CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

SACUBITRIL/VALSARTAN (ENTRESTO — NOVARTIS PHARMACEUTICALS CANADA INC.)
Indication: Heart failure, NYHA Class II or III

RECOMMENDATION
The CADTH Canadian Drug Expert Committee recommends that sacubitril/valsartan be reimbursed for the treatment of heart failure with reduced ejection fraction in patients with New York Heart Association class II or III heart failure to reduce the incidence of cardiovascular death and heart failure hospitalization, only if the following conditions are met.

Conditions for Reimbursement
1. Patient has reduced left ventricular ejection fraction (< 40%).
2. Patient has New York Heart Association class II to III symptoms despite at least four weeks of treatment with a stable dose of an angiotensin-converting enzyme inhibitor or an angiotensin II receptor antagonist in combination with a beta blocker and other recommended therapies, including an aldosterone antagonist (if tolerable).
3. Patient has plasma B-type natriuretic peptide ≥ 150 pg/mL or N-terminal prohormone B-type natriuretic peptide ≥ 600 pg/mL; or plasma B-type natriuretic peptide ≥ 100 pg/mL or N-terminal prohormone B-type natriuretic peptide ≥ 400 pg/mL levels if the patient has been hospitalized for heart failure within the past 12 months.

Service Line:	CADTH Drug Reimbursement Recommendation
Version:	1.0
Publication Date:	March 2021
Report Length:	12 Pages

CADTH

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

CADTH

SACUBITRIL/VALSARTAN (ENTRESTO — NOVARTIS PHARMACEUTICALS CANADA INC.)

Indication: Heart failure, New York Heart Association (NYHA) Class II or III

This recommendation supersedes the CADTH Canadian Drug Expert Committee (CDEC) recommendation for this drug and the indication dated March 18, 2016.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that sacubitril/valsartan be reimbursed for the treatment of heart failure with reduced ejection fraction (HFrEF) in patients with NYHA class II or III heart failure (HF) to reduce the incidence of cardiovascular (CV) death and HF hospitalization, only if the following conditions are met.

Conditions for Reimbursement

1. Patient has reduced left ventricular ejection fraction (LVEF) (< 40%).
2. Patient has NYHA class II to III symptoms despite at least four weeks of treatment with a stable dose of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin II receptor antagonist (ARB) in combination with a beta blocker and other recommended therapies, including an aldosterone antagonist (if tolerable).
3. Patient has plasma B-type natriuretic peptide (BNP) ≥ 150 pg/mL or N-terminal prohormone B-type natriuretic peptide (NT-proBNP) ≥ 600 pg/mL; or plasma BNP ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL levels if the patient has been hospitalized for HF within the past 12 months.

Reasons for the Recommendation

1. One double-blind, randomized controlled trial (RCT) (PARADIGM-HF; N = 8,442) demonstrated that treatment with sacubitril/valsartan reduced the risk of CV mortality or hospitalization for HF by 20% compared with enalapril (hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.73 to 0.87). Patients enrolled in PARADIGM-HF were receiving stable doses of an ACEI or an ARB in combination with a beta blocker and often an aldosterone antagonist.
2. One double-blind, RCT (PIONEER-HF; N = 887) enrolled a mixed population of ACEI and ARB treatment-naive and experienced patients with HFrEF, who were hemodynamically stabilized during hospitalization for acute decompensated HF. Sacubitril/valsartan, initiated during hospitalization, resulted in a reduction in the primary outcome of time-averaged (weeks 4 and 8) proportional change from baseline in NT-proBNP levels as compared with enalapril in the eight-week double-blind treatment period. However, clinical outcomes including those important to patients — such as CV events, health-related quality of life (HRQoL), and mortality — were analyzed as exploratory composite endpoints, some post hoc, and without adjustment for multiplicity. Therefore, the trial did not clearly demonstrate that initiating treatment with sacubitril/valsartan in patients who are ACEI and ARB treatment-naive during hospitalization, compared to enalapril, resulted in improved clinical outcomes.
3. CADTH reanalysis of a cost-utility model provided by the sponsor for the original submission estimated that sacubitril/valsartan is associated with an incremental cost-utility ratio (ICUR) of $42,787 per quality-adjusted life-year (QALY), compared with ramipril, in patients who had been receiving a stable dose of an ACEI or an ARB. For the resubmission, CADTH could not determine the cost-effectiveness of using sacubitril/valsartan for the treatment of patients stabilized from an HF hospitalization without prior exposure to an ACEI or an ARB because of limitations with the submitted economic evaluation that could not be addressed given model structure, and the lack of robust comparative clinical evidence.

Implementation Considerations

- CDEC noted the availability of BNP and NT-proBNP testing varies across the jurisdictions, which may have some implications for the implementation of the clinical criterion based on BNP and NT-proBNP levels.

Discussion Points

- Although there were statistically significant benefits for all-cause mortality and CV-related deaths in PARADIGM-HF, sacubitril/valsartan did not demonstrate a statistically significant improvement for myocardial infarction, stroke, new-onset atrial fibrillation, or change in NYHA functional class over time.
- Patients in PARADIGM-HF were highly selected. Fewer than 60% of patients screened for the trial entered the treatment phase, with most patients excluded due to low BNP or NT-proBNP levels. Furthermore, 20% of patients who entered the run-in phase were excluded, mainly due to tolerability issues. CDEC heard clinical expert input that the randomized population was not representative of the HF population currently being treated in Canada.
- A relatively small proportion of the patients were recruited from North America (7%). Important differences between the trial population and the typical Canadian population were noted for baseline disease and demographic characteristics, background therapy, use of cardiac resynchronization therapy and implantable cardioverter-defibrillators.
- Most patients in PARADIGM-HF (89%) had LVEF of 35% or less at baseline and there is limited evidence for patients with LVEF greater than 35% to 40% or less.
- Most patients in PARADIGM-HF (70%) were NYHA class II at baseline; there is less evidence of clinical benefit from sacubitril/valsartan compared with enalapril for patients with NYHA class III or IV HF.
- Patients enrolled in PARADIGM-HF were required to have BNP plasma levels ≥ 150 pg/mL or NT-proBNP levels ≥ 600 pg/mL unless the patient had been hospitalized for HF in the past year, then patients were required to have BNP plasma levels ≥ 100 pg/mL or NT-proBNP ≥ 400 pg/mL.
- CDEC discussed the possibility of collecting data on the rate of hospitalizations due to HF for patients who are treated with sacubitril/valsartan, while noting the many confounders that would make such a collection of uncertain usefulness.
- CDEC noted that the product monograph states that sacubitril/valsartan must not be administered until at least 36 hours have elapsed following discontinuation of ACEI therapy.
- PARADIGM-HF trial was an event-driven trial that was stopped early based on the pre-specified stopping criteria for the primary composite outcome as well as CV mortality. CDEC noted that trials that are stopped early often overestimate treatment effects and underestimate harms.
- The resubmission for sacubitril/valsartan requested expanded reimbursement with initiation of sacubitril/valsartan in patients stabilized from a heart failure hospitalization without prior exposure to ACEI or ARB. CDEC discussed that the PIONEER-HF trials had several limitations, including not being specifically designed or analyzed to evaluate the comparative treatment effects of sacubitril/valsartan for clinical outcomes (e.g., mortality, CV events, HRQoL) in the requested reimbursement subpopulation of patients stabilized from a heart failure hospitalization without prior exposure to ACEI or ARB. The limitations precluded CDEC from determining whether initiating treatment with sacubitril/valsartan instead of an ACEI or an ARB is associated with improved outcomes in this subpopulation of patients with HF and reduced ejection fraction.
- The sponsor suggested in the resubmission that initiating sacubitril/valsartan treatment during HF hospitalization in patients who have not previously received an ACEI or an ARB would confer other benefits related to patient monitoring, safety, or a smoother transition to the community setting. However, CDEC did not consider that any of the reviewed evidence supported these assertions.
- The primary outcome in PIONEER-HF was time-averaged proportional change from baseline in NT-proBNP through weeks 4 and 8. Although changes in NT-proBNP during admissions for acute decompensated HF have been associated with reduced HF mortality and readmissions, NT-proBNP targeted therapy has not been demonstrated to consistently improve outcomes. Accordingly, the validity of NT-proBNP as a surrogate end point for mortality and CV outcomes, and the clinical relevance of the observed decline in NT-proBNP in PIONEER-HF, is uncertain.
- While treatment for 8 weeks with sacubitril/valsartan appeared to be associated with fewer HF rehospitalizations than enalapril in PIONEER-HF (8.0% with sacubitril/valsartan versus 13.8% with enalapril), CDEC could not conclude that the finding was due to the effects of sacubitril/valsartan because of the limitations with the design and statistical analysis. PIONEER-HF was not designed to specifically evaluate this clinical outcome. HF-rehospitalizations were captured as a component of two separate but similar composite clinical endpoints comprised of four components (in the “serious” composite clinical end point) and seven components (in the “overall” composite clinical end point). Furthermore, the analyses of these composite end points and their components were described as exploratory in the statistical analysis plan of the trial, and they were not controlled for multiplicity.

As a result, the evidence for the benefit of sacubitril/valsartan on the occurrence of HF-rehospitalizations in ACEI or ARB naive patients is of low certainty.

- CDEC discussed results from TRANSITION-HF (N = 991), a supportive phase IV RCT with the primary objective to evaluate the safety and tolerability of sacubitril/valsartan initiation before or after discharge from hospital in patients with HFrEF who were hospitalized for an acutely decompensated HF. However, limitations regarding the internal validity (i.e., open-label design, imbalances in baseline patient characteristics, potential for reporting bias), external validity (enrolled patients may not reflect those seen in clinical practice settings), exploratory efficacy analyses, and unclear relevance to the ACEI/ARB treatment-naive subpopulation (approximately 24% of enrolled patients) prevented CDEC from drawing conclusions on the results that would inform the reimbursement request.

Background

Sacubitril/valsartan is a sodium hydrate complex of two active drugs: sacubitril, a first-in-class neprilysin inhibitor, and valsartan, an ARB. Sacubitril/valsartan is indicated for the treatment of HFrEF in patients with NYHA class II or III, to reduce the incidence of CV death and HF hospitalization. It is available as combination tablets that contain sacubitril/valsartan in the following fixed-dose ratios: 24 mg/26 mg, 49 mg/51 mg, and 97 mg/103 mg, respectively. The recommended starting dose for most patients is sacubitril 49 mg/valsartan 51 mg twice daily orally, increased every two to four weeks, as tolerated, to the target dose of sacubitril 97 mg/valsartan 103 mg twice daily.

Submission History

Sacubitril/valsartan was previously reviewed by CADTH for the treatment of HF and received a CDEC recommendation to be reimbursed, with criteria and conditions, for the treatment of HFrEF in patients with NYHA class II or III HF to reduce the incidence of CV death and HF hospitalization (March 2016).

The original CADTH systematic review of sacubitril/valsartan included the PARADIGM-HF RCT, which was the pivotal trial supporting market authorization in Canada and the CDEC recommendation to reimburse sacubitril/valsartan.

This resubmission is based on additional clinical evidence of the treatment effects of sacubitril/valsartan compared with enalapril among patients stabilized during hospitalization for acute decompensated HF who have not previously received an ACEI or an ARB.

Based on the new clinical evidence, the sponsor requested the following addition to the existing criteria: initiation of sacubitril/valsartan in patients stabilized from an acute decompensated HF hospitalization without prior exposure to ACEI or ARB.

Summary of Evidence Considered by CDEC

CDEC considered the following information prepared by CADTH: systematic reviews of RCTs and supportive studies of sacubitril/valsartan, and a critique of the sponsor's pharmacoeconomic evaluations. The committee also considered input from clinical experts with experience in treating patients with heart failure, and patient group–submitted information about outcomes and issues important to patients.

Summary of Patient Input

One patient group, the Heart and Stroke Foundation of Canada (HSF), provided input for the initial review of sacubitril/valsartan. Information was gathered via an online survey circulated using social media, the HSF Canada website, and emails to patients and caregivers.

The HeartLife Foundation provided input for the resubmission of sacubitril/valsartan. Patient perspectives were gathered through virtual workshops with peers, peer-reviewed publications, in-person round-table workshop, and interviews with patients and caregivers. The following is a summary of key input from the perspective of the patient groups:

- HF is a serious, progressive health problem that affects patients' quality of life and often limits their ability to work as well as recreational and day-to-day activities.

- Patients described shortness of breath, extreme fatigue, low blood pressure, dizziness, edema, and bloating as notable symptoms of HF that impact their daily lives. Patients also experience disturbed sleep, the need for frequent rest periods during daily tasks, and a negative impact on mental health such as anxiety, depression, or a decline in cognitive ability. Caregivers of patients with HF also described the significant impact of the disease on family life and how it takes a toll on their (caregiver's) own physical and mental health.
- Patient groups recognized that there are multiple medications available to treat HF and that existing therapies can be quite effective in managing HF. For some patients; however, management of their condition is suboptimal and for some the adverse events are intolerable. It was also emphasized that early adoption of and access to therapies is paramount.
- Patients with HF expressed a desire for therapies that improved symptom control, quality of life and reduced their risk of hospitalization and death. HF patient also put a priority on access to medication and health care services in general and at an earlier stage of their disease progression.

Clinical Trials

Initial Submission

The CADTH clinical review included one double-blind, randomized, active-controlled superiority trial (PARADIGM-HF, N = 8,442). The trial compared the safety and efficacy of sacubitril/valsartan versus enalapril, in patients with HF and reduced ejection fraction (≤ 40% or ≤ 35%) with NYHA functional class II to IV who were treated with an ACEI or ARB plus a beta blocker (unless contraindicated). All patients enrolled were required to meet criteria for BNP or NT-proBNP plasma levels, and to complete run-in periods with enalapril and sacubitril/valsartan at the target doses. Those who were able to tolerate the study drugs were randomized to double-blind treatment with enalapril 10 mg twice daily or sacubitril 97 mg/valsartan 103 mg twice daily, and continued on background HF medications (except for prior ACEI or ARB therapy).

The patients enrolled had a mean age of 64 years, LVEF of 29%, were predominantly male (78%), and had NYHA functional class II HF (70%). The median treatment duration was 24 months. Death was the primary reason for discontinuing among the 20% of patients in the enalapril group and 18% in sacubitril/valsartan group who did not complete the trial. The event-driven trial was stopped at the third interim analysis based on pre-specified efficacy stopping criteria.

PARADIGM-HF was an event-driven trial, powered for an estimated 2,410 events (CV deaths or HF hospitalizations) to signal the end of the trial. The trial was stopped early based on pre-specified criteria for the primary composite outcome as well as CV mortality, analyzed by an independent statistician. The overall alpha error was controlled across the interim analyses and for the primary and secondary endpoints. Several exploratory outcomes and subgroups were analyzed but did not use procedures to control for multiplicity of statistical testing. The enrichment design applied in the screening phase to the selection of patients for inclusion and exclusion of patients limits the external validity of the trial. Likewise, the enrolment criteria were restrictive and likely included only a subset of patients who would likely be considered for treatment with sacubitril/valsartan. The efficacy of sacubitril/valsartan as a first-line treatment for patients with HF has not been evaluated in the trial. The study likely underestimates the incidence of adverse events because it was stopped early and the study design excluded patients who were unable to tolerate specific dosages of the study drugs during the run-in phase. The long-term safety profile of sacubitril/valsartan requires further evaluation.

Resubmission

The CADTH review for the resubmission included one study, PIONEER-HF (N = 887). PIONEER-HF was a phase III, double-blind, active-controlled, RCT, designed to assess the effect of in-hospital initiation of sacubitril/valsartan versus enalapril in patients who have been stabilized following hospitalization for acute decompensated HF with reduced ejection fraction (LVEF ≤ 40%). Patients were randomized in a 1:1 ratio to receive twice daily sacubitril/valsartan (24/26, 49/51, or 97/103 mg) or twice daily enalapril (2.5, 5.0, or 10 mg) within 10 days after presenting to the hospital for acute decompensated HF. Doses were gradually titrated to the target or maximum level, based on patient's tolerability and investigator's decision. The study was divided into an 8-week double-blind phase, followed by a 4-week open-label phase. Approximately 20% patients in both groups discontinued study treatment during the double-blind phase, primarily due to adverse events and patient decision.

The percentages of patients enrolled in PIONEER-HF who aligned with the reimbursement request were 52% ACEI or ARB treatment-naive, 34.4% with newly diagnosed HF, and approximately 88% with NYHA class II-III symptoms. Few outcomes were

analyzed by prior ACEI or ARB treatment experience, and none were analyzed by NYHA class II-III or by history of HF. The subgroup analyses were likely underpowered and not included in the randomization scheme, and therefore imbalances in the subgroups may exist. The primary efficacy end point in the trial was change in NT-proBNP, a biomarker-based outcome, for which there is uncertainty regarding its validity as a surrogate outcome for mortality and CV events. Several clinical end points were assessed as pre-specified or post hoc exploratory, composite outcomes, analyzed without controlling for multiplicity.

Outcomes

Outcomes of interest for both the initial and resubmission of sacubitril/valsartan were defined a priori in CADTH's systematic reviews. Of these, CDEC discussed the following:

- all-cause and CV mortality
- all-cause and HF-related hospitalization
- HRQoL – measured in PARADIGM-HF and PIONEER-HF as the change from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score and the clinical summary score (which includes the HF symptom and physical limitation domains). The KCCQ is a HF-specific HRQoL questionnaire with scores ranging from 0 to 100. The minimal clinically important difference for the overall score is five points.
- change in NYHA functional class
- other CV outcomes: myocardial infarction, stroke, sudden cardiac death, and atrial fibrillation
- change from baseline in NT-proBNP
- total adverse events, serious adverse events, withdrawals due to adverse events, and adverse events.

Mortality and morbidity outcomes in both trials were analyzed mainly as composite endpoints, with separate analyses for the individual components.

The primary efficacy outcome in PARADIGM-HF was the time to CV mortality or first HF-related hospitalization. The primary efficacy outcome in PIONEER-HF was the time-averaged proportional change from baseline in NT-proBNP.

Efficacy

Initial Submission

Sacubitril/valsartan demonstrated a statistically significant improvement over enalapril in all-cause mortality (17% versus 20%, respectively; HR 0.84; 95% CI, 0.76 to 0.93). There were fewer CV-related deaths in the sacubitril/valsartan versus enalapril groups (13% versus 17%, respectively; HR 0.80; 95% CI, 0.71 to 0.89), including fewer sudden deaths (6.0% versus 7.4%) and pump failures (3.5% versus 4.4%). The differences in CV mortality or first HF hospitalization were statistically significant for sacubitril/valsartan (22%) compared with enalapril (27%) (HR 0.80; 95% CI, 0.73 to 0.87).

Sacubitril/valsartan was not associated with clinically important differences in NYHA functional class or the KCCQ clinical summary score (mean difference 1.6 points) and KCCQ overall score (mean difference 1.9 points).

The incidence of other CV outcomes (myocardial infarction, stroke, or new-onset atrial fibrillation) was similar in the sacubitril/valsartan and enalapril groups.

Resubmission

Among patients who were ACEI/ARB treatment-naive, a smaller percentage of patients in the sacubitril/valsartan group (7.3%) had an occurrence of the serious composite end point (death, HF rehospitalization, requirement of left ventricular assistive device, or listed for cardiac transplantation) compared to the enalapril group (13.2%; HR 0.52; 95% CI, 0.29 to 0.95). Results were similar in the ACEI/ARB treatment-experienced subgroup; no treatment by subgroup interaction was found. In the full population, 9.3% of patients

in the sacubitril/valsartan group had an occurrence of the serious composite end point compared to 16.8% in the enalapril group. The largest difference observed in the individual components was for HF rehospitalization, reported in 8.0% and 13.8% patients in the sacubitril/valsartan and enalapril group, respectively. Notably, this composite end point was not pre-specified in the study's protocol, instead analyzed before database lock.

A similar frequency of overall composite end point events (death, HF rehospitalization, requirement of left ventricular assistive device, listed for cardiac transplantation, unplanned acute HF visits requiring intravenous diuretics, additional HF drug, or increase in > 50% of the diuretic dose) were reported in both treatment groups (sacubitril/valsartan 56.6%, enalapril 59.9%). Among the individual components, HF rehospitalization occurred at a lower frequency between the treatment groups (sacubitril/valsartan 8.0% versus enalapril 13.8%, P = 0.0049). Results were available for the full population only.

Among patients who were ACEI/ARB treatment-naive, 7.8% of patients in the sacubitril/valsartan group and 12.8% in the enalapril group had an occurrence of the composite end point, time to first occurrence of positively adjudicated HF rehospitalization or positively adjudicated CV death (HR 0.57; 95% CI, 0.32 to 1.03). Results were similar in the ACEI/ARB-experienced subgroup, with no treatment by subgroup interaction noted. In the full population, 8.9% patients in the sacubitril/valsartan group had an occurrence of this composite end point, compared to 14.7% in the enalapril group. Notably, this was a post hoc analysis.

The mean difference between sacubitril/valsartan and enalapril in the full population of PIONEER-HF was 0.14 points (95% CI,–3.48 to 3.75) for the KCCQ clinical summary score.

Among patients who were ACEI or ARB treatment-naive, there was a numerical benefit in favour of sacubitril/valsartan versus enalapril (ratio of geometric mean of values obtained at weeks 4 and 8 of 0.72, 95% CI, 0.60 to 0.86). The time-averaged proportional change from baseline in NT-proBNP was similarly improved with sacubitril/valsartan versus enalapril in each of the other study populations.

Harms (Safety)

Initial Submission

In PARADIGM-HF, 81% and 83% of patients reported an adverse event, 46% and 51% reported a serious adverse event, and 11% and 12% stopped treatment due to adverse events in the sacubitril/valsartan and enalapril groups, respectively.

Besides cardiac failure, the most commonly reported adverse events in both groups were cough, hyperkalemia, renal impairment, and hypotension (10% to 18%).

Hypotension was reported more frequently among patients who received sacubitril/valsartan than enalapril (exposure-adjusted incidence rate 13.2 versus 9.5 events/100 patient-years, respectively); however, the incidence of serious hypotensive events was similar between groups.

Renal dysfunction, hyperkalemia, and cough were reported more frequently in the enalapril group than in the sacubitril/valsartan group.

Angioedema was reported by 19 patients in the sacubitril/valsartan group compared with 10 patients in the enalapril group during the double-blind period.

Resubmission

[redacted]

A secondary analysis of the following notable adverse events was conducted by prior ACEI/ARB exposure: symptomatic hypotension, hyperkalemia, and all angioedema. The frequency of these adverse events was similar between the treatment groups among ACEI/ARB treatment-naive or experienced patients.

Indirect Treatment Comparisons

No indirect comparisons were submitted by the sponsor or identified by CADTH in a supplemental search literature search.

Other Relevant Evidence

Initial Submission

No additional studies were reviewed.

Resubmission

TRANSITION-HF (N = 991) was a supportive, phase IV randomized, multicenter, open-label, parallel-group study, designed to assess the safety and tolerability of sacubitril/valsartan initiated before discharge from the hospital versus after discharge from the hospital, in patients with HFrEF who were hospitalized for an acute decompensated HF event. Patients were stratified based on whether they were ACEI treatment experienced, ARB treatment-experienced, or ACEI or ARB treatment-naive, and randomized to treatment period groups (pre-discharge sacubitril/valsartan initiation, and post-discharge sacubitril/valsartan initiation). The characteristics of the enrolled patients were generally similar to those of the PIONEER-HF patient population.

[redacted]

The open-label design, imbalances in baseline patient characteristics, potential for reporting bias, lack of an active comparator group, limitations with generalizability, and exploratory efficacy analyses, make it difficult to interpret the results of this study. Furthermore, approximately 24% of enrolled patients were ACEI or ARB treatment-naive; therefore, the applicability of the results to this subpopulation is uncertain.

Cost and Cost-Effectiveness

Initial Submission

The sponsor submitted a cost-utility analysis comparing sacubitril 97 mg/valsartan 103 mg twice daily to ACEI (both in addition to background therapy) in adult patients with HF with reduced ejection fraction (NYHA class II or III). The analysis was undertaken from a Canadian publicly funded health care system perspective over a 20-year time horizon. The analysis was based on a Markov model consisting 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 reduced ejection fraction based on the health states they experienced. Patient improvement and deterioration were modelled as movement between NYHA classes. Transitions between NYHA classes in years 0 to 3 were based on PARADIGM-HF, comparing sacubitril/valsartan with enalapril 10 mg twice daily. In 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-Dimenions Questionnaire (EQ-5D) utilities from PARADIGM-HF. Mortality was based on all-cause age-specific mortality from Statistics Canada and CV mortality data from PARADIGM-HF. CV mortality data for years 0 to 3 were based on deaths observed in PARADIGM-HF, while a survival model was used to extrapolate values for years 3 to 20. All-cause hospitalization rates were obtained from PARADIGM-HF for years 0 to 3 and extrapolated using a

regression model. Rates of adverse events for each treatment were also based on the results of PARADIGM-HF. Drug acquisition costs (both primary and background therapy), costs of hospitalization and monthly management of HF, and costs for management of adverse events were considered in the analysis.

The sponsor reported that when added to background therapy, the ICUR for sacubitril/valsartan compared with ACEI was $29,999 per QALY.

CADTH noted a number of limitations with the sponsor's analysis.

- It is unclear whether the results are generalizable to Canadian patients with HF due to concerns regarding the external validity of PARADIGM-HF.
- The 20-year time horizon of the model may not be ideal due to uncertainty in the long-term extrapolation of treatment effectiveness, and considering that the mean age of the Canadian HF patient population is older than 75 years.
- There is uncertainty regarding the appropriateness of assumptions regarding NYHA distribution after year three and extrapolation of trial results.
- There is uncertainty in data and assumptions used to estimate QALY loss from hospitalization.
- Resource use associated with adverse events is overestimated.
- Given that ramipril is both cheaper than enalapril and more frequently used among Canadian HF patients, it would have been more appropriate to use ramipril as the ACEI comparator.

Based on CADTH reanalyses to account for the above limitations (e.g., use of a 10-year horizon, adjusting patient demographics, correcting for costs of adverse events, assuming a different disutility of hospitalization, and use of ramipril cost in place of enalapril), sacubitril 97 mg/valsartan 103 mg was associated with an ICUR of $42,787 per QALY when compared with ACEI.

Resubmission

Sacubitril/valsartan is available at $3.71 per tablet, regardless of dose, with an annual cost of $2,705 per patient.

The sponsor submitted a cost-utility analysis that compared sacubitril/valsartan to enalapril, in ACEI and ARB treatment-naive patients with NYHA class II or III HFrEF who are stabilized from hospitalization for acute decompensated HF, over an 8-week time horizon. This population reflects a specific point in the care pathway for patients with HFrEF, compared to the broader Health Canada indication, and aligns with the sponsor's reimbursement request which seeks to expand the prior CADTH recommendation that restricts sacubitril/valsartan to patients with at least four weeks of ACEI or ARB experience.

The sponsor's decision tree model followed patients hospitalized with HFrEF, who were treated with either sacubitril/valsartan or enalapril. Patients were hospitalized for four weeks, during which they accrued health utility decrement and costs associated with the HF hospitalization. Beyond this initial hospitalization, patients could experience one of three outcomes: recurrent HF hospitalization, death, or, event-free status at eight weeks post-treatment. Patients were assumed to experience the latter four weeks of the eight-week time horizon without further impact on their QALYs, unless they died. The sponsor considered costs, but not disutility, of recurrent HF hospitalizations occurring at eight weeks. Baseline patient characteristics were not explicitly reflected as model inputs. However, treatment-specific recurrent HF hospitalization and all-cause mortality rates for sacubitril/valsartan and enalapril were sourced from the PIONEER-HF trial (which included patients who had previous treatment with ACEI or ARB medications, 48%), and health utility inputs were based on EQ-5D data from the sponsor's PARADIGM-HF trial (which required ACEI or ARB experience for study participation).

CADTH identified the following key limitations with the sponsor's pharmacoeconomic analysis:

- The submitted model did not accurately reflect the clinical pathway associated with HF patients and had a short time horizon that did not adequately consider all relevant costs and clinical outcomes.
- The sponsor did not sufficiently capture parameter uncertainty in the model. The sponsor's approach to probabilistic analysis inappropriately correlated all model parameters and assumed a smaller probabilistic distribution than is observed from the available evidence.

- The cost of HF hospitalizations was overestimated and was a key cost driver.
- The cost of the ACEI/ARB comparator is based on enalapril, rather than the least costly ACEI/ARB (ramipril).
- CADTH clinical reviewers deemed that clinical efficacy (i.e., HF rehospitalization and all-cause mortality) of sacubitril/valsartan compared to enalapril from the sponsor's PIONEER-HF trial was not robust.

While CADTH corrected a number of identified issues in the reanalyses (independent random sampling of model parameters; larger standard errors for clinical outcome parameters; updated HF hospitalization costs from 2017/2018; and using ramipril for the comparator cost), the cost-effectiveness of sacubitril/valsartan remains uncertain as major structural limitations could not be addressed. Based on CADTH reanalysis, sacubitril/valsartan may be dominant compared to ramipril (incremental cost savings of $89 and incremental health benefit of 0.0007 QALYs per patient) over the eight-week period described by the model. These findings, however, were highly sensitive to assumptions around the comparative effectiveness of sacubitril/valsartan. CADTH exploratory analyses suggested that sacubitril/valsartan would no longer be dominant if the rate of hospitalizations or death was 20% to 25% lower than was observed in PIONEER-HF.

The results of these analyses focused on the effects of treatment in patients with HFrEF who are stabilized from hospitalization, who may have not had a previous treatment with ACEI and ARBs over an eight-week period. This is insufficient to capture the longer-term treatment effects for a chronically progressive condition. The clinical impact of treatment with sacubitril/valsartan during hospitalization after stabilization beyond 8 weeks is unknown, as is the longer-term cost-effectiveness of sacubitril/valsartan.

CDEC Members

Initial Submission

Dr. Lindsay Nicolle (Chair), Dr. James Silvius (Vice-Chair), Dr. Silvia Alessi-Severini, Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Mr. Frank Gavin, Dr. Peter Jamieson, Dr. Anatoly Langer, Mr. Allen Lefebvre, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. Adil Virani, and Dr. Harindra Wijeysundera.

February 17, 2016 Meeting

Regrets

Three CDEC members were unable to attend the meeting.

Conflicts of Interest

None

Resubmission

Dr. James Silvius (Chair), Dr. Ahmed Bayoumi, Dr. Sally Bean, Dr. Bruce Carleton, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Mr. Allen Lefebvre, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, Dr. Yvonne Shevchuk, and Dr. Adil Virani.

October 21, 2020 Meeting

Regrets

None

Conflicts of Interest

None