider competing risks. CDR questions this statement, as a Markov model using tunnel states would have allowed an economic evaluation that was more transparent and easier to review while fully reflecting the complexity of disease progression.

2.2 Clinical inputs

The manufacturer made a number of statements within the Pharmacoeconomic Review Report, stating which information was used in the discrete event simulation. As the model submitted to CDR lacked transparency, these claims could not be verified. The following information is a summary of what the manufacturer reported in its economic submission.

Comparator treatment and concomitant medications

The economic model compared eplerenone in combination with standard optimal therapy with standard optimal therapy alone. The manufacturer indicated that standard optimal therapy includes an ACE inhibitor (and/or an ARB) in combination with a beta blocker given at optimal dose, which is appropriately represented by the placebo arm from the EMPHASIS-HF trial within the population of interest. Concomitant medication used by the patient population in the model is based on the EMPHASIS-HF baseline data; 78% of patients were receiving a concomitant ACE inhibitor, 87% were receiving a concomitant beta blocker, and 19% were receiving a concomitant ARB. Other concomitant medications included diuretics (85%), antithrombotic medications (88%), and lipid-lowering drugs (63%).

2.2.1 Efficacy

The manufacturer stated that the effectiveness estimates used to evaluate the cost-effectiveness of eplerenone were based directly on the EMPHASIS-HF trial, although verification of this was not possible. The model distinguishes between hospitalizations due to HF and hospitalizations due to other cardiovascular reasons (CV). The manufacturer did acknowledge that the clinical data used within the model were different from those detailed in the EMPHASIS-HF trial publications. The model used data on the recurrence of events such as hospitalizations and adverse events, which were not explicitly captured in the EMPHASIS-HF trial.

The manufacturer stated that survival analysis techniques were used to derive the likelihood of events occurring in the model from patient-level data from the EMPHASIS-HF trial. The Manufacturer's Pharmacoeconomic Evaluation Report[2] stated that parametric methods were chosen to extrapolate these data to a lifetime time horizon, as well as for recurring events. Kaplan-Meier survival estimates for the eplerenone and placebo treatment arms were fitted to the data and a log-rank test was used to test for significance. Weibull, exponential, log-normal and log-logistic curves were tested and compared with the Kaplan-Meier data. Goodness of fit was tested using the Akaike Information Criterion and prediction error was evaluated using the integrated Brier score. Covariate analyses showed that the number of previous hospitalizations and adverse events was a significant factor in the time of the next event. As stated previously, these assertions could not be verified due to a lack of transparency within both the model and the written report. The lack of transparency in reporting makes it problematic in interpreting the shape of the survival distributions used within the model. Several of the distributions presented in the Excel model appear to have an incongruous shape and further clarifications are required before an assessment of their appropriateness can be made.

As reported in the CDR Clinical Review Report, device implantation in the EMPHASIS-HF trial did not significantly differ between groups; thus, the manufacturer combined totals of both groups to calculate the distribution of implantation events. The model allowed for the implantation of only one device, and

device lifespan was estimated based upon a systematic review and an economic model for cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD),[3] which indicated that the average lifespan of an ICD was five years, while CRT devices had a lifespan of 6.5 years. The manufacturer noted that device life may have increased since the publication of the systematic review, but that the use of a shorter device life biases the model against eplerenone, as patients receiving eplerenone are expected to live longer and are more likely to be fitted with a device. The failure to consider the use of more than one device in the model is not appropriate, as devices and device parts can be replaced, enabling patients to live for well beyond the time stated within the model.

Mortality of patients who experienced a device implantation event is calculated based on hazard ratios (HRs) shown in Table 2. These HRs were derived from a meta-analysis to assess the clinical and cost-effectiveness of CRT for people with HF and evidence of dyssynchrony by comparing CRT devices, CRT-P and CRT with defibrillation (CRT-D), each with optimal pharmaceutical therapy, and with each other.[3] While, as the manufacturer indicated, advances in device technology may have led to an improvement in device life, this may have translated into other benefits, such as altering the HRs presented by the manufacturer.

TABLE 2: HAZARD RATIOS FOR DEVICE IMPLANTATION RELATIVE TO STANDARD CARE

	All-Cause Mortality	CV Mortality
CRT	0.68 (0.54 to 0.88)	0.62 (0.46 to 0.83)
ICD	0.95 (0.74 to 1.21)	0.95 (0.74 to 1.21)

CRT = cardiac resynchronization therapy; CV = cardiovascular; ICD = implantable cardioverter-defibrillator.
Source: Manufacturer's Pharmacoeconomic Evaluation Report,[2] Table 7, page 14.

Within the model, eplerenone discontinuation can occur due to an adverse event, a hospitalization, or other reasons, at which point the eplerenone group receives standard optimal care. The risk of discontinuation after a hospitalization or an adverse event was derived from patient-level data from the eplerenone group in the EMPHASIS-HF trial. A total of 188 patients in the eplerenone group discontinued, of whom 55 were due to HF hospitalization. From this, the following discontinuation probabilities were used in the model:

- 20.1% of HF hospitalizations result in discontinuation (standard error [SE] 0.029)
- 10.2% of other CV hospitalizations result in discontinuation (SE 0.022)
- 6.7% of modelled adverse events result in discontinuation (SE 0.018).

A time-dependent discontinuation rate that was not linked to events ("Other Reasons") was also used in the model. These rates are higher than those reported in the primary EMPHASIS-HF publication (Zannad et al.),[4] as recurrent events are included in the model.

2.2.2 Harms

Five main adverse events were identified in the EMPHASIS-HF trial and were modelled: hyperkalemia, hypokalemia, renal failure, hypotension, and gynecomastia. Overall, the number of adverse events was comparable for the eplerenone and placebo groups, with a trend toward more adverse events leading to withdrawal being seen in the placebo group. However, there were significantly more cases of hyperkalemia in the eplerenone group (8.0%) compared with the placebo group (3.7%). Hypokalemia was more prevalent in the placebo group (2.2%) compared with the eplerenone group (1.2%).

2.2.3 Disease progression

Disease progression or improvement from NYHA class II HF was not specifically captured within the Manufacturer's Pharmacoeconomic Evaluation Report, although disease progression was inherent in patients exiting the model due to hospitalization, adverse events, and spironolactone use.[2]

2.2.4 Quality of life

Quality of life was not measured in the EMPHASIS-HF study.

2.2.5 Costs

Three cost elements were included in the study:

- Drug costs: eplerenone and concomitant medications.
- Hospitalization, adverse events, and device implantation costs.
- Disease management and monitoring costs.

2.2.6 Drug costs: eplerenone and concomitant medications

The use of concomitant medications (includes ACE inhibitor, BB, ARB, diuretics, antithrombotic medications, lipid-lowering drugs, antiarrhythmic medications, and digitalis glycosides) was based on data from the EMPHASIS-HF trial. The weighted costs of each concomitant drug were calculated based on the cost and number of Régie de l'assurance maladie du Québec (RAMQ) claims in 2011 and weighted within each drug type based on market share reported by IMS Brogan PharmaStat. The weighted cost of concomitant medications was calculated by the manufacturer to be $951. The cost of eplerenone was calculated to be $1,090 based on RAMQ pricing (post-wholesaler markup and pharmacy dispensing fee).

2.2.7 Hospitalization, adverse events, and device implantation costs

The manufacturer reported that the cost for hospitalizations and adverse events was based on the Ontario Case Costing Initiative, while the distributions of clinical outcomes within a modelled event category were based on the EMPHASIS-HF trial. The distribution of CV hospitalizations for the eplerenone treatment pathway was assumed to be the same as for the standard optimal care. The model allowed for two separate distributions of adverse events based on the differences seen in the EMPHASIS-HF trial. The costs of gynecomastia and other breast disorders were assumed to be zero, which was considered a conservative assumption. The costs of other CV hospitalizations were calculated as a weighted average of all possible CV hospitalization costs. Similarly, the cost of adverse events was calculated per event from hospitalization and adverse event distributions derived from the rates of the five main adverse events in EMPHASIS-HF.

The costs of CRT and ICD device implantation were calculated weighted by the proportions of devices implemented. The costs were based on a 2003 device assessment by the Technology Assessment Unit of McGill University Health Centre[5] and were indicated to have been inflated to 2011 Canadian dollars using the Consumer Price Index for Health Care. Again, the calculations of these costs are not transparent and, thus, the validity of these values cannot be verified. These costs were applied for fitting the initial device and then approximately each 5.6 years during the remaining lifespan, taken as a weighted average of the lifespan of ICD and CRT devices.

2.2.8 Disease management and monitoring costs

The costs associated with the management of the disease include monitoring costs (general practitioner, specialist visits, and lab tests) and the amount of monitoring required. It was assumed that each patient would undergo two cardiologist visits, four general practitioner visits, and four sets of laboratory tests

per year. This was reported to be consistent with clinician advice and the National Institute for Health and Care Excellence (NICE) guidelines.

2.3 Utilities

The EMPHASIS-HF trial did not collect utility data; thus, a targeted review was conducted to identify articles reporting utility data in NYHA class II HF patients. Various sources were used to provide utility information. Göhler et al. (2009)[6] reported health utility values that were calculated from EQ-5D data based on coefficients for patient characteristics. The patient population was derived from a subset of the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial population, the pivotal trial investigating the use of eplerenone in addition to optimal medical therapy for the reduction of mortality and morbidity among patients with acute myocardial infarction complicated by left ventricular dysfunction and HF. The manufacturer indicated that the EPHESUS patient population was similar to the EMPHASIS-HF patient population, stating that while it recognized patients in the EPHESUS trial did not have chronic HF when they were enrolled, throughout the trial some of the patients did develop chronic HF, thus making this a relevant source of utilities. CDR had previously questioned the appropriateness of the utility values derived from the EPHESUS trial,[1] and the current clinical report questions the comparability of the subpopulation of EPHESUS and the EMPHASIS-HF population.[7]

The baseline utility for patients within the model was 0.84. Lifetime utility decrements taken from EPHESUS were applied within the current model as patients experienced hospitalization for HF or CV causes (Table 3), while other sources were stated as being used for other utility decrements (atrial fibrillation,[8] renal failure,[9] and gynecomastia[10]). Utility decrements for hyperkalemia, hypokalemia, and hypotension were assumed to be zero, based on clinical advice that these events were transient and did not significantly affect lifetime utility.

TABLE 3: UTILITY DECREMENTS FOR MAJOR EVENTS

Event	Utility Decrement	Standard Error
Atrial Fibrillation	–0.084	Unknown
Hospitalizations:		
One hospitalization	–0.024	0.007
Two hospitalizations	–0.031	0.009
Three or more hospitalizations	–0.055	0.001
Adverse Events:		
Hyperkalemia	0	Not applicable
Hypokalemia	0	Not applicable
Renal failure	–0.084	Unknown
Hypotension	0	Not applicable
Gynecomastia	–0.003	0.007

Source: Manufacturer's Pharmacoeconomic Evaluation Report,[2] Table 9, page 17.

2.4 Time horizon

The model time horizon was set over the lifetime of the patient (actual length unspecified), although one-year, two-year, and five-year time horizons were considered in sensitivity analyses. As the time between events was fluid, based on individual patients, no cycle length was used. This is appropriate as per CADTH guidelines.

2.5 Discounting

A discount rate of 5% was applied to both health and economic outcomes. A sensitivity analysis of the base case scenario has been conducted with no discounting (discount rate of 0%) and a discount rate of 3%, as recommended by the CADTH guidelines.

2.6 Validation

The manufacturer attempted to validate the model using the actual trial data from EMPHASIS-HF, but was unable to achieve this due to the censoring of data in the trial compared with the extrapolation and assumptions used in the model. Aside from the aforementioned issue, CDR questions the validity, as several of the stated assumptions that are used to determine the structure of the model were determined to be inappropriate (see Discussion section).

3. RESULTS

3.1 Manufacturer's base case

The modelled costs, life-years, and quality-adjusted life-years (QALYs) are presented in Table 4. The main advantage of eplerenone as an adjunct to standard optimal therapy was the gain in life-years and reduction of costs of hospitalization for HF. The incremental cost-utility ratio (ICUR) was $7,347 per QALY gained, with an incremental cost-effectiveness ratio (ICER) per life-year of $5,940.

TABLE 4: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE

Discount Rate: 5%	Eplerenone	Standard Optimal Care	Difference
Cost of CV Hospitalizations	$9,957	$10,094	–$137
Cost of HF Hospitalizations	$9,725	$12,335	–$2,610
Cost of Active Treatment	$5,759	$0	$5,759
Cost of Concomitant Treatment	$6,261	$5,173	$1,088
Cost of Device Implantation	$15,168	$13,282	$1,887
Cost of Disease Management	$4,282	$3,538	$744
Cost of Adverse Events	$225	$154	$71
Total Costs	**$51,378**	**$44,576**	**$6,803**
QALYs	5.29	4.36	0.93
Life-years	6.59	5.44	1.15
ICER per QALY Gained			**$7,347**
ICER per Life-Year Gained			**$5,490**

CV = cardiovascular; HF = heart failure; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.
Source: Manufacturer's Pharmacoeconomic Evaluation Report,[2] Table 15, page 37.

When CDR attempted to run the model to replicate the manufacturer's base case, different results were generated ($8,232 per QALY gained and $5,939 per life-year [LY] gained). The manufacturer indicated that the patient input sheet had been updated since the model report was written and, thus, the "results are slightly different to the base case presented (as simulation models have inherent variation included in their outputs)".[11] This adds to the uncertainty of the manufacturer's submitted results.

CDR could not verify these results, as it was not able to view the model logic. Further, based on clinical feedback, CDR reanalyses would have been warranted, as some assumptions made by the manufacturer required examination (see DISCUSSION section for further clarification).

3.2 Summary of manufacturer's sensitivity analyses

3.2.1 One-way sensitivity analyses

The manufacturer reported the results of deterministic sensitivity analyses on key model parameters that found the upper bound of the ICER remained below $11,000, indicating that the model predictions are stable and robust. The parameters for which uncertainty has the greatest impact on the ICER are:

- distributional parameter for implantation of devices (ICD/CRT) with eplerenone
- distributional parameter of CV and HF hospitalizations with eplerenone when no previous hospitalizations were experienced
- distributional parameter for CV mortality for placebo (standard care) when three previous hospitalizations were experienced.

Ten scenario analyses were also undertaken:

- Scenario analyses using both a one-year and two-year time horizon found eplerenone plus standard optimal therapy to dominate standard optimal therapy alone. The five-year time horizon resulted in an ICUR of $610 per QALY.
- Other scenario analyses using trial-based data, no utility decrement for adverse events and hospitalization, revised curves for various variables, and revised costs of eplerenone indicated that the ICUR was between $4,933 and $9,555 per QALY.

3.2.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was performed by running the model 100 times with a cohort of 25,000 patients for both eplerenone and placebo. Although there is considerable combined uncertainty surrounding outcomes, the manufacturer reported that in 100% of cases, eplerenone provides a substantial QALY benefit over standard optimal care only, and in 100% of cases, the ICERs simulated fall below a $20,000 per QALY willingness-to-pay threshold.

3.2.3 Subgroup analysis

A series of subgroup analyses were undertaken by the manufacturer that looked at populations with diabetes at baseline, no diabetes at baseline, ischemic heart disease, non-ischemic heart disease, poor renal function at baseline (epidermal growth factor receptor [eGFR] < 60), good renal function at baseline (eGFR ≥ 60), males, and females. The ICUR ranged from $6,919 to $8,511 per QALY.

3.2.4 CDR analyses

Given the lack of transparency with the submitted model, CDR was unable to either validate the manufacturer's base case analysis or undertake any sensitivity or scenario analyses to test the model based on the limitations identified.

4. DISCUSSION

4.1 Key limitations

4.1.1 Lack of transparency with the model

The manufacturer stated that it undertook a discrete event simulation to model eplerenone plus standard optimal therapy compared with placebo plus standard optimal therapy. The results of the discrete event simulation were then incorporated into an Excel model that allowed alteration to a limited number of inputs. The lack of transparency of the model, which appears to be inherent in presenting the results of discrete event simulation models,[12] is a key limitation. It was not possible to determine how the majority of clinical information was included in the model. A more transparent

approach would have greatly assisted CDR, as several assumptions that affected the structure of the model may be inappropriate, which may have invalidated the model (based upon the model write-up). However, without having access to the inner working of the model, the actual impact of these assumptions cannot be seen. Further, the lack of accessibility of the model did not allow CDR to examine the reason why the model rerun could not replicate (or at least be similar to) the manufacturer's base case results when no parameters were modified from the original settings.

4.1.2 Appropriateness of the modelled population — transitioning between New York Heart Association classes

The manufacturer does not specify what happens to patients once they move out of NYHA class II. Clinical input has indicated that patients can move between NYHA classes, and that it does not take much for a patient to move between classes on a temporary basis. The manufacturer acknowledged that patients did move between classes throughout the trial — device use is associated with progression to NYHA class III or IV — but that this was not modelled, as it did not believe there were any significant changes in NYHA class between the two arms. Given that NYHA class may be a transient health state and patients may switch easily between classes, a scenario analysis that includes transitions to other classes of disease and the use of spironolactone would have been informative to CDR (if the model was transparent). The exclusion of patients in other NYHA classes is likely to have an impact on the model; however, it is unclear as to what this impact is likely to be, as there are various issues that need to be considered that can affect the economic evaluation in improving or worsening the ICUR.

4.1.3 The modelling and assumptions surrounding hospitalizations in the model

It is unclear as to how the time to subsequent events (hospitalizations and adverse events) were modelled. Because the EMPHASIS-HF trial collected only the initial time to hospitalization for the first event, it is not entirely clear how the subsequent hospitalizations were captured (other than this was a post-hoc measurement), and as such was thus simulated in the model. Given this, combined with the process of extrapolating very small numbers of subsequent events, there is the high likelihood that these measurements are subject to bias. Clinical input has also queried the modelling of a continued effect of eplerenone after multiple subsequent hospitalizations. Clinical input suggested that a patient who experiences a third or more hospitalization is likely no longer in class II disease and may have various comorbidities. Thus, it is unclear what, if any, impact eplerenone could have on stopping or extending the time to future hospitalizations. The analysis should have assumed no differences after the second hospitalization. The way it has been modelled may bias the results in favour of eplerenone.

The additional key limitations, listed in Table 5, may have been accounted for within the model; however, it is not possible to determine whether this is the case, due to the lack of transparency with the submitted model.

TABLE 5: OTHER LIMITATIONS OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Parameter/Assumption	Issue	Impact
Patients who discontinue return to standard optimal therapy	There is the potential that this patient has progressed to class III or IV disease and, thus, the patient may be eligible to receive spironolactone.	A scenario analysis including modelling cost of spironolactone in patients who discontinue should have been considered.
Device implantation	Device implantation is captured only as a single event in the model. Once a patient has a device, they are censored from the model.	This underestimates the impact of the device. Clinical input indicated patients received eplerenone before device implantation may continue eplerenone. Devices can be replaced and batteries changed; thus, a patient can live substantially longer than about 5 to 6.5 years, potentially increasing expected lifetime and cost in both treatment groups.
Number of events in EMPHASIS-HF were large enough for distributions to be modelled	The number of patients in EMPHASIS-HF who had an event was small, as was the overall number of events.	Increases the uncertainty in the magnitude of the results.
Baseline utility value of 0.84; various utility decrements associated with parameters	Quality of life was not captured in EMPHASIS-HF. An assumed starting utility value for patients with NYHA class II HF which were based on a subset of the EPHESUS trial. The quality of life data from the EPHESUS were previously questioned by CDR.[a] The comparability of these two patient populations is questionable.	Dependent upon whether class III/IV patients are included in the model. If they are, the baseline utility value is likely to be lower than the value used in the model. The transient nature of the health state indicates that there is potentially a wide range of utility values, thus the total QALYs are uncertain.
AF	AF should be included based on EMPHASIS-HF data and only captured as a single event in the model. AF often presents as a comorbidity with HF and is correlated with worsening NYHA class. New-onset AF/flutter in EMPHASIS-HF was infrequent, non-adjudicated events and an exploratory outcome — firm conclusions cannot be drawn from the data.	Increases uncertainty in the results.
Age of patients in the simulations	Patients could be aged up to 130 years and have had class II HF for 50 years by the time they exited the model.	Increases uncertainty in the results.

AF = atrial fibrillation; CDR = Common Drug Review; CEDAC = Canadian Expert Drug Advisory Committee; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; HF = heart failure; NYHA = New York Heart Association; QALY = quality-adjusted life-year.

[a]CEDAC recommendation for eplerenone, 2009[1] indicated that interpretation of these (quality of life) results is limited, and that data are too incomplete to draw conclusions.

4.2 Issues for consideration

Other health technology assessment findings

Eplerenone has been recommended for listing for this indication by the following health technology assessment bodies: L'Institut National d'Excellence en Santé et en Services Sociaux (INESSS), Scottish Medicines Consortium (SMC), and All Wales Medicines Strategy Group (AWMSG). Further information pertaining to these recommendations is located in APPENDIX 2: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS.

4.2.1 Clinical findings

Given the issues previously identified with the model, CDR could not undertake any reanalysis or verify the submitted model. However, as summarized in the CDR Clinical Review Report, eplerenone appears to reduce the proportion of patients requiring hospitalization (Table 6).

TABLE 6: COMMON DRUG REVIEW SUMMARY OF COSTS AND CLINICAL OUTCOMES

Parameters	Value	Eplerenone[a]	Placebo	Difference
Drug cost (excluding concomitant treatments[b])	21 months[c] (per year)	$1,670 ($955)	$0 ($0)	$1,670
Primary outcome:				
Composite outcome: death from cardiovascular causes or hospitalization for heart failure	N (%)	249 (18.3)	356 (25.9)	7.6%
Selected secondary outcomes:				
Death from cardiovascular causes	N (%)	147 (10.8)	185 (13.5)	2.7%
Hospitalization for heart failure	N (%)	164 (12.0)	253 (18.4)	6.4%
Hospitalization for cardiovascular causes	N (%)	304 (22.3)	399 (29.1)	6.8%

[a]Based on submitted eplerenone price ($2.61). Eplerenone cost calculated as follows: ((365.25/12)*21)*2.6137.
[b]Concomitant drug costs have been excluded but are expected to be similar in both groups, although slightly higher in the eplerenone group (see manufacturer's Pharmacoeconomic Review Report).[2]
[c]The clinical data are based on Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) data from Zannad et al.,[4] which states that the trial was stopped prematurely, according to pre-specified rules, after a median follow-up period of 21 months. Thus, 21 months of drug costs was deemed appropriate.

4.3 Off-label/expanded use

- **Length of time on treatment — Age:** The current requested indication for eplerenone is based on the EMPHASIS-HF trial. The trial population (patients aged 55 years or older) and warnings provided in the product monograph (no benefit in CV mortality is seen in patients older than 75 years) appear to restrict the population; however, clinical input has suggested that patients substantially younger than 55 are likely to receive eplerenone in clinical practice. Information on the cost-effectiveness in this population is unknown.
- **Length of time on treatment — HF class:** Clinical input suggests that once a patient is initiated on eplerenone, unless the patient does not tolerate it, they would remain on treatment indefinitely (even if they progress to class III or IV disease, received a device, or are older than 75 years). Information on the cost-effectiveness in these populations is unknown.

4.4 Patient input

- The Heart and Stroke Foundation provided input for the eplerenone submission. The patient group stated that HF is often associated with a range of comorbidities, frequent hospitalizations, and an unpredictable course of disease. These aspects were included in the manufacturer's economic evaluation.
- They also state that burden of this disease is also felt by caregivers. It is a long-term commitment of time and energy and requires prominent changes in daily life that can be stressful. As individuals with HF have deteriorating physical abilities, the support required from caregivers increases, sometimes to the point that caregivers report an impact on their own health, which can negatively affect their ability to provide care. Challenges in increasing levels of needed care can also contribute to psychiatric and physical morbidities in caregivers. Information on the impact to caregivers was not provided by the manufacturer.
- HF is an expensive medical condition in Canada in terms of hospitalization costs, end-of-life care being a major contributing factor. The manufacturer's economic evaluation takes into account hospitalization, quality of life (through other sources), and mortality information captured in the EMPHASIS-HF trial.

5. CONCLUSIONS

Given the issues with lack of transparency in the submitted model and the ability to run analyses of interest independently, CDR was unable to verify the manufacturer's economic evaluation. CDR is unable to provide an appropriate estimate of the cost-effectiveness of eplerenone in the requested population, although the CDR Clinical Report does indicate that eplerenone appears to reduce the number of initial hospitalizations for patients with NYHA class II HF and an LVEF ≤ 35%, but will increase drug treatment costs.

APPENDIX 1: COST COMPARISON TABLES

The comparators presented in Table 7 have been deemed to be appropriate by clinical experts. Comparators may be recommended (appropriate) practice, versus actual practice. Comparators are not restricted to drugs, but may be devices or procedures. Costs are manufacturer list prices, unless otherwise specified.

TABLE 7: COST COMPARISON TABLE FOR COMPARATORS/CONCOMITANT MEDICATIONS WITH HEART FAILURE INDICATION

Drug/Comparator[a]	Strength	Dosage Form	Price ($)[b]	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Aldosterone Antagonists						
Eplerenone (Inspra)	25 mg 50 mg	Tablet	2.6137[c]	25 mg to 50 mg daily	2.61	955
Spironolactone (generic)[d]	25 mg 100 mg	Tablet	0.1057 0.2461	25 mg to 200 mg daily	0.11 to 0.49	39 to 180
ARBs						
Candesartan (generics)	4 mg 8 mg 16 mg 32 mg	Tablet	0.1700 0.2850 0.2850 0.2932	4 mg daily initially, doubled every two weeks to target 32 mg dose	0.29	107
Valsartan (generics)	80 mg 160 mg 320 mg	Tablet	0.2958 0.2958 0.2843	80 mg to 160 mg twice daily	0.28 to 0.29	104 to 108
ACEs						
Captopril (generics)	12.5 mg 25 mg 50 mg 100 mg	Tablet	0.2120 0.3000 0.5590 1.0395	25 mg to 100 mg three times daily	0.90 to 3.12	328 to 1,138
Cilazapril (generics)	1 mg 2.5 mg 5 mg	Tablet	0.1557 0.1795 0.2085	1 mg to 2.5 mg daily	0.16 to 0.18	57 to 66
Enalapril (generics)	2.5 mg 5 mg 10 mg 20mg	Tablet	0.1863 0.2203 0.2647 0.3195	5 mg to 20 mg daily in one or two doses	0.22 to 0.53	80 to 193
Fosinopril (generics)	10 mg 20mg	Tablet	0.2178 0.2619	20 mg to 40 mg once daily	0.26 to 0.52	96 to 191
Lisinopril (generics)	5 mg 10 mg 20 mg	Tablet	0.1347 0.1619 0.1945	2.5 mg to 30 mg once daily	0.07 to 0.36	25 to 130
Perindopril (Coversyl)	2 mg 4 mg 8 mg	Tablet	0.6527 0.8168 1.1325	2 mg to 4 mg daily	0.65 to 0.82	238 to 298
Quinapril (Accupril)	5 mg 10 mg 20 mg 40 mg	Tablet	0.9156	10 mg once to 20 mg twice daily	0.92 to 1.83	334 to 668

Drug/Comparator[a]	Strength	Dosage Form	Price ($)[b]	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
BBs						
Carvedilol (generics)	3.125 mg 6.25 mg 12.5 mg 25 mg	Tablet	0.3377	3.125 mg to 25 mg twice daily	0.68	247

ACE = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta blocker; HF = heart failure; NYHA = New York Heart Association.
[a]For details of other comparators with a different mechanism of action, see Table 8 below.
[b]All prices are from the Ontario Drug Benefit Formulary (accessed Feb 2013) unless otherwise indicated and do not include dispensing fees.
[c]Manufacturer-submitted price.
[d]Spironolactone is not indicated for use in NYHA class II HF patients.

TABLE 8: COST COMPARISON TABLE FOR COMPARATORS/CONCOMITANT MEDICATIONS WITHOUT HF HEART FAILURE INDICATION

Drug/ Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
ARBs						
Eprosartan (Teveten)	400 mg 600 mg	Tablet	0.7182 1.1000	600 mg daily	1.10	402
Irbesartan (generics)	75 mg 150 mg 300 mg	Tablet	0.3025	150 mg to 300 mg daily	0.30	110
Losartan (generics)	25 mg 50 mg 100 mg	Tablet	0.3147	50 mg to 100 mg daily	0.31	115
Olmesartan (Olmetec)	20 mg 40 mg	Tablet	1.0524	20 mg to 40 mg daily	1.05	384
Telmisartan (generics)	40 mg 80 mg	Tablet	0.2824	80 mg daily	0.2824	101
ACEs						
Benazepril (generics)	5 mg 10 mg 20 mg	Tablet	0.5577 0.6595 0.7567	20 mg to 40 mg daily	0.76 to 1.51	276 to 552
Ramipril (generics)	1.25 mg 2.5 mg 5 mg 10 mg	Capsule	0.1274 0.1470 0.1470 0.1862	2.5 mg to 5 mg twice daily[b]	0.294	107
Trandolapril (Mavik)	1 mg 2 mg 4 mg	Capsule	0.6901 0.7931 0.9785	2 mg to 4 mg daily[b]	0.79 to 0.98	289 to 357
BBs						
Atenolol (generics)	50 mg 100 mg	Tablet	0.1437 0.2362	50 mg to 100 mg daily	0.14 to 0.24	52 to 86
Bisoprolol (generics)	5 mg 10 mg	Tablet	0.0994 0.1450	10 mg daily[c]	0.10 to 0.29	36 to 106

Drug/ Comparator	Strength	Dosage Form	Price ($)[a]	Recommended Dose	Average Daily Drug Cost ($)	Average Annual Drug Cost ($)
Labetalol (Trandate)	100 mg 200 mg	Tablet	0.3050 0.5392	200 mg to 400 mg twice daily	1.08 to 2.16	394 to 787
Metoprolol (generics)	50 mg 100 mg	Tablet	0.0624 0.1361	50 mg to 100 mg twice daily	0.12 to 0.27	46 to 99
	100 mg 200 mg	SR Tablet	0.1415 0.2568	100 mg to 200 mg daily	0.14 to 0.26	52 to 94
Nadolol (generics)	40 mg 80 mg 160 mg	Tablet	0.2465 0.3515 1.2046	80 mg to 320 mg daily	0.35 to 2.41	128 to 858
Nebivolol (Bystolic)	2.5 mg 5 mg 10 mg 20 mg	Tablet	1.3020[d]	5 mg to 20 mg daily	1.30	475
Propranolol (generics)	10 mg 20 mg 40 mg 80 mg 120 mg	Tablet	0.0172 0.0277 0.0306 0.0509 0.3091	160 mg to 320 mg daily	0.11 to 0.20	37 to 74
Sotalol (generics)	80 mg 160 mg	Tablet	0.2966[e] 0.1623	160 mg to 320 mg daily in two doses[f]	0.16 to 0.32	59 to 118

ACE = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; BB = beta blocker; HF = heart failure.
[a]All prices are from the Ontario Drug Benefit Formulary (accessed May 2013) unless otherwise indicated and do not include dispensing fees. Dosing based on hypertension indication unless otherwise indicated.
[b]Dosing based on post-myocardial infarction to reduce hospitalization due to HF indication.
[c]Dosing based on off-label use in HF patients from the 2010 Canadian Pharmacist Association bisoprolol monograph.
[d]McKesson Wholesale Price (August 2013).
[e]Saskatchewan Formulary (May 2013).
[f]Dosing based on ventricular arrhythmia indication.

APPENDIX 2: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

Three health technology assessment bodies have published recommendations regarding eplerenone in this indication: Scotland (Scottish Medicines Consortium), Wales (All Wales Medicines Strategy Group), and Quebec (L'Institut National d'Excellence en Santé et en Services Sociaux). Summaries of these recommendations are provided below.

TABLE 9: OTHER HEALTH TECHNOLOGY ASSESSMENT FINDINGS

	SMC	AWMSG	INESSS
Drug	Eplerenone (Inspra), 25 mg to 50 mg once daily		
Price[a]	£555 (C$913) p.a.	£557 (C$919) p.a.	$77 per month (formulary price $2.5563 per tablet)
Treatment	Eplerenone in addition to SOT		
	SOT = ACE inhibitor +/- ARB+ beta blocker Spironolactone considered relevant comparator	SOT = ACE inhibitor +/- ARB + beta blocker Spironolactone not considered a comparator	Did not provide any definition of SOT
Comparator	SOT alone		
Population Modelled	Adult patients with chronic systolic HF associated with NYHA class II symptoms and LVEF ≤30%, based on the EMPHASIS-HF trial. **AWMSG** noted that the population in EMPHASIS-HF is wider than licensed indication.		
Time Horizon	Lifetime		Same
Discount Rate	Not reported	3.5% p.a. on both costs and outcomes (0% and 6% tested in sensitivity analyses)	Not reported
Study Question	Cost-effectiveness of eplerenone + SOT versus SOT alone in patients with NYHA class II HF and LVEF ≤30%.	CUA of eplerenone + SOT versus SOT, to reduce the risk of CV mortality and morbidity in adult patients with NYHA class II CHF and LVSD (LVEF ≤ 30%).	Estimate ICER of eplerenone + SOT versus SOT for patients with NYHA class II HF.
Type of Model	All HTA agencies reported the economic evaluation was based on discrete event simulation that took into account mortality due to both CV and non-CV risk, hospitalization due to HF and other CV causes, with the clinical data indicated to have been taken primarily from the EMPHASIS-HF study. **AWMSG** specified that a cohort of 25,000 patients was used.		
Key Outcomes	QALYs	QALYs	LYs and QALYs
Results	• Base case: £3,140 per QALY (C$5,191) • SA robust; using trial data only increased the QALY estimate to £8,894 (C$14,675)	• Base case: £3,534 per QALY (C$5,831) • SA generally robust; model was found highly sensitive to a short time horizon (£37,300 per QALY over one year; C$61,545) • Testing extrapolation of hospitalization and CV mortality, ICERs: £2,846 to £31,047 per QALY (C$4,696 to $51,227)	• Base case: $5,490 per LY gained and $7,347 per QALY gained • DSA range: dominant to $8,060 per QALY • CEAC indicated 100% ICER <$50,000/QALY

	SMC	AWMSG	INESSS
Sources of Uncertainty	Comparator, patient population, long-term issues	Utility values, hospitalization	Utility values, patient population
CDR Assessment	None of the other HTA agencies reported the same difficulties CDR had with verifying and validating the model, although **AWMSG** did report that due to the computational demands of the model, they were unable to verify the PSA.		

ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; AWMSG = All Wales Medicines Strategy Group; C$ = Canadian dollars; CDR = Common Drug Review; CEAC = cost-effectiveness acceptability curve; CHF = congestive heart failure; CUA = cost-utility analysis; CV = cardiovascular; DSA = deterministic sensitivity analysis; EMPHASIS-HF = Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; HF = heart failure; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; INESSS = L'Institut National d'Excellence en Santé et en Services Sociaux; LVEF = left ventricular ejection fraction; LY = life-year; NYHA = New York Heart Association; p.a. = per annum; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; SA = sensitivity analysis; SMC = Scottish Medicines Consortium; SOT = standard optimal therapy.

* The model results indicated base case results of $8,232 per QALY gained and $5,939 per LY gained. The manufacturer indicated that this was due to new data in the patient input sheet of the model.

Other European countries also reimburse eplerenone for its new indication.[2]

[a]£1.00 ≈ $1.65 (16 October 2013).

APPENDIX 3: SUMMARY OF KEY OUTCOMES

TABLE 10: SUMMARY ASSESSMENT OF EPLERENONE AS AN ADJUNCT TO STANDARD OPTIMAL THERAPY COMPARED WITH STANDARD OPTIMAL THERAPY ALONE

DRUG Versus COMPARATOR	Attractive	Slightly Attractive	Equally Attractive	Slightly Unattractive	Unattractive	NA
Costs (total)				X		
Drug treatment costs alone					X	
Clinical outcomes		X				
Quality of life		X				
Incremental CE ratio or net benefit calculation[a]	Manufacturer's base case: $7,347 per QALY $5,490 per LY					

CDR = Common Drug Review; CE = cost-effectiveness; LY = life-year; NA = not applicable; QALY = quality-adjusted life-year.
[a]Results presented in the Manufacturer's Pharmacoeconomic Evaluation Report. Neither CDR nor the manufacturer could reproduce these results. The data results in base case results of $8,232 per QALY gained and $5,939 per LY gained. The manufacturer indicated that this was due to new data in the patient input sheet of the model.

APPENDIX 4: ADDITIONAL INFORMATION

TABLE 11: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?			X
Comments	The model lacked transparency. No relationship between the input parameters and outputs could be established. The manufacturer's base case could not be replicated.		
Was the material included (content) sufficient?			X
Comments	The written report was insufficient to allow a complete understanding of the model structure. The full model (including discrete event simulation) was not provided. In addition, the modelling of long-term events was unclear.		
Was the submission well organized and was information easy to locate?		X	
Comments	The written report and model user guide were not easy to navigate and information that should have been presented was missing. Some statements were not congruent with other statements located in the report.		

TABLE 12: AUTHOR INFORMATION

Authors	Affiliations		
Unspecified (Model User Guide and Pharmacoeconomic Report) Unspecified (Pharmacoeconomic Report) Dawn Lee (Model and Model User Guide) Adrian Vickers (Model and Model User Guide) Becky Winn (Model and Model User Guide) Nic Brereton (Model and Model User Guide) Ron Akehurst (Model and Model User Guide)	Pfizer Canada Inc. Groupe d'analyse, Ltée BresMed Health Solutions BresMed Health Solutions BresMed Health Solutions BresMed Health Solutions BresMed Health Solutions		
	Yes	**No**	**Uncertain**
Authors signed a letter indicating agreement with entire document			X
Authors had independent control over the methods and right to publish analysis			X

Note: No documentation was provided regarding author agreement with the submitted documents or control over the methods.

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