

CADTH CANADIAN DRUG EXPERT COMMITTEE FINAL RECOMMENDATION

SACUBITRIL/VALSARTAN

(Entresto — Novartis Pharmaceuticals)

Indication: Heart Failure With Reduced Ejection Fraction

Recommendation:

The Canadian Drug Expert Committee (CDEC) recommends that sacubitril/valsartan be listed for the treatment of heart failure (HF) with reduced ejection fraction in patients with New York Heart Association (NYHA) class II or III HF to reduce the incidence of cardiovascular (CV) death and HF hospitalization, if all of the following clinical criteria are met:

Clinical Criteria:

- Reduced left ventricular ejection fraction (LVEF) (< 40%).
- 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).
- Plasma B-type natriuretic peptide (BNP) \geq 150 pg/mL or N-terminal prohormone B-type natriuretic peptide (NT-proBNP) \geq 600 pg/mL; or plasma BNP \geq 100 pg/mL or NT-proBNP \geq 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 (DB), 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).
2. At the submitted price (\$3.62 per 50 mg, 100 mg, or 200 mg tablet), the CADTH Common Drug Review (CDR) 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.
3. 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.

Of Note:

- 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.
- Patients in PARADIGM-HF were likely different from the usual Canadian HF population and optimization of HF treatment to Canadian standards of practice may attenuate the relative benefit of sacubitril/valsartan compared with standard ACEI/ARB treatment.
- Although there were statistically significant benefits for all-cause mortality and CV-related deaths, 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.
- The design and duration of the PARADIGM-HF trial limited the ability to detect adverse events (AEs).

Background:

Entresto 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 HF with reduced ejection fraction 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 24.3 mg/valsartan 25.7 mg, sacubitril 48.6 mg/valsartan 51.4 mg, and sacubitril 97.2 mg/valsartan 102.8 mg. The recommended starting dose for most patients is sacubitril 48.6 mg/valsartan 51.4 mg twice daily orally, increased every two to four weeks, as tolerated, to the target dose of sacubitril 97.2 mg/valsartan 102.8 mg twice daily.

Summary of CDEC Considerations

CDEC considered the following information prepared by CDR: a systematic review of RCTs of sacubitril/valsartan, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients living with HF.

Patient Input Information

One patient group, the Heart and Stroke Foundation of Canada (HSF), responded to the CDR call for patient input. Information was gathered via an online survey circulated using social media, the HSF website, and emails to patients and caregivers. The following is a summary of information that was provided:

- 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 with HF and their caregivers frequently experience a substantial impact emotionally, psychologically, and financially as a result of the disease.
- Although multiple medications are available to treat HF, management is suboptimal for many patients and for some the AEs are intolerable.

Clinical Trials

The systematic review included one DB, 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 ($\leq 40\%$ or $\leq 35\%$) 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 DB treatment with enalapril 10 mg twice daily or sacubitril 97.2 mg/valsartan 102.8 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.

Outcomes

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

- Time to all-cause mortality.
- Time to CV mortality or first HF-related hospitalization.
- Change from baseline to eight months 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 health-related quality of life questionnaire with scores ranging from 0 to 100. The minimal clinically important difference for the overall score is 5 points.
- Change in NYHA functional class.
- Other CV outcomes: myocardial infarction, stroke, sudden cardiac death, and atrial fibrillation.
- Total AEs, serious adverse events (SAEs), and withdrawals due to AEs.

The primary outcome in the trial was the time to CV mortality or first HF-related hospitalization.

Efficacy

- 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 [MD] 1.6 points) and KCCQ overall score (MD 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.

Harms (Safety and Tolerability)

- In PARADIGM-HF, 81% and 83% of patients reported an AE, 46% and 51% reported an SAE, and 11% and 12% stopped treatment due to AEs in the sacubitril/valsartan and enalapril groups, respectively.

- Besides cardiac failure, the most commonly reported AEs 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 DB period.

Cost and Cost-Effectiveness

The manufacturer submitted a cost-utility analysis comparing sacubitril 97.2 mg/valsartan 102.8 mg twice daily to ACEI (both in addition to background therapy) in adult patients with HF with reduced ejection fraction (HFrEF) (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 HFrEF 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-Dimensions 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 AEs 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 AEs were considered in the analysis.

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

CDR noted a number of limitations with the manufacturer'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 over 75 years.
- There is uncertainty regarding the appropriateness of assumptions regarding NYHA distribution after year 3 and extrapolation of trial results.
- There is uncertainty in data and assumptions used to estimate QALY loss from hospitalization.

- Resource use associated with AEs 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 CDR reanalyses to account for the above limitations (e.g., use of a 10-year horizon, adjusting patient demographics, correcting for costs of AEs, assuming a different disutility of hospitalization, and use of ramipril cost in place of enalapril), sacubitril 97.2 mg/valsartan 102.8 mg was associated with an ICUR of \$42,787 per QALY when compared with ACEI.

Other Discussion Points:

CDEC noted the following:

- 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. According to the clinical expert consulted for this review, the randomized population was not representative of the HF population currently being treated in Canada.
- The majority of patients in PARADIGM-HF (89%) had LVEF of 35% or less at baseline and there is limited evidence for patients with LVEF > 35% to 40% or less.
- 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.
- The majority of 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.
- 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.

Research Gaps:

CDEC noted that there is insufficient evidence regarding the following:

- The efficacy of sacubitril/valsartan as a first-line treatment for patients with HF has not been evaluated.
- The long-term safety profile of sacubitril/valsartan requires further evaluation.

CDEC Members:

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 Wijeyesundera.

February 17, 2016 Meeting**Regrets:**

Three CDEC members were unable to attend the meeting.

Conflicts of Interest:

None

About This Document:

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

The manufacturer has reviewed this document and has not requested the removal of confidential information.

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