CADTH

CADTH COMMON DRUG REVIEW

CADTH Canadian Drug Expert Committee Recommendation

(Final)

IVABRADINE HYDROCHLORIDE (LANCORA — SERVIER CANADA INC.)
Indication: Heart Failure, NYHA class II to III

RECOMMENDATION:
The CADTH Canadian Drug Expert Committee (CDEC) recommends that ivabradine hydrochloride (ivabradine) be reimbursed for the treatment of stable chronic heart failure with reduced left ventricular ejection fraction (LVEF) (≤ 35%) in adult patients with New York Heart Association (NYHA) classes II or III who are in sinus rhythm with a resting heart rate ≥ 77 beats per minute (bpm), to reduce the incidence of cardiovascular mortality and hospitalizations for worsening heart failure, administered in combination with standard chronic heart failure therapies, if the following clinical criteria are met:

Clinical Criteria:

- Patients with 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 blocker (ARB) in combination with a beta blocker and, if tolerated, a mineralocorticoid receptor antagonist (MRA).
- Patients with at least one hospitalization due to heart failure in the last year.
- Resting heart rate must be documented to be ≥ 77 bpm on average using either an ECG on at least three separate visits or by continuous monitoring.

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- Patients with at least one hospitalization due to heart failure in the last year.
- Resting heart rate must be documented as ≥ 77 bpm on average using either an ECG on at least three separate visits or by continuous monitoring.

Reasons for the Recommendation:

1. One double-blind, randomized, placebo-controlled superiority trial (SHIfT, N = 6,558) demonstrated a statistically significant improvement in the primary composite end point (cardiovascular [CV] mortality and hospitalization for worsening heart failure) for patients treated with ivabradine compared with placebo in the pre-specified subgroup of patients (N = 3,357) with a baseline heart rate of ≥ 77 bpm (27.4% versus 34.2%, respectively, hazard ratio [HR] 0.75; 95% confidence interval [CI], 0.67 to 0.85, $P < 0.0001$).
2. The CADTH Common Drug Review base-case incremental cost-utility ratio (ICUR) was estimated to be $12,895 per quality-adjusted life-year (QALY) for ivabradine plus standard of care (SOC) compared with SOC alone, based on an incremental cost of $3,355 and an incremental gain of 0.2602 QALY.

Of Note:

CDEC noted that sacubitril/valsartan received a CDEC recommendation to reimburse with criteria in March 2016. Sacubitril/valsartan has a Health Canada–approved indication for the treatment of heart failure with reduced ejection fraction in patients with NYHA class II or III, and is to be used in combination with other heart failure therapies in place of an ACEI or ARB. CDEC recognized that patients who are eligible for treatment with ivabradine may also be eligible for treatment with sacubitril/valsartan; however, there is no evidence to assess the combined use of ivabradine and sacubitril/valsartan and no evidence to assess the comparative efficacy or safety of ivabradine versus sacubitril/valsartan.

Discussion Points:

- CDEC recognized that the Health Canada–approved indication for ivabradine was based on a pre-specified subgroup of patients (N = 3,357) from the overall SHIfT trial. While the CDR review and CDEC discussion focused on the results from the subgroup of patients with an average resting heart rate of ≥ 77 beats per minute, the subgroup results were consistent with the overall trial results (including patients with a resting heart rate of ≥ 70 bpm on average); this demonstrated a statistically significant improvement in the ivabradine treatment group compared with the placebo group for the composite primary outcome of CV death or hospitalization due to worsening heart failure (24.5% versus 28.7%, respectively, HR 0.82; 95% CI, 0.75 to 0.90, $P < 0.0001$).

- CDEC noted that the pharmacoeconomic model submitted by the manufacturer lacked flexibility and transparency. Hence, the CADTH Common Drug Review (CDR) was unable to perform sufficient model validations, vary parameters, and test scenarios of relevance. This limits confidence in the model results.

Background:

Ivabradine has a Health Canada–approved indication for the treatment of stable chronic heart failure with reduced LVEF (≤ 35%) in adult patients with New York Heart Association (NYHA) classes II or III who are in sinus rhythm with a resting heart rate ≥ 77 bpm, to reduce the incidence of CV mortality and hospitalizations for worsening heart failure, administered in combination with standard chronic heart failure therapies. Ivabradine is available as film-coated tablets that contain ivabradine hydrochloride 5 mg and 7.5 mg. The recommended starting dose is 5 mg twice daily orally; dose adjustments are permitted after two weeks of treatment, depending on the resulting heart rate, up to a maximum dose of 7.5 mg taken twice daily orally.

Summary of CDEC Considerations:

CDEC considered the following information prepared by CDR: a systematic review of randomized controlled trials of ivabradine, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group–submitted information about outcomes and issues important to patients living with heart failure.

Patient Input Information

Two patient groups, The HeartLife Foundation (HLF) and Heart Failure Support Group of Manitoba (HFSGM), responded to the CDR call for patient input. Much of the information in the HLF submission was based on the lived experience of the two co-founders of HLF (both of whom have been patients with heart failure). Other information in the submission was gathered from published materials the authors had reviewed and from conversations with health care professionals, other patients, caregivers, and family members. Information in the HFSGM was mainly gathered from a discussion at an education session for patients and caregivers and from conversations with individual patients and caregivers.

- Heart failure is a serious and progressive health problem that affects patients' quality of life, and often limits their ability to participate in work, recreational, and day-to-day activities. Patients identified fatigue, breathlessness, and difficulty sleeping as particular and very common problems.
- Patients with heart failure frequently experience anxiety, depression, confusion, and stress as a result of their condition. Caregivers also experience increased stress and — like patients — often must deal with added financial burdens.
- Although multiple medications are available to treat heart failure, some patients are unable to tolerate some elements of the standard therapy, most often an optimal dose of beta-blocker. Thus, the management of their condition is suboptimal.

Clinical Trials

The CDR systematic review included one event-driven, double-blind, randomized, placebo-controlled superiority trial (SHIfT, N = 6,558). The study compared the safety and efficacy of ivabradine versus placebo, for the treatment of stable chronic heart failure with reduced LVEF (≤ 35%) in adult patients with NYHA classes II or IV who are in sinus rhythm with a resting heart rate ≥ 70 beats per minute, to reduce the incidence of cardiovascular mortality and hospitalizations for worsening heart failure, administered in combination with standard chronic heart failure therapies. Patients were randomized and titrated to ivabradine hydrochloride 2.5 mg (half of the 5 mg tablet), 5 mg, and 7.5mg oral film-coated tablets twice daily in combination with standard chronic heart failure treatment or were randomized to placebo in combination with standard chronic heart failure treatment. The SHIfT study comprised a two-week run-in period, a four-week titration period, and an event driven (up to 52 months) treatment follow-up period. The median treatment duration and median follow-up times were approximately 21 and 22 months.

The Health Canada–approved indication and the manufacturer's reimbursement request were for the treatment of patients with heart rates ≥ 77 bpm. Therefore, the CDR review focused on the pre-specified subgroup of patients enrolled in the SHIfT study with heart rates ≥ 77 bpm (N = 3,357). Patients in the heart rate ≥ 77 bpm subgroup of the SHIfT trial had a mean age of [redacted], of whom [redacted] were younger than 65 years of age and [redacted] were 75 years or older. [redacted]

[redacted]. Almost all patients were [redacted], and [redacted]. The median resting heart rate was [redacted] and [redacted] of patients had mean LVEF between > 30% and ≤ 35% ([redacted] of patients had LVEF ≤ 30%). The [redacted]. Approximately [redacted] of patients were receiving target daily doses of beta-blockers and approximately [redacted] were taking ≥ 50% of the target daily dose of beta-blockers.

Key limitations of the SHIfT study included randomization not being stratified based on heart rate; the lack of control for multiple statistical testing across end points, subgroups of interest, and sensitivity analyses; and the differences in patient and practice characteristics between the study centres in the SHIfT trial (mainly located in eastern European countries), and what would be seen in a Canadian setting (for example, the mean age of patients, and the use of optimal standard chronic heart failure treatment).

Outcomes

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

- Mortality (all-cause mortality, CV mortality, and death from heart failure): adjudicated by a blinded Endpoint Validation Committee (EVC).
- Hospitalization (all-cause hospitalization, CV hospitalization, and hospitalization for worsening heart failure): adjudicated by a blinded EVC.
- Composite of CV mortality and hospitalization for worsening heart failure: adjudicated by a blinded EVC.
- Change in NYHA functional class: evaluated by investigator by questioning patients about their heart failure symptoms.
- Change in Global Assessment: evaluated by patients and investigators by completing the global assessment questionnaires.
- Change in heart rate: measured on 12-lead ECG at each scheduled visit.
- Other CV outcomes: myocardial infarction, stroke, sudden cardiac death, and atrial fibrillation adjudicated by a blinded EVC.
- Total adverse events, serious adverse events, and withdrawal due to adverse events.

The primary outcome in the SHIfT study was the composite of CV mortality and hospitalization for worsening heart failure. Other outcomes identified in the CDR systematic review protocol included health-related quality of life and change in LVEF; however, the results for these outcomes were not reported separately for the subgroup of patients with heart rates ≥ 77 bpm.

Efficacy

Ivabradine demonstrated a statistically significant improvement compared with placebo in the primary composite end point (CV mortality and hospitalization for worsening heart failure) in the pre-specified subgroup of patients with a baseline heart rate of ≥ 77 bpm (27.4% versus 34.2%, respectively, HR 0.75; 95% CI, 0.67 to 0.85, $P < 0.0001$). The primary composite end point was statistically significant for both cardiovascular mortality and for hospitalization for worsening heart failure (15.4% versus 18.4%, HR 0.81; 95% CI, 0.69 to 0.96, $P = 0.0137$; 18.0% versus 24.6%, HR 0.69; 95% CI, 0.59 to 0.80, $P < 0.0001$, respectively).

Ivabradine also demonstrated a statistically significant improvement compared with placebo in the pre-specified subgroup of patients with a baseline heart rate of ≥ 77 bpm for some secondary outcomes of interest such as fewer all-cause deaths (17.2% versus 20.6%, HR 0.81; 95% CI, 0.69 to 0.94, $P = 0.0074$), deaths related to heart failure (4.0% versus 6.3%, HR 0.61; 95% CI, 0.45 to 0.83, $P = 0.0017$), all-cause hospitalizations (40.3% versus 45.8%, HR 0.82; 95% CI, 0.74 to 0.91, $P = 0.0002$), and CV hospitalizations (32.2% versus 38.1%, HR 0.79; 95% CI, 0.71 to 0.89, $P < 0.0001$).

Other secondary CV outcomes such as sudden cardiac death, fatal or non-fatal myocardial infarction and stroke, and new onset atrial fibrillation were similar between treatment groups.

Results based on post-hoc subgroup analyses for patients within four categories of per cent target daily beta-blocker dose (i.e., < 25%, ≥ 25% to < 50%, ≥ 50% to < 100% and ≥ 100%) in the pre-specified subgroup of patients with a baseline heart rate of

≥ 77 bpm, suggested that the differences in the treatment effects in the primary composite outcome between ivabradine and placebo [redacted].

[redacted]

The pre-specified ≥ 50% target daily beta-blocker dose and the post-hoc < 50% target daily beta-blocker dose subgroups also demonstrated that there was [redacted]:

[redacted]

Harms (Safety and Tolerability)

Treatment emergent adverse events (TEAEs) were experienced by [redacted] of patients in the ivabradine group and [redacted] of patients in the placebo group during the SHIfT trial. The most common TEAEs were [redacted]

Serious adverse events (SAEs) were experienced by [redacted] of patients in the ivabradine treatment group and [redacted] in the placebo group. The most common SAEs were [redacted].

The percentage of patients who stopped treatment due to adverse events was similar between the ivabradine ([redacted]) and placebo ([redacted]) groups where [redacted] were the most commonly reported reasons for stopping treatment ([redacted]).

Notable harms that were more commonly reported in the ivabradine group than in the placebo group included [redacted] ([redacted], respectively), [redacted] ([redacted], respectively), and [redacted] ([redacted], respectively). The percentage of patients [redacted].

Cost and Cost-Effectiveness

Ivabradine is available as 5 mg and 7.5 mg tablets, at the marketed price of $0.85 per 5 mg tablet and $1.56 per 7.5 mg tablet. The recommended starting dose of ivabradine is 5 mg twice daily, with dose increase to 7.5 mg twice daily after two weeks of treatment if required. The daily cost of ivabradine is from $1.70 to $3.11 (5 mg to 7.5 mg twice daily).

The manufacturer submitted a cost-utility analysis, assessing adult patients with stable chronic heart failure with reduced LVEF ≤ 35%, with NYHA classes II or III who are in sinus rhythm with a resting heart rate ≥ 77 bpm and are being treated with optimized standard therapy. The analysis compared ivabradine as an add-on therapy to SOC with SOC alone, which includes an ACEI or an ARB if an ACEI is not tolerated, a beta-blocker, and/or a mineralocorticoid receptor antagonist. A Markov cohort model was used with two health states — “alive” and “dead” — and followed patients with heart failure through the progression of the disease using monthly cycles run over a lifetime time horizon (approximately 30 years). The model considered NYHA classes and hospitalization events within the “alive” health state. The modelling approach was based on predictive equations for outcomes including transitions between NYHA classes, and risk of mortality and of hospitalization derived from SHIfT trial data. EuroQol 5-dimensions (EQ-5D) data from SHIfT were used to estimate utility values for each NYHA class. Resource use was estimated based on data from the SHIfT trial, expert opinion and assumption, while costs were obtained from Canadian sources and the literature. In the manufacturer’s base-case probabilistic analysis, the ICUR for ivabradine plus SOC was $7,969 per QALY compared with SOC alone.

CDR identified several key limitations with the submitted economic model:

- Sacubitril/valsartan was not considered as a comparator to ivabradine but it was included as part of SOC. The clinical expert consulted for this review indicated that for the target population, sacubitril/valsartan would be a relevant treatment option and is unlikely to be combined with ivabradine.
- The generalizability of the SHIfT trial population to the Canadian setting is unclear. Patients in SHIfT were on average younger than those in most Canadian practices. There was also a lower proportion of patients receiving guideline–recommended target doses of concomitant beta blocker, and the rates of hospitalization may be higher than likely seen in Canadian clinical practice.
- A utility increment was applied to patients receiving ivabradine, which was not justified.
- The proportion of patients requiring the 7.5 mg twice daily dose of ivabradine was lower than expected in Canadian clinical practice, which underestimates the cost of ivabradine.
- The majority of the clinical benefit (90% to 97%) associated with ivabradine was realized after the 21-month SHIfT trial treatment period, which raises some uncertainty regarding the likelihood of the predicted clinical benefits.
- The submitted model lacks transparency and flexibility, which limited CDR's ability to perform model validation and vary parameters.

CDR considered reanalyses excluding the use of sacubitril/valsartan as part of SOC, increased the average cost per patient of ivabradine in increasing the proportion of users of the 7.5 mg dose, removed the utility increment associated with taking ivabradine, reduced the incremental risk of hospitalization between compared treatment groups using the lower 95% confidence interval for the rates of hospitalization, and reduced the time horizon to 10 years to reduce the uncertainty associated with the extrapolation of the clinical benefits in the long term.

CDR estimated an ICUR of $12,895 per QALY for ivabradine plus SOC compared with SOC alone, based on an incremental cost of $3,355 and an incremental gain of 0.2602 QALYs. Stratified analyses of the CDR base case by beta blocker usage at baseline suggested that ICURs increased as patients received close to or above the target dose of a beta-blocker; with the ICUR increasing to $16,729 per QALY in patients receiving 100% or more of the target beta-blocker dose. However, a major limitation that could not be accounted for by CDR reanalyses is the lack of transparency and flexibility with the manufacturer's model, which limits the confidence that can be placed on the results.

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 Wijeysundera.

April 19, 2017 Meeting

Regrets:

None

Conflicts of Interest:

None