Common Drug Review
Pharmacoeconomic Review Report

March 2016

Drug	sacubitril/valsartan (Entresto)
Indication	For the treatment of heart failure with reduced ejection fraction in patients with NYHA Class II or III, to reduce the incidence of cardiovascular death and heart failure hospitalization
Listing request	As per indication
Dosage form(s)	sacubitril 24.3 mg/valsartan 25.7 mg, sacubitril 48.6 mg/valsartan 51.4 mg and sacubitril 97.2 mg/valsartan 102.8 mg combination tablets
NOC date	October 2, 2015
Manufacturer	Novartis Pharmaceuticals

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
CDR	CADTH Common Drug Review
CRT	cardiac resynchronization therapy
CV	cardiovascular
EQ-5D	EuroQol 5-Dimensions Questionnaire
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
ICUR	incremental cost-utility ratio
ICD	implantable cardioverter-defibrillator
NYHA	New York Heart Association
QALY	quality-adjusted life-year

TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION

Drug Product	Sacubitril/valsartan (Entresto)
Study Question	"The objective of this economic evaluation is to assess the value of ENTRESTO for the treatment of HFrEF Class II-III in adult patients. The value of ENTRESTO (in addition to background therapy) as compared to the current standard of care, ACEI (in addition to background therapy) was assessed within the framework of a cost-effectiveness analysis."
Type of Economic Evaluation	Cost-utility analysis Cost-effectiveness analysis
Target Population	Adult patients with heart failure with reduced ejection fraction (HFrEF) (NYHA Class II or III).
Treatment	Sacubitril 97.2 mg/valsartan 102.8 mg twice daily + background therapy
Outcomes	QALYs Life-years
Comparator	ACEI + background therapy
Perspective	Canadian publicly funded health care system
Time Horizon	20 years
Results for Base Case	Sacubitril/valsartan compared with ACEI: • $29,999 per QALY • $25,730 per life-year.
Key Limitations	CDR noted the following limitations of the manufacturer's submission: • It is unclear whether results are generalizable to Canadian heart failure patients due to issues with external validity of the PARADIGM-HF trial. • The length of the model time horizon creates uncertainty, considering the uncertainty in the long-term extrapolation of treatment effectiveness and the mean age of the Canadian heart failure patient population (over 75 years old). • Uncertain assumptions regarding NYHA distribution after year 3 and the extrapolation of the trial results. • Uncertainty in data and assumptions used to estimate QALY loss from hospitalization. • Overestimation of resource use associated with adverse events. • Cost of enalapril for ACEI is a less conservative choice than ramipril considering their relative prices; ramipril is also the more frequently used ACEI in heart failure in Canadians.
CDR Estimates	CDR performed a number of reanalyses related to the above limitations. Using an alternative model horizon (10 years), adjusting patient demographics, correcting for costs of adverse events, assuming a different disutility of hospitalization and use of the cost of ramipril in place of enalapril, CDR calculated an ICUR of $42,787. Of note, this ICUR is valid to the extent that the trial population used for the economic assessment is reflective of the Canadian HF population. In the CDR base case, price reductions of 25% and 35% are necessary to lower the ICUR to below $30,000/QALY and $25,000/QALY, respectively.

ACEI = angiotensin-converting enzyme inhibitor; CDR = CADTH Common Drug Review; HFrEF = heart failure with reduced ejection fraction; ICUR = incremental cost-utility ratio; NHYA = New York Heart Association; QALY = quality-adjusted life-year.

EXECUTIVE SUMMARY

Background

Sacubitril/valsartan (Entresto) is a first-in-class oral angiotensin receptor–neprilysin inhibitor (ARNI) indicated for the treatment of heart failure (HF) with reduced ejection fraction (HFrEF) among patients with New York Heart Association (NYHA) functional class II or III HF.[1] The manufacturer is requesting listing of sacubitril/valsartan as per the indication.[2] According to the product monograph, sacubitril/valsartan should be used in clinically stable patients in conjunction with other HF treatments, such as diuretics, beta blockers and aldosterone antagonists, and in place of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy.[1] The recommended starting dose for most patients is sacubitril 48.6 mg/valsartan 51.4 mg twice daily, increased every two to four weeks (as tolerated) to the target dose of sacubitril 97.2 mg/valsartan 102.8 mg twice daily.[1] Sacubitril/valsartan is available in 24.3 mg/25.7 mg, 48.6 mg/51.4 mg and 97.2 mg/102.8 mg combination tablets, all of which have a price of $3.62 per tablet. At a recommended dose of sacubitril 97.2 mg/valsartan 102.8 mg twice daily sacubitril/valsartan costs $7.24 daily.

The manufacturer submitted a cost-utility analysis based on a Markov model comparing sacubitril 97.2 mg/valsartan 102.8 mg twice daily with an ACEI (enalapril 10 mg twice daily), both in addition to background therapy (consisting of beta blockers, mineralocorticoid receptor antagonists, digoxin, lipid-lowering drugs, diuretics, acetylsalicylic acid, anticoagulants, and adenosine diphosphate antagonists, according to rates of use in PARADIGM-HF), in patients with NYHA class II or III HFrEF.[3] The economic model is comprised of five health states: four corresponding to NYHA classes I to IV (in increasing order of HF severity) and death. All patients were in NYHA class II or III at the start of the model. As patients progressed through the model, they incurred the costs and outcomes associated with HFrEF based on the health states they experienced. The analysis used a 20-year horizon and was undertaken from the Canadian public payer perspective. Patient improvement and deterioration were modelled as movement between NYHA classes. Transitions between NYHA classes in years 0 to 3 were based on the PARADIGM-HF trial comparing sacubitril/valsartan with enalapril 10 mg twice daily.[4] From years 3 to 20 the distribution of patients among NYHA classes was assumed to remain constant. Each state was associated with a utility weight, cost, and risk of mortality or hospitalization. Utilities were based on directly measured EuroQol 5-Dimensions Questionnaire (EQ-5D) utilities from PARADIGM-HF. Mortality was based on all-cause age-specific mortality from Statistics Canada[5] and cardiovascular (CV) mortality data from PARADIGM-HF. CV mortality data for years 0 to 3 were based on deaths observed in PARADIGM-HF while for years 3 to 20 a survival model was used to extrapolate values. All-cause hospitalization rates were from PARADIGM-HF for years 0 to 3, and were then extrapolated based on a negative binomial regression model. Rates of adverse events (AEs) for each treatment were also based on trial values. Costs considered were drug acquisition costs (both primary and background therapy), costs of hospitalization and monthly management of HF, and costs for management of AEs.

The manufacturer reported that when added to background therapy, the incremental cost-utility ratio (ICUR) for sacubitril/valsartan compared with ACEI was $29,999 per quality-adjusted life-year (QALY).

Summary of Identified Limitations and Key Results

CADTH Common Drug Review (CDR) noted several limitations of the manufacturer's economic submission. First, and most important, it is unclear whether results are generalizable to Canadian HF patients due to issues with external validity of the PARADIGM-HF trial, on which the economic evaluation is based. In particular, very few patients were enrolled at North American sites (602/8,442

randomized, or 7%), the average patient was younger than average Canadian HF patients for whom sacubitril/valsartan is a treatment option (63.9 years versus over 75, as per clinical expert input), and females were underrepresented (22% of PARADIGM-HF patients versus more than 50% of Canadian patients).[6] Furthermore, the use of a safety run-in period potentially underestimates the incidence of AEs. Finally, the low use of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) in the global trial population (16%) compared with what is expected in Canada may bias estimates of mortality benefit, given the favourable effects of ICD/CRT on HF mortality.[7] As such, it remains to be seen whether the observed effectiveness and cost-effectiveness of sacubitril/valsartan reported by the manufacturer would be realized in Canadian clinical practice.

Further limitations with the economic submission were identified, including:

- the use of a model time horizon length associated with high uncertainty, when considering the uncertainty in long-term extrapolation of treatment efficacy, and also the age of patients in Canadian clinical practice
- uncertain assumptions regarding NYHA distribution after year 3
- uncertainty in the data used to estimate QALY loss due to hospitalization
- overestimation of resource use associated with treatment of AEs
- the use of enalapril instead of the more widely used and inexpensive ramipril as the basis for the cost of the ACEI comparator.

Conclusions

A key limitation of the manufacturer's submission was the uncertain generalizability of results to a Canadian HF population based on the use of a non-representative patient population in PARADIGM-HF. CDR conducted analyses addressing identified limitations regarding model horizon (reduced to 10 years), patient demographic characteristics, cost of ramipril, costs of AEs, and disutility of hospitalization; resulting in a CDR base case with an incremental cost-utility ratio (ICUR) estimate of $42,787. It should be noted that these results apply only to the extent that the population of PARADIGM-HF reflects the Canadian HF population, and that the PARADIGM-HF outcomes can be generalizable to the Canadian context of care in HF. The cost-effectiveness of sacubitril/valsartan may be found to differ as further data become available. In the CDR base case, price reductions of 25% and 35% are necessary to lower the ICUR to below $30,000/QALY and $25,000/QALY, respectively.

INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility analysis based on a Markov model comparing sacubitril/valsartan with an angiotensin-converting enzyme inhibitor (ACEI) (both administered in addition to background therapy consisting of beta blockers, mineralocorticoid receptor antagonists, digoxin, lipid-lowering drugs, diuretics, acetylsalicylic acid, anticoagulants, and adenosine diphosphate antagonist) among adult patients with heart failure with reduced ejection fraction (HFrEF) (New York Heart Association [NYHA] class II or III). Patients in the model were assumed to have characteristics similar to patients included in the PARADIGM-HF trial,[4] with a mean age of 63.9 and 22% female. All patients began with NYHA class II or III HFrEF with a starting distribution of 75% and 25% respectively, based on PARADIGM-HF. The base-case time horizon was 20 years and cycle length was four months. The analysis was undertaken from a Canadian publicly funded health care system perspective.[3]

The model is based on five health states: four corresponding to NYHA classes I to IV (in increasing order of disease severity) and death. As patients progressed through the model they incurred the costs and outcomes associated with HFrEF based on the health states they experienced. The transitions observed between the four NYHA classes during the PARADIGM-HF trial were used to provide treatment- and cycle-specific transition probabilities for the first three years. From years 3 to 20, the manufacturer assumed that the NYHA distribution at the end of the third year would remain constant for the rest of the model time horizon.

Utilities for each NYHA class were based on directly measured EuroQol 5-Dimensions Questionnaire (EQ-5D) utilities from the PARADIGM-HF trial. Mortality was based on all-cause age-specific mortality (from Statistics Canada) and cardiovascular (CV)-specific mortality. CV mortality for years 0 to 3 was based on deaths observed in PARADIGM-HF. CV mortality rates for years 3 to 20 were based on extrapolating the survival data from PARADIGM-HF using a parametric survival model (Gompertz regression). All-cause hospitalization rates for each treatment and NYHA class were from PARADIGM-HF for years 0 to 3, and were extrapolated after based on a negative binomial regression model. The proportions of hospitalization types seen in PARADIGM-HF (heart failure [HF] 25.24%, CV non-HF 36.98%, non-CV 37.78%) were used. Hospitalization was associated with a disutility of –0.086 based on EQ-5D data from PARADIGM-HF, and was assumed to apply for 30 days. Rates and types of adverse events (AEs) considered by the model were also from PARADIGM-HF.

Costs considered were drug acquisition costs (both primary and background therapy), non-drug health care costs (costs of hospitalization and monthly management costs of HF) and costs for management of AEs. Drug dosages were the recommended doses from product monographs. The cost of sacubitril/valsartan treatment was calculated using the manufacturer's submitted price, while the costs of all other medications were from the Ontario Drug Benefit (ODB) formulary (2015).[8] Rates of background medication use were based on values observed in PARADIGM-HF. The costs of hospitalizations were derived from an IMS/Brogan study on HF hospitalizations in Canada. In-hospital mortality rates were based on those seen in PARADIGM-HF. Monthly monitoring consisted of general practitioner and specialist visits as well as laboratory and diagnostic testing; costs were based on a Canadian study.[9] The costs of AEs covered the additional physician visits, hospitalization/ER visits, lab

tests and medication. This AE-related resource utilization was estimated based on feedback from a Canadian clinical advisor. The costs of physician visits were obtained from the Ontario Health Insurance Plan (OHIP) 2014 schedule of benefits,[10] while the costs of laboratory tests were obtained from the 1999 Schedule of Benefits for Laboratory Services.[11]

2. MANUFACTURER'S BASE CASE

The manufacturer reported in its base case that sacubitril/valsartan is associated with an incremental cost-utility ratio (ICUR) of $29,999 ($25,730 per life-year) when compared with ACEI (costed as enalapril). Further details on these results are available in Table 13 and Table 14.

TABLE 2: MANUFACTURER'S BASE CASE

	Sacubitril/valsartan	ACEI	Incremental
Total costs (discounted)	$71,323	$52,377	$18,946
Total QALYs (discounted)	6.12	5.49	0.63
Incremental cost/QALY			$29,999
Total life-years (discounted)	7.46	6.73	0.74
Incremental cost/life-year gained			$25,730

ACEI = angiotensin-converting enzyme inhibitor; QALY = quality-adjusted life-year.

3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer varied the following parameters in scenario and deterministic sensitivity analyses: discount rate; time horizon; perspective; source of utilities; estimation of NYHA distribution after three years; CV mortality; CV mortality regression coefficient for sacubitril/valsartan; hospitalization regression coefficient for sacubitril/valsartan; monthly cost of HF management; annual cost of hospitalization; ACEI costs; and target population. Only varying the model time horizon had a significant impact on the base-case ICUR (with shorter time horizons producing larger ICURs — use of a three-year horizon reflecting the length of PARADIGM-HF leads to an ICUR of more than $80,000 per quality-adjusted life-year [QALY]).

The manufacturer assessed the full analysis set data from the PARADIGM-HF trial, including class II, III and IV NYHA patients in a scenario analysis. This analysis resulted in an ICUR of $33,349 per QALY. As noted by the manufacturer, given that 95% of patients were in class II to III at baseline of PARADIGM-HF, the cost-effectiveness results were not expected to shift appreciably.

The manufacturer reported the results of a probabilistic sensitivity analysis, in which there is a 50% chance that the ICUR for sacubitril/valsartan is less than $30,000 per QALY, and a 99.5% chance that the ICUR is below $50,000 per QALY.

4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

Unclear whether results are generalizable to Canadian HF patients due to issues with external validity of the PARADIGM-HF trial:
The use of enrichment criteria during patient selection and elimination of patients during the run-in period of PARADIGM-HF limits its external validity. Additionally, according to the clinical expert consulted during this review, the enrolled population was not representative of the HF population currently being treated in Canada. In particular:

- Of the 8,442 participants only 602 (7%) were North American. Treatment effects seen in global trials, especially where the bulk of evidence comes from other regions (such as the more than 50% of patients receiving care in Europe) may not be applicable to the decision-maker's context. Regional heterogeneity of outcomes has been observed in multiple global trials of HF medications.[12] As such, application of these study results to Canada must be undertaken with caution.
- Use of implantable cardioverter-defibrillators (ICDs) and cardiac resynchronization therapy (CRT) in North American patients was notably higher than the aggregate trial percentage (60% versus 16%). As ICDs and CRTs reduce mortality among HF patients,[7] it is unclear whether the observed mortality benefit applies to North American patients. The manufacturer conducted a subgroup analysis and found no differences between the ICD/CRT and non-ICD/CRT subgroups in effects on CV hospitalization (however, the 95% confidence intervals for all outcomes included the null value for the ICD/CRT subgroup).
- Demographic characteristics differ between PARADIGM-HF and Canadian HF patients for whom sacubitril/valsartan is a treatment option. Mean age in the model was 63.9 years and 22% of participants were female.[4] However, HF patients in Canada are older on average (over 75 years as per clinical expert input). Furthermore, the proportion of female patients is higher in Canadian practice (in excess of 50%).[6] Extrapolation of the results from a younger, predominantly male cohort to Canadian practice should be undertaken with caution.
- A high proportion (89%) of patients had a left ventricular ejection fraction (LVEF) of < 35% and most patients were in NYHA class II (70%). Thus, evidence of efficacy in those with higher ejection fractions and NYHA class III HF is less certain than for those with lower LVEFs and functional class.
- The use of a safety run-in period (with 20% attrition and only retaining patients that could tolerate both enalapril and sacubitril/valsartan) likely underestimates the true incidence of AEs.

As such, it remains to be seen whether the observed efficacy and cost-effectiveness corresponds with real-world effectiveness and value in Canada.

Length of the model time horizon associated with high uncertainty, considering the lack of long-term evidence available and also the age of the patient population to be treated in real-life clinical practice in Canada:
The manufacturer makes use of a 20-year model time horizon, noting that the average patient age in PARADIGM-HF and assumed for the model is 63.9 years, and that life expectancies for 64-year-old Canadian males and females are 19.6 and 22.6 years, respectively, thus making 20 years appropriate for capturing relevant costs and outcomes. However, the age of Canadian HF patients for whom sacubitril/valsartan is a treatment option is older in clinical practice (75.8 years), which would decrease life expectancy. Further and more importantly, there is a lack of long-term evidence for the comparative effectiveness of the treatment options assessed. Use of a shorter model time horizon may reduce the uncertainty of the long-term extrapolation of treatment effects.

Uncertain assumptions regarding NYHA distribution after year 3 and the extrapolation of trial results:
NYHA distributions from years 0 to 3 were based on what was observed during PARADIGM-HF. From years 3 to 20, the manufacturer assumed that NYHA distribution at year 3 in PARADIGM-HF would stay constant up to 20 years, implying maintenance of treatment efficacy and no progression of disease severity. Although recent evidence suggests that sacubitril/valsartan may be better than ACEIs at slowing the progression of HF,[13] there is no evidence to suggest absolute lack of progression. This assumption, coupled with assumptions of 100% treatment compliance and no treatment discontinuation, emphasizes the uncertainty of the long-term cost-effective results presented by the manufacturer, which are likely to favour sacubitril/valsartan.

Uncertainty in the data used to estimate QALY loss from hospitalization:
The manufacturer applied a disutility of –0.09 to hospitalizations based on EQ-5D data from patients in PARADIGM-HF. This value was obtained from patients who had been hospitalized during the previous 30 days and was assumed to apply additively for 30 days. However, given that median length of HF hospitalization in Ontario is 8 to 12 days,[14] this likely overestimates the disutility of hospitalization.

Overestimation of resource use associated with adverse events:
The assumptions regarding resource use for AEs was thought to be excessive by the clinical expert. In particular, the assumption of two cardiologist visits for treatment-emergent hypotension, cough, elevated serum potassium or elevated serum creatinine was thought to be more than would be seen in practice and would serve to overestimate the costs of AEs.

The use of the cost of enalapril as ACEI comparator is a less conservative choice than that of ramipril considering their relative prices and use in HF in the Canadian context:
Ramipril is the most widely prescribed ACEI in Canada, with IMS/Brogan data showing 10 times more claims for ramipril than enalapril. Ramipril is also less expensive than enalapril. The manufacturer acknowledged this and included a sensitivity analysis in which the price of ramipril is used in place of enalapril (assuming equal efficacy), finding that sacubitril/valsartan has an ICUR of $31,462 per QALY compared to ramipril.

5. CADTH COMMON DRUG REVIEW REANALYSES

To account for several of the limitations above, the following analyses were undertaken:

1. Horizon
CADTH Common Drug Review (CDR) considered a 10-year horizon in its base case to address the limitation of a long model time horizon and uncertainty in extrapolation of trial results.

2. Corrected costs for management of adverse events
CDR changed the number of cardiologist visits for hypotension (from two to one), cough, and elevated serum potassium or elevated serum creatinine (all from two to zero) to address the overestimation of resource use associated with AEs.

3. Patient demographic characteristics
Age was set to 75.8 years and 51% of patients were assumed to be female, better reflecting Canadian clinical values and partially addressing the limited external validity of the model population.

4. Ramipril

The cost of ACEIs was set to the cost of ramipril instead of enalapril. This addresses the limitation relating to choice of ACEI.

5. Hospital disutility

The manufacturer's 30-day value of –0.09 was set to 40% of its original value to reflect a mean hospitalization length of 12 days among Ontario HF patients,[14] thus addressing overestimation of QALY loss due to hospitalization.

Note that use of Canadian demographics, costs and utilities affected ICURs minimally and did not change the conclusions to be drawn from the manufacturer's results.

TABLE 3: CADTH COMMON DRUG REVIEW BASE CASE

Analysis		Scenario	ICUR ($/QALY)
	Manufacturer's base case	-	$29,999
1	Horizon 10 years	-	$39,587
2	Corrected costs for management of adverse events	1 cardiologist visit for hypotension (previously 2), 0 for cough, elevated serum potassium, or creatinine (all previously 2)	$29,993
3	Canadian patient demographics	Mean age 75.8 years, 51% female	$31,630
4	Ramipril as ACEI	Costs of ramipril were used in place of enalapril	$31,462
5	Hospital disutility	Model disutility was set to 40% of the base case value (reflecting median 12 day hospitalization in place of 30 day in Ontario[14])	$30,015
6	**CDR base case**	**Scenarios 1-5**	**$42,787**

ACEI = angiotensin-converting enzyme inhibitor; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year.

Price reduction analysis

CDR undertook a price reduction analysis to assess the effects of drug price on cost-effectiveness estimates (Table 16). In the CDR base case, price reductions of 25% and 35% result in ICURs of less than $30,000 and less than $25,000 respectively for sacubitril/valsartan compared to enalapril.

6. PATIENT INPUT

Input was received from the Heart and Stroke Foundation Canada. Patients noted that HF produces symptoms that have a significant impact on quality of life and the activities of daily living. These were accounted for in the economic analysis by inclusion of utility weights reflecting disease severity. Further, there is a high caregiver burden due to the required long-term commitment of time and energy that may require stressful changes in daily life. The costs and disutilities accruing to caregivers were not considered in the economic analysis. Patients noted that other available treatments for HF include ACEIs, angiotensin receptor blockers (ARBs), aldosterone inhibitors, beta blockers, digoxin, diuretics, oral anticoagulants, and statins. Concerns were voiced over the large number of medications necessary, as well as the need for time-specific dosing, multiple medications at multiple points throughout the day, and the need for frequent doctor visits, all of which affect patients' daily life.

Of the 13 patients that had experience with sacubitril/valsartan, six reported that sacubitril helped control their condition while another six were unsure and one reported that it did not help. Furthermore, five patients reported experiencing side effects. AEs (and their treatment) were considered in the economic model. However, discontinuation due to lack or loss of efficacy was not considered.

7. CONCLUSIONS

A key limitation of the manufacturer's submission was the uncertain generalizability of results to a Canadian HF population based on the use of a non-representative patient population in PARADIGM-HF. CDR conducted an analysis addressing identified limitations regarding model horizon (reduced to 10 years), patient demographic characteristics, cost of ramipril, costs of AEs, and disutility of hospitalization, resulting in a CDR base-case ICUR estimate of $42,787. It should be noted that these results apply only to the extent that the population of PARADIGM-HF reflects the Canadian HF population, and that PARADIGM-HF results are envisaged as plausible in the Canadian context. The cost-effectiveness of sacubitril/valsartan may be found to differ as future effectiveness data become available. In the CDR base case, price reductions of 25% and 35% are necessary to lower the ICUR to below $30,000/QALY and $25,000/QALY, respectively.

APPENDIX 1: COST COMPARISON

The comparators presented in the following tables 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 from the Ontario Drug Benefit list prices, unless otherwise specified. Existing product listing agreements are not reflected in the table and as such may not represent the actual costs to public drug plans.

TABLE 4: COST COMPARISON TABLE FOR HEART FAILURE TREATMENTS — ANGIOTENSIN RECEPTOR–NEPRILYSIN INHIBITORS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Annual Cost ($)
Angiotensin receptor–neprilysin inhibitor (ARNI)					
sacubitril/valsartan (Entresto)	**24.3mg/25.7 mg 48.6mg/51.4 mg 97.2mg/102.8 mg**	**Tablet**	**$3.6200[a]**	**97.2 mg/102.8 mg twice daily[b]**	**$2,642.60**

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor.

[a] Manufacturer's submitted price.[2]

[b] Target dose is 97.2 mg/102.8 mg twice daily with a recommended starting dose of 48.6 mg/51.4 mg twice daily. A starting dose of 24.3 mg/25.7 mg twice daily may be considered for certain patients such as those at risk for hypotension or those on lower doses of ACEI or ARB prior to starting sacubitril/valsartan.[1] The dose should be increased every 2 to 4 weeks to reach the target dose according to patient tolerance.

TABLE 5: COST COMPARISON TABLE FOR HEART FAILURE TREATMENTS — ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Annual Cost ($)
Angiotensin receptor–neprilysin inhibitor (ARNI)					
sacubitril/valsartan (Entresto)	**24.3 mg/25.7 mg 48.6 mg/51.4 mg 97.2 mg/102.8 mg**	**Tablet**	**$3.6200[a]**	**97.2 mg/102.8 mg twice daily[b]**	**$2,642.60**
Angiotensin-converting enzyme inhibitors (ACEIs) with an HF indication					
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	328.50 to 1,138.25
cilazapril (generics)	1 mg 2.5 mg 5 mg	Tablet	0.1557 0.1795 0.2085	1 mg to 2.5 mg daily	56.83 to 65.52
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	80.41 to 193.23
fosinopril (generics)	10 mg 20 mg	Tablet	0.2178 0.2619	20 mg to 40 mg once daily	95.59 to 191.19
lisinopril (generics)	5 mg 10 mg	Tablet	0.1347 0.1619	2.5 mg to 30 mg once daily	24.58 to 130.09

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Annual Cost ($)
	20 mg		0.1945		
perindopril (Coversyl)	2 mg 4 mg 8 mg	Tablet	0.6527 0.8168 1.1325	2 mg to 4 mg daily	238.24 to 298.13
quinapril (Accupril)	5 mg 10 mg 20 mg 40 mg	Tablet	0.2321	10 mg once to 20 mg twice daily	84.71 to 169.43
Angiotensin-converting enzyme inhibitors (ACEIs) without an HF indication					
benazepril (generics)	5 mg 10 mg 20 mg	Tablet	0.5577 0.6595 0.7567	20 mg to 40 mg daily	276.20 to 552.39
ramipril (generics)	1.25 mg 2.5 mg 5 mg 10 mg	Capsule	0.1274 0.1470 0.1470 0.1862	2.5mg to 5 mg twice daily[c]	107.31
trandolapril (Mavik)	1 mg 2 mg 4 mg	Capsule	0.6901 0.7931 0.9785	2 mg to 4 mg daily[c]	289.48 to 357.15

ACEI = angiotensin-converting enzyme inhibitor; ARNI = angiotensin receptor–neprilysin inhibitor; HF = heart failure.
[a] Manufacturer's submitted price.[2]
[b] Target dose is 97.2 mg/102.8 mg twice daily with a recommended starting dose of 48.6 mg/51.4 mg twice daily. A starting dose of 24.3 mg/25.7 mg twice daily may be considered for certain patients such as patients at risk for hypotension or those on lower doses of ACEI or ARB prior to starting sacubitril/valsartan.[1] The dose should be increased every 2 to 4 weeks to reach the target dose according to patient tolerance.
[c] Dosing based on post-myocardial infarction-reduce hospitalization due-heart failure indication.
Source: Ontario online drug plan formulary November 2015[8] unless indicated otherwise.

TABLE 6: COST COMPARISON TABLE FOR HEART FAILURE TREATMENTS — ANGIOTENSIN RECEPTOR BLOCKERS

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Annual Cost ($)
Angiotensin receptor–neprilysin inhibitor (ARNI)					
sacubitril/valsartan (Entresto)	**24.3 mg/25.7 mg 48.6 mg/51.4 mg 97.2 mg/102.8 mg**	**Tablet**	**$3.6200[a]**	**97.2 mg/102.8 mg twice daily[b]**	**$2,642.60**
Angiotensin receptor blockers (ARBs) with an HF indication					
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; target 32 mg dose	First year: 105.06 Subsequent years: 107.02
valsartan (generics)	80 mg 160 mg 320 mg	Tablet	0.2958 0.2958 0.2843	80 mg to 160 mg twice daily	215.93
Angiotensin receptor blockers (ARBs) without an HF indication					
eprosartan (Teveten)	400 mg 600 mg	Tablet	0.7246 1.1079	600 mg daily	404.38

Drug/Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Annual Cost ($)
irbesartan (generics)	75 mg 150 mg 300 mg	Tablet	0.3025	150 mg to 300 mg daily	110.41
losartan (generics)	25 mg 50 mg 100 mg	Tablet	0.3147	50 mg to 100 mg daily	114.87
olmesartan (Olmetec)	20 mg 40 mg	Tablet	1.1165	20 mg to 40 mg daily	407.52
telmisartan (generics)	40 mg 80 mg	Tablet	0.2824	80 mg daily	103.08

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = Angiotensin receptor–neprilysin inhibitor; HF= heart failure.

TABLE 7: COST COMPARISON TABLE FOR HEART FAILURE TREATMENTS — OTHER TREATMENTS

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Annual Cost ($)
Aldosterone antagonists with an HF indication					
eplerenone (Inspra)	25 mg 50 mg	Tablet	2.6660[a]	25 mg to 50 mg daily	973.09
spironolactone (generic)	25 mg 100 mg	Tablet	0.1057 0.2461	25 mg to 200 mg daily	38.58 to 179.65
Beta blockers with an HF indication					
carvedilol (generics)	3.125 mg 6.25 mg 12.5 mg 25 mg	Tablet	0.3377	3.125 mg to 25 mg twice daily	246.52
Beta blockers without an HF indication					
atenolol (generics)	50 mg 100 mg	Tablet	0.1437 0.2362	50 mg to 100 mg daily	52.45 to 86.21
bisoprolol (generics)	5 mg 10 mg	Tablet	0.0994 0.1450	10 mg daily[a]	52.93
labetalol (Trandate)	100 mg 200 mg	Tablet	0.3360 0.5939	200 mg to 400 mg twice daily	433.55 to 867.09
metoprolol (generics)	50 mg 100 mg	Tablet	0.0624 0.1361	50 mg to 100 mg twice daily	45.55 to 99.35
	100 mg 200 mg	Sustained Release Tablet	0.1415 0.2568	100 mg to 200 mg daily	51.65 to 93.73
nadolol (generics)	40 mg 80 mg 160 mg	Tablet	0.4512 0.3710 1.2046	80 to 320 mg daily	135.41 to 879.36
nebivolol (Bystolic)	2.5 mg 5 mg 10 mg 20 mg	Tablet	1.3900[b]	5 mg to 20 mg daily	507.35

Drug/ Comparator	Strength	Dosage Form	Price ($)	Recommended Dosage	Annual Cost ($)
propranolol (generics)	10 mg 20 mg 40 mg 80 mg 120 mg	Tablet	0.0689 0.1107 0.1225 0.2034 0.3091	160 mg to 320 mg daily	74.24 to 148.42
sotalol (generics)	80 mg 160 mg	Tablet	0.2966[d] 0.1623	160 mg to 320 mg daily in two doses[e]	59.24 to 118.48

HF = heart failure.
[a] Dosing based on off-label use in heart failure patients from the e-Therapeutics Heart Failure entry, last revised June 2015.[15]
[b] Based on PharmaStat (IMS Brogan) 2015 private claims data for Ontario, figure includes a markup.
[c] Saskatchewan Formulary (November 2015).
[d] Dosing based on ventricular arrhythmia indication, sotalol product monograph.[16]
Pricing source: Ontario Drug Benefit Formulary (November 2015) unless otherwise indicated. Dosing based on hypertension indication unless otherwise indicated.

APPENDIX 2: SUMMARY OF KEY OUTCOMES

TABLE 8: WHEN CONSIDERING ONLY COSTS, OUTCOMES AND QUALITY OF LIFE, HOW ATTRACTIVE IS SACUBITRIL/VALSARTAN RELATIVE TO ACEI?

Sacubitril/valsartan vs. ACEI	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	$29,999 per QALY $25,730 per life-year					

ACEI = angiotensin-converting enzyme inhibitor; CE = cost-effectiveness; NA = not applicable; QALY = quality-adjusted life-year; vs. = versus.
Based on manufacturer's results.[3]

APPENDIX 3: ADDITIONAL INFORMATION

TABLE 9: SUBMISSION QUALITY

	Yes/ Good	Somewhat/ Average	No/ Poor
Are the methods and analysis clear and transparent?	X		
Comments	None		
Was the material included (content) sufficient?	X		
Comments	None		
Was the submission well organized and was information easy to locate?	X		
Comments	None		

TABLE 10: AUTHOR INFORMATION

Authors of the pharmacoeconomic evaluation submitted to CDR			
☐ Adaptation of Global model/Canadian model done by the manufacturer ☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer ☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer ☐ Other (please specify)			
	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

CDR = CADTH Common Drug Review.

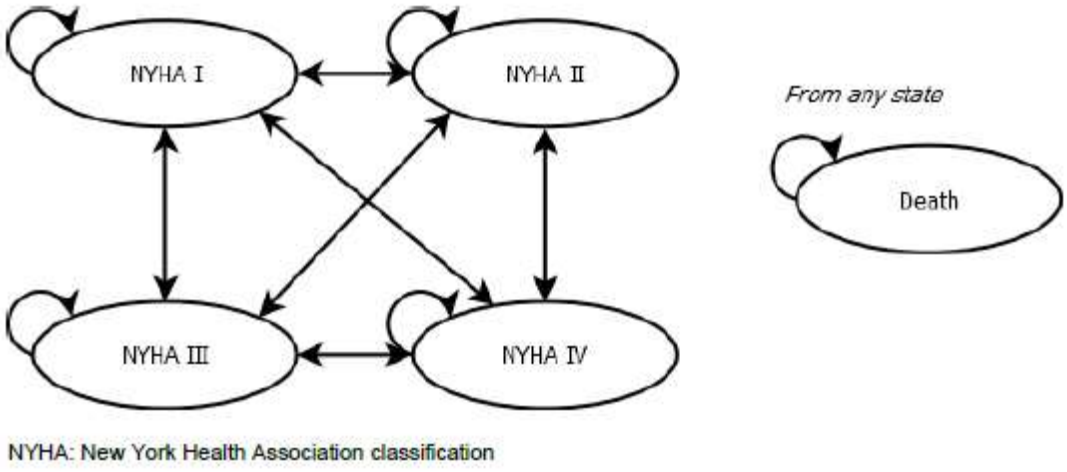
APPENDIX 4: REVIEWER WORKSHEETS

Manufacturer's Model Structure

The manufacturer submitted a cost-utility analysis based on a Markov model comparing sacubitril/valsartan with angiotensin-converting enzyme inhibitor (ACEI), both in addition to background therapy, among adult heart failure with reduced ejection fraction (HFrEF) patients in New York Heart Association (NYHA) class II or III. Patients in the model were assumed to have characteristics similar to patients included in the PARADIGM-HF trial, with a mean age of 63.9 and 22% of patients being female. All patients began with NYHA class II or III HFrEF with a starting distribution of 75% and 25% based on PARADIGM-HF. The base-case time horizon was 20 years and cycle length was four months. The analysis was undertaken from a Canadian publicly funded health care system perspective.[3]

The model is based on five health states — four corresponding to NYHA classes I to IV (in increasing order of disease severity), and death. All patients begin the model in NYHA class II or III (75% and 25%, respectively). As patients progressed through the model they incurred the costs and outcomes associated with HFrEF based on the health states they experienced. The transitions observed between the four NYHA classes during the PARADIGM-HF trial were used to provide treatment- and cycle-specific transition probabilities for the first three years. From years 3 through 20 the manufacturer assumed that the NYHA distribution at the end of the third year would remain constant for the rest of the model lifetime.

FIGURE 1: SCHEMATIC OF MANUFACTURER'S ECONOMIC MODEL



NYHA = New York Heart Association.
Source: Manufacturer's pharmacoeconomic submission.[3]

Utilities for each NYHA class were based on directly measured EuroQol 5-Dimensions Questionnaire (EQ-5D) utilities from the PARADIGM-HF trial. Mortality was based on all-cause age-specific mortality (from Statistics Canada) and cardiovascular (CV)-specific mortality. CV mortality for years 0 to 3 was based on deaths observed in PARADIGM-HF. CV mortality rates for years 3 to 20 were based on extrapolating the survival data from PARADIGM-HF using a parametric survival model (Gompertz regression). All-cause hospitalization rates for each treatment and NYHA class were from PARADIGM-HF for years 0 to 3, and were predicted based on a negative binomial regression model fitted to PARADIGM-HF hospitalization data for years 3 to 20. The proportion of hospitalization types seen in PARADIGM-HF (heart failure [HF]

25.24%, CV non-HF 36.98%, non-CV 37.78%) were used to estimate the number of each type of visit. Hospitalization was associated with a 30-day disutility of –0.086 based on EQ-5D data from PARADIGM-HF patients who had been hospitalized in the previous 30 days. Rates of adverse events (AEs) used in the model were estimated based on observed AEs among class II to III patients in PARADIGM-HF.

Costs considered were drug acquisition costs (both primary and background therapy), non-drug health care costs (hospitalization and monthly management of HF), and costs for management of AEs. Drug dosages were the recommended doses from product monographs. The cost of sacubitril/valsartan was based on the manufacturer's submitted price, while the costs of all other medications were from the Ontario Drug Benefit (ODB) 2015 formulary.[8] Rates of background medication use were based on values observed in PARADIGM-HF. The costs of hospitalization were derived from an IMS/Brogan study on HF hospitalizations in Canada. In-hospital mortality rates were based on those seen in PARADIGM. Monthly monitoring consisted of general practitioner and specialist visits, as well as laboratory and diagnostic testing, and costs were based on a Canadian study.[9] The costs of AEs covered the additional physician visits, hospitalization/ER visits, and lab tests. The number of visits and required medications were based on feedback from a Canadian clinical advisor. The following AEs and their associated resource use were considered: hypotension (two cardiologist visits); cough (two cardiologist visits); milder angioedema (two outpatient contacts and antihistamines); severe angioedema (emergency department visit, two cardiologist visits and glucocorticoids); elevated serum creatinine (two cardiologist visits and cost of serum creatinine testing) and; elevated serum potassium (two cardiologist visits and cost of serum potassium testing). The costs of physician visits were obtained from the Ontario Health Insurance Plan (OHIP) 2014 schedule of benefits,[10] while the costs of laboratory tests were obtained from the 1999 Schedule of Benefits for Laboratory Services.[11]

TABLE 11: DATA SOURCES

Data Input	Description of Data Source	Comment
Efficacy	Treatment efficacy was measured in terms of movement between NYHA classes and patient distribution between said classes (as lower classes reflect less-severe disease, a distribution skewed toward lower numbers represents more effective treatment). Movement between NYHA classes in years 0 to 3 was based on what was observed during PARADIGM-HF; observations were used to estimate treatment- and cycle-specific transition probability matrices. For years 3 to 20 it was assumed that values remained constant.	Appropriate for years 0 to 3. For years 3 to 20 this makes a strong (and unsupported) assumption that treatment efficacy is maintained over time and that there is no progression of disease. This was assessed by CDR in its sensitivity analyses.
Natural history	From years 3 to 20 it was assumed that there was no progression of NYHA scores.	Unclear whether this is appropriate given the paucity of existing data.
Utilities	Utilities for each NYHA state were based on directly measured EQ-5D utilities from PARADIGM-HF trial. The disutility of hospitalization was based on EQ-5D values from patients who had been hospitalized 0 to 30 days prior to their EQ-5D measurement visit. In particular, the value of	Given the low number of North American patients in the trial, it is questionable whether utility values are applicable to a Canadian cohort. Given that the mean length of hospital stay for HF in Ontario is between 9 and 12 days,[14] the

Data Input	Description of Data Source	Comment
	–0.09 per hospitalization was assumed to be additive as it was applied for 30 days.	assumption that patients incur 30 days' worth of disutility overestimates QALY loss due to hospitalization.
Resource use	Drugs (primary therapy): dose of sacubitril/valsartan was based on the product monograph. Dose of enalapril was based on values reflecting the CONSENSUS trial. Drugs (background therapy): based on proportions of concomitant medication use in PARADIGM-HF. Hospitalization: treatment and NYHA dependent rate calculated based on negative binomial regression. HF management: assumed to accrue to all non-hospitalized patients AEs: treatment specific rates were estimated (regardless of NYHA class) based on PARADIGM-HF; resource use associated with AEs were estimated based on expert opinion.	Appropriate, apart from assumptions regarding resource use for AEs and proportion of patients receiving background therapy. Management of AEs was altered in the CDR base case; background therapy cost variations were also tested. Both were found to have negligible impact on results.
AEs	AEs were based on pre-specified AEs from PARADIGM-HF (hypotension, cough, angioedema, and elevated serum potassium or creatinine). Treatment specific rates were estimated (regardless of NYHA class) based on PARADIGM-HF.	Appropriate, although the assumption of constant rate across time and lack of dependence on NYHA are questionable. CDR acknowledges that there is limited information in this area.
Hospitalization	All-cause hospitalization rates were estimated by negative binomial regression for each treatment and NYHA class.	Appropriate; however, the negative binomial regression assumes the hospitalization rate is constant across time, whereas there is evidence the rate increases with age.[17]
Withdrawal from treatment	Not considered.	Possibly inappropriate. Although both treatment arms had similar withdrawals during the double-blind phase, the manufacturer did not provide an option to assess treatment withdrawal in the model.
Mortality	Mortality was modelled as the sum of age-specific all-cause mortality (minus CV deaths) and CV mortality. Age-specific all-cause mortality (without CV mortality) was from Statistics Canada life tables. CV-specific mortality from PARADIGM-HF. Directly observed deaths were made into cycle-specific mortalities for years 0 to 3 (using Kaplan–Meier	Appropriate. While some sources posit that Weibull models are more appropriate than Gompertz models for modelling cause-specific mortality[18] this made little difference in practice.

Data Input	Description of Data Source	Comment
	estimators). From years 3 to 20 mortality was extrapolated using a parametric Gompertz survival model.	
Costs		
Drug	Primary therapy – manufacturer's submitted price (sacubitril/valsartan), ODB formulary (enalapril). Background therapy – ODB.	Treatment of primary therapy is appropriate; however, ramipril is more widely prescribed than enalapril by an order of magnitude (IMS/Brogan data) and is less costly than enalapril, thus CDR considered ramipril as the ACEI in its base case. The clinical expert noted that the observed rates of background therapy in PARADIGM-HF are likely higher than what would be seen in practice, in particular the prior use of an ACEI/ARB and high proportions of patients on concomitant therapy (including 93% of patients on beta blockers). CDR assessed this by varying the cost of background medication and finding that it made no significant difference on the ICUR.
Hospitalization	Based on IMS/Brogan analyses of hospitalization costs for Canadian HF patients.	Appropriate.
AEs	Based on clinical expert opinion, costs of services, drugs and lab tests from OHIP, ODB and schedule of laboratory benefits, respectively.	While unit costs were appropriate, resource use was thought to be excessive. Corrected in CDR base case.
HF management	A per-cycle cost was derived for each NYHA class (regardless of treatment) derived based on IMS/Brogan analyses of non-hospital HF management.	Appropriate, as this cost did not accrue to hospitalized patients (thereby avoiding double counting).

AE = adverse event; ACEI = angiotensin receptor blocker; ARB = angiotensin receptor blocker; CDR = CADTH Common Drug Review; CV = cardiovascular; EQ-5D = EuroQol 5-Dimensions Questionnaire; HF = heart failure; ICUR = incremental cost-utility ratio; NYHA = New York Heart Association; ODB = Ontario Drug Benefit; QALY = quality-adjusted life-year.

TABLE 12: MANUFACTURER'S KEY ASSUMPTIONS

Assumption	Comment
Global efficacy results from PARADIGM-HF are generalizable to the Canadian context.	Highly questionable due to demographic characteristics (age, % female), clinical characteristics (low prevalence of ICD/CRT use, low ejection fraction and low functional class), the use of a run-in period, and the low proportion of North American patients (7%). The issue of generalizability is the main problem with the manufacturer's submission.
Enalapril is representative of all ACEIs.	Plausible. Some publications have posited a class effect for ACEIs[19] and this was thought to be true by the clinical expert.
ACEIs and ARBs are similarly efficacious.	Acceptable.
NYHA distribution holds constant at years 3	Unclear whether appropriate or not given a paucity of long-term

Assumption	Comment
to 20 (i.e., treatment efficacy maintained across the time horizon and there is no progress of disease in terms of NYHA class).	data. However, it was felt to be unlikely by the clinical expert, especially given the 20-year horizon. Assessed in the CDR sensitivity analyses.
Patients do not withdraw from treatment.	Possibly inappropriate. No option was provided to assess this in the manufacturer's model. There were similar rates of withdrawal from both treatments in PARADIGM-HF, thus this is likely to result in a negligible impact in an incremental analysis.
Utilities from global trial are generalizable to Canadian context.	Questionable given the low proportion of North American patients.
Rate of adverse events remains constant across time and regardless of class (i.e., only depends on treatment).	Unclear whether appropriate given paucity of data, although it is expected that adverse events might increase with age/frailty.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association.

Manufacturer's Base Case

The manufacturer reported in its base case that sacubitril/valsartan is associated with a cost of $71,323, 6.12 quality-adjusted life-years (QALYs) and 7.46 life-years. When compared with ACEI, sacubitril/valsartan was $18,946 more costly, with a gain of 0.63 QALYs and 0.74 life-years, for an incremental cost-utility ratio (ICUR) of $29,999 (and incremental cost-effectiveness ratio [ICER] of $25,730 per life-year.)

TABLE 13: MANUFACTURER'S BASE CASE — CLINICAL OUTCOMES

Outcomes	sacubitril/valsartan	ACEI	Incremental
Hospitalizations			
HF hospitalizations	0.74	0.75	–0.01
Other CV hospitalizations	1.08	1.10	–0.02
Non-CV hospitalizations	1.10	1.12	–0.02
No. of hospitalizations per year	0.28	0.33	–0.04
Survival			
CV mortality at year 2	11%	14%	–3%
CV mortality at year 5	21%	26%	–5%
CV mortality at year 10	46%	54%	–8%
All-cause mortality at year 2	12%	15%	–3%
All-cause mortality at year 5	29%	35%	–6%
All-cause mortality at year 10	54%	62%	–8%
Expected survival (years)	10.26	9.04	1.22
Time in NYHA class			
I	1.39	1.14	0.25
II	6.80	5.82	0.98
III	2.03	2.04	–0.01
IV	0.04	0.04	0.00
Adverse events			
Hypotension	0.64	0.38	0.26
Cough	0.51	0.57	–0.06
Angioedema	0.02	0.01	0.01

Outcomes	sacubitril/valsartan	ACEI	Incremental
Elevated serum creatinine	0.16	0.19	–0.03
Elevated serum potassium	0.74	0.70	0.04

ACEI = angiotensin receptor blocker; CV = cardiovascular; HF = heart failure; NYHA = New York Heart Association.

TABLE 14: MANUFACTURER'S BASE CASE — DISCOUNTED DISAGGREGATED COSTS

Costs	ENTRESTO	ACEI	Incremental
Primary therapy	$19,736	$1,280	$18,456
Background therapy	$1,851	$1,642	$210
Hospitalization	$38,891	$39,773	–$882
HF management	$10,722	$9,575	$1,148
Adverse events	$122	$108	$15
Average annual therapy costs	$2,892	$434	$2,458
Average annual non-therapy costs	$6,664	$7,352	–$688

ACEI = angiotensin receptor blocker.

CADTH Common Drug Review Sensitivity Analyses

Utilities

Utility values from Göhler et al.[20] were considered instead of the PARADIGM-HF utilities, given the higher proportion of North American patients in Göhler et al. (31% versus 7%).

Hospitalization rates and New York Heart Association progression

Use of an exposure-adjusted rate model for hospitalization was considered in place of the manufacturer's negative binomial regression. This accounts for the effects of time (and, implicitly, age and disease length) on hospitalization risk.[21] Notably, age has been associated with increased risk of hospitalization.[17] The manufacturer's assumed value of 2% annual risk of NYHA progression was used to assess the effects of disease progression on results.

All of the above were used to calculate a "conservative" scenario in which sacubitril/valsartan has an ICUR of $69,757 per QALY compared to ACEIs.

TABLE 15: CADTH COMMON DRUG REVIEW SENSITIVITY ANALYSES FOR SACUBITRIL/VALSARTAN VERSUS ANGIOTENSIN-CONVERTING ENZYME INHIBITOR

Analysis		Scenario	ICUR ($/QALY) – 10 year horizon
	CDR base case	-	**$42,787**
1	Utilities	Use of Göhler et al.'s utilities,[20] which include a higher proportion of North American patients than the PARADIGM-HF utilities	$45,932
2	Alternative model of hospitalization rates	Use of an exposure-adjusted rate instead of negative binomial model, accounting for increased length of treatment exposure (and implicitly increased age and length of disease) on hospitalization[21]	$57,998
3	NYHA progression risk	Assumes an annual risk of 2% of moving to the next most severe NYHA class	$49,887
4 (1-3)	**CDR conservative scenario**	**All of the above scenario analyses applied to the CDR base cases**	$69,757

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; NYHA = New York Heart Association; QALY = quality-adjusted life-year.

Price reduction analysis

CDR considered the effects of price reductions on cost-effectiveness estimates for the five- and 10-year base cases.

TABLE 16: CADTH COMMON DRUG REVIEW PRICE REDUCTION ANALYSIS

ICURs of sacubitril/valsartan ($/QALY)	
Price of sacubitril/valsartan	**CDR 10-Year Base Case (ICUR vs. enalapril)**
List price ($3.620/tablet)	42,787
10% reduction ($3.258/tablet)	38,061
15% reduction ($3.077/tablet)	35,698
20% reduction ($2.896/tablet)	33,335
25% reduction ($2.715/tablet)	30,972
30% reduction ($2.534/tablet)	28,609
35% reduction ($2.353/tablet)	26,246
40% reduction ($2.172/tablet)	23,833
45% reduction ($1.991/tablet)	21,520
50% reduction ($1.810/tablet)	19,157

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; vs. = versus.

Use of an exposure-adjusted rate model for hospitalization was considered in place of the manufacturer's negative binomial regression. This accounts for the effects of time (and, implicitly, age and disease length) on hospitalization risk.[21] Notably, age has been associated with increased risk of hospitalization.[17] The manufacturer's assumed value of 2% annual risk of NYHA progression was used to assess the effects of disease progression on results.

All of the above were used to calculate a "conservative" scenario in which sacubitril/valsartan has an ICUR of $69,757 per QALY compared with ACEIs.

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