# Common Drug Review
## *Pharmacoeconomic Review Report*

**June 2017**

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| **Drug** | Ivabradine hydrochloride (Lancora) |
| **Indication** | For the treatment of stable chronic heart failure with reduced left ventricular ejection fraction (≤ 35%) in adult patients with NYHA classes II or III who are in sinus rhythm with a resting heart rate ≥ 77 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. |
| **Reimbursement request** | As per Health Canada indication |
| **Dosage form(s)** | 5 mg and 7.5 mg, film-coated tablets |
| **NOC date** | December 23, 2016 |
| **Manufacturer** | SERVIER Canada Inc. |

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# ABBREVIATIONS

| | |
|---|---|
| **ACEI** | angiotensin-converting enzyme inhibitor |
| **ARB** | angiotensin receptor blocker |
| **bpm** | beats per minute |
| **CDR** | CADTH Common Drug Review |
| **CV** | cardiovascular |
| **EQ-5D** | EuroQol 5-Dimensions questionnaire |
| **HF** | heart failure |
| **ICUR** | incremental cost-utility ratio |
| **NICE** | National Institute for Health and Care Excellence |
| **LVEF** | left ventricular ejection fraction |
| **NYHA** | New York Heart Association |
| **QALY** | quality-adjusted life-year |
| **QoL** | quality of life |
| **SHIfT** | Systolic Heart Failure Treatment with the $I_f$ inhibitor Ivabradine Trial |
| **SOC** | standard of care |

**TABLE 1: SUMMARY OF THE MANUFACTURER'S ECONOMIC SUBMISSION**

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| **Drug Product** | **Ivabradine (Lancora) 5 mg and 7.5 mg Film-Coated Tablets** |
| **Study Question** | What is the incremental cost-effectiveness (cost per quality-adjusted life-year [QALY] gained) of adding ivabradine to standard of care compared with standard of care alone for the treatment of chronic heart failure (CHF), in patients with baseline heart rate ≥ 77 bpm? |
| **Type of Economic Evaluation** | Cost-utility analysis |
| **Target Population** | The results from the model were presented by the manufacturer for patients with NYHA class II to IV CHF, in sinus rhythm and with a left ventricular ejection fraction (LVEF) ≤ 35% and baseline resting heart rate ≥ 77 bpm, treated with optimized standard therapy, including beta-blocker therapy when tolerated.<br><br>The population indicated for treatment by Health Canada is the same as the population assessed by the manufacturer but excludes patients with NYHA class IV CHF (2% of patients). |
| **Treatment** | Ivabradine plus standard of care (SOC), where SOC is comprised of an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker [ARB] if the ACEI is not tolerated, a beta-blocker, and/or a mineralocorticoid receptor antagonist (MRA). |
| **Outcome** | Quality-adjusted life-year |
| **Comparator** | SOC alone |
| **Perspective** | Canadian health care system |
| **Time Horizon** | Lifetime (approximately 30 years) |
| **Results for Base Case** | ICUR: $7,969 per QALY for ivabradine + SOC vs SOC |
| **Key Limitations** | • Sacubitril/valsartan was not considered as a comparator to ivabradine, but part of SOC. Feedback from a Canadian clinical expert indicated that for the target population, sacubitril/valsartan would be a relevant treatment option.<br>• The generalizability of the SHIfT study population to the Canadian setting is unclear. Patients in SHIfT were, on average, younger than likely in Canadian practice. There was also a lower proportion of patients receiving guideline-recommended target doses of concomitant beta-blocker therapy in SHIfT than likely in Canadian clinical practice (particularly in specialist centres), and the rates of hospitalization may be lower in Canadian practice.<br>• The model was based on predictive algorithms for mortality and hospitalization derived using different populations from the SHIfT study, which did not align with the specific patient population for which ivabradine is indicated. The impact on the model results for the indicated population is unclear and could not be tested by CDR.<br>• A utility increment was applied to patients receiving ivabradine. This was not justified and removed from the CDR base case.<br>• The cost of ivabradine may be underestimated. The proportion of patients requiring 7.5 mg daily was increased for the CDR base case.<br>• The majority of the clinical benefit (~90% to 97%) associated with ivabradine was realized after the 21-month SHIfT study treatment period.<br>• The submitted model lacks flexibility and transparency. Some results do not meet face validity and lack consistency, which affects the confidence that may be placed on the results. |
| **CDR Estimates** | • CDR emphasizes that the lack of transparency, flexibility, and consistency with the submitted model renders the results highly uncertain for reanalysis. |

| Drug Product | Ivabradine (Lancora) 5 mg and 7.5 mg Film-Coated Tablets |
|---|---|
| | • For the CDR base case, the following revisions to the manufacturer's base case were undertaken: excluded sacubitril/valsartan as part of SOC; shortened the time horizon and time of ivabradine effect; used a lower rate of hospitalization and shorter duration of hospitalization; removed the utility increment associated with ivabradine; revised the weighted monthly cost of ivabradine; and, excluded dispensing fees. The resulting ICUR was $12,895 per QALY for ivabradine plus SOC compared with SOC alone.<br>• CDR also considered stratified analyses by beta-blocker use at baseline. Reanalyses showed that ICURs increased with patients receiving closer to or above the target dose of a beta-blocker.<br>• CDR could not fully assess the generalizability of the modelled trial population to the Canadian population or the proportion of treatment-related benefit occurring in the post-trial period due to the lack of flexibility and transparency with the submitted model. These factors may have a notable impact on the results. |

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; bpm = beats per minute; CDR = CADTH Common Drug Review; CHF = chronic heart failure; ICUR = incremental cost-utility ratio; LVEF = left ventricle ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; QALY = quality-adjusted life-year; SOC = standard of care.

# EXECUTIVE SUMMARY

## Background

Ivabradine (Lancora) is a heart-rate regulating drug for the management of heart failure (HF) that acts by selectively inhibiting the $I_f$ current in the sinus node. Ivabradine is indicated for the treatment of stable chronic HF with reduced left ventricular ejection fraction (LVEF) ≤ 35% in adult patients with New York Heart Association (NYHA) functional class II or III HF who are in sinus rhythm with a resting heart rate ≥ 77 beats per minute (bpm).[1] Ivabradine is intended to be used in combination with standard chronic HF treatments. The recommended starting dosage of ivabradine is 5 mg twice daily. After two weeks of treatment, the dose may be adjusted as required; if a patient's resting heart rate is persistently at or above 60 bpm, then the dose should be increased to 7.5 mg twice daily.[1] 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, for a daily cost of $1.70 to $3.11.[2]

The manufacturer submitted a cost-utility analysis of ivabradine as an add-on therapy to standard of care (SOC) compared with SOC alone, which includes an angiotensin-converting enzyme inhibitor (ACEI) (or an angiotensin receptor blocker [ARB] if the ACEI is not tolerated), a beta-blocker, and/or a mineralocorticoid receptor antagonist. The submitted model was based on a Markov model previously submitted to the National Institute for Health and Care Excellence (NICE) in the UK, in 2012. The Markov cohort model has two health states — "alive" and "dead" — and follows patients with HF through the progression of the disease using monthly cycles run over a lifetime time horizon (approximately 30 years).[2] The model considered NYHA classes and hospitalization events within the "alive" health state. The modelling approach was based on predictive equations for outcomes developed using data from the full population of the Systolic Heart Failure Treatment with the $I_f$ inhibitor Ivabradine Trial (SHIfT) (heart rate ≥ 70 bpm, NYHA class II to IV patients), though this was a broader population than the one indicated for treatment (heart rate ≥ 77 bpm, NYHA class II or III). The manufacturer noted that the broader (full trial) population was used to develop predictive functions to avoid breaking randomization and avoid reducing the predictive power of the risk equations from a smaller sample size. Adjusted predictive risk equations were used to model transitions between NYHA classes, cardiovascular (CV) mortality and hospitalization, while adjusted trial-derived EuroQol 5-Dimensions questionnaire (EQ-5D) data were used to estimate utility values. The model was set to allow assessment of different populations based on the SHIfT study, including the base case population for which ivabradine is indicated (heart rate ≥ 77 bpm, NYHA class II or III).

In the manufacturer's base case probabilistic analysis, the incremental cost-utility ratio (ICUR) for ivabradine plus SOC was $7,969 per quality-adjusted life-year (QALY) compared with SOC alone.

## Summary of Key Limitations

CDR identified several key limitations with the submitted economic model:

- The manufacturer considered sacubitril/valsartan as part of SOC, but not as a direct comparator for ivabradine. Feedback from the clinical expert consulted by CADTH Common Drug Review (CDR) indicated that sacubitril/valsartan would also be considered for use in patients that meet the Health Canada criteria for ivabradine, and thus sacubitril/valsartan was judged to be a relevant comparator for ivabradine in Canadian clinical practice.
- The generalizability of the clinical trial population to the Canadian context may be limited. The SHIfT study was conducted primarily in [redacted], and results of cardiovascular studies have previously indicated discordant results between [redacted] and North America.[3] This is of particular

concern for rates of hospitalization. Also, the proportion of patients in the SHIfT study who received guideline-recommended target doses of beta-blockers was [redacted] than likely in Canadian practice. This is important as the SHIfT study results revealed that the relative treatment effect for ivabradine plus SOC versus SOC alone was [redacted] in patients who received closer to or above 100% of the guideline-recommended target beta-blocker dose.

- The model was based on predictive algorithms for mortality and hospitalization derived using data from different populations within the SHIfT study which did not align with the specific population for which ivabradine is indicated. This limits the validity of the model results for the target population (i.e., patients with a heart rate ≥ 77 bpm).
- The majority of the clinical benefits for ivabradine were realized in the model in the time period beyond the SHIfT study (after 21 months). Only ~3% of the clinical benefits were accrued during the trial's 21-month median treatment period.
- The submitted economic model lacked transparency and flexibility, which limited CDR's ability to perform model validation. CDR noted issues with the validity of results and the model structure during testing, such as a decrease in total QALYs associated with SOC when removing a treatment-specific utility increment associated with ivabradine.

Other limitations include: an unjustified utility increment applied to patients receiving ivabradine , underestimation of the proportion of patients likely to receive the 7.5 mg dose of ivabradine, and the inclusion of dispensing fees in the base-case analysis.

### Key Results and Conclusions

CDR undertook several reanalyses with the manufacturer's submitted model to evaluate the previously identified limitations. The CDR base case considered: revisions to SOC to exclude sacubitril/valsartan; removal of dispensing fees; increasing the proportion of users of the 7.5 mg dose of ivabradine to 85%; removal of the utility increment associated with ivabradine; use of the lower 95% confidence interval for the rates of hospitalization; removing the cost of the length of hospital stay for non-CV hospitalizations; reducing the time horizon to 10 years.

The CDR base case ICUR was estimated to be $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. However, this estimate is highly uncertain due to the differences in the populations used for predictive modelling compared with the target population of the analysis. As a result of the lack of transparency and flexibility of the submitted model, CDR was unable to further evaluate this issue. Further, notable differences between the components of the probabilistic and deterministic analyses were observed (deterministic: incremental cost of $2,016 and incremental gain of 0.1946 QALYs).

Stratified analyses of the CDR base case by beta-blocker usage at baseline indicated that ICURs increased as patients received close to or more than the target dose of a beta-blocker: from $11,849 per QALY in patients receiving less than 50% of the target beta-blocker dose to $16,729 per QALY in patients receiving 100% or more of the target beta-blocker dose.

CDR could not assess factors such as the generalizability of the modelled trial population to the population indicated by Health Canada and the proportion of the benefits occurring in the post-trial period due to the lack of flexibility and transparency with the submitted model. These factors may have a notable impact on the ICUR estimated by the manufacturer.

The relative safety, efficacy, and cost-effectiveness of ivabradine compared with sacubitril/valsartan are unknown due to the lack of comparative data.

# INFORMATION ON THE PHARMACOECONOMIC SUBMISSION

## 1. SUMMARY OF THE MANUFACTURER'S PHARMACOECONOMIC SUBMISSION

The manufacturer submitted a cost-utility ratio comparing ivabradine plus standard of care (SOC) with SOC alone in patients with chronic heart failure (HF), based on a subgroup of patients from the Systolic Heart Failure Treatment with the $I_f$ inhibitor Ivabradine Trial (SHIft). The SHIfT study included patients with symptomatic HF who had a left ventricle ejection fraction (LVEF) of 35% or lower, who had a resting heart rate of 70 beats per minute (bpm) or higher, who had been admitted to hospital for HF within the previous year, and who received stable background treatment including a beta-blocker, if tolerated. The population assessed by the manufacturer's base-case analysis was a subpopulation of patients from the SHIfT study that fulfilled the indication initially requested from Health Canada: patients with HF who were in New York Heart Association (NYHA) class II to IV, with LVEF ≤ 35% and a baseline resting heart rate of ≥ 77 bpm. This differs from the final, Health Canada–approved population described in the Lancora product monograph: "treatment of stable chronic HF with reduced LVEF ≤ 35% in adult patients with NYHA class II or III who are in sinus rhythm with a resting heart rate ≥ 77 bpm."[1] The proportion of NYHA class IV HF patients excluded by the final Health Canada indication represents 2% of SHIfT study participants.

The submitted Markov cohort model followed patients through the progression of their disease through "alive" and "dead" health states, with alive patients grouped by NYHA class (I through IV). The model was run over a lifetime time horizon (approximately 30 years) with monthly cycles from the perspective of the Canadian health care system.

The manufacturer used risk equations to predict the risk of patients moving between the four NYHA classes, as well as the risk of hospitalization events, the risk of death, and changes in utility value estimates (derived from the EuroQol 5-Dimensions [EQ-5D] health-related quality of life measure). The risk equations were adjusted for variables the manufacturer determined had an impact on the measured outcomes, which differed between outcomes. The risk equations and transition probabilities were developed using data from different subpopulations within the SHIfT study; specifically, while many predictive equations were derived using data from the full trial population, those relating to cardiovascular (CV) mortality appeared to be based on a subgroup of patients who had a heart rate ≥ 75 bpm.

Utility estimates were derived for each NYHA class from a subset of SHIfT's full trial population ([redacted] out of 6,505 patients; [redacted]%). In addition to these base utility values, a static utility increment was included for patients receiving ivabradine, while a single utility decrement was applied for hospitalization events regardless of treatment. The treatment-specific utility increment and hospitalization disutility values were estimated from a multivariate multi-level regression analysis conducted using the same subset of trial patients.

The manufacturer included direct medical costs in the economic model. Drug costs were derived from the Ontario Drug Benefit Formulary, while drug administration and follow-up visit costs were derived from the Ontario Schedule of Physician Benefits. Hospitalization costs were derived from the Ontario Case Costing Initiative and other published sources,[4] and additional costs for the management of HF

(excluding hospital costs) were derived from the published literature.[4] Resource use was estimated based on data from the SHIfT population, expert opinion, and assumptions. The weighted average cost of ivabradine was $80.64 per month (60% use of the 7.5 mg tablet, 40% use of the 5 mg tablet), which includes dispensing fees.

# 2. MANUFACTURER'S BASE CASE

The estimated incremental cost-utility ratio (ICUR) for ivabradine plus SOC compared with SOC alone was $7,969 per quality-adjusted life-year (QALY) gained. The probabilistic analysis indicated that at a threshold value of $20,000 per QALY, ivabradine plus SOC had a 99% probability of being cost-effective versus SOC alone.

**TABLE 2: SUMMARY OF RESULTS OF THE MANUFACTURER'S BASE CASE**

| | Total Costs | Incremental Cost with Ivabradine | Total QALYs | Incremental QALYs with Ivabradine | Incremental Cost per QALY |
|---|---|---|---|---|---|
| Ivabradine + SOC | $53,191 | $2,746 | 4.170 | 0.345 | $7,969 |
| SOC | $50,445 | | 3.826 | | |

QALY = quality-adjusted life-year; SOC = standard care.

# 3. SUMMARY OF MANUFACTURER'S SENSITIVITY ANALYSES

The manufacturer undertook various sensitivity analyses to assess the robustness of the base case results. One-way sensitivity analyses reported that the ICUR was less than $25,000 per QALY in all tested parameters. The parameters that had the largest impact on the ICUR were the rate ratio of hospitalization and stopping ivabradine treatment effect in the post-trial period.

# 4. LIMITATIONS OF MANUFACTURER'S SUBMISSION

CADTH Common Drug Review (CDR) identified the following limitations with the submitted economic model:

- **Consideration of sacubitril/valsartan in the economic analysis.** Feedback from the clinical expert consulted by CDR indicated that sacubitril/valsartan would also be considered for use in patients who meet the Health Canada criteria for ivabradine; therefore, sacubitril/valsartan was judged to be a relevant comparator in Canadian clinical practice. Sacubitril/valsartan was not considered a direct comparator for ivabradine in the submitted economic model and the manufacturer did not attempt to undertake an analysis comparing ivabradine and sacubitril/valsartan via indirect treatment comparison. Instead, the manufacturer included sacubitril/valsartan as a component of SOC. The clinical expert noted that the use of ivabradine in combination with sacubitril/valsartan is questionable in Canadian clinical practice. The impact of sacubitril/valsartan as a component of SOC is uncertain in terms of the comparative effectiveness of adding ivabradine or not to SOC. Additionally, no patients in SHIfT received sacubitril/valsartan. The assumption that sacubitril/valsartan is part of standard care was removed from the model.

- **Generalizability of the trial data to the Canadian setting.** There is substantial uncertainty regarding the applicability of the results of the SHIfT study to the Canadian setting:
  - *Geographic variability in the clinical trial population.* The majority of patients recruited in SHIfT were from [redacted], compared with approximately [redacted]% from [redacted]. Given that the primary composite end point of the trial included the clinician-decision end point of hospitalization, it is possible that Canadian clinical decision rules relating to hospital admission may not align with the clinical practices observed in countries which [redacted]. Furthermore, feedback from the clinical expert consulted by CDR specifically indicated discordant results between [redacted] and North America in a previous CV trial[3] to highlight the uncertain generalizability of the SHIfT study. To take into account the uncertainty for the risks of hospitalization, the CDR base case applied the lower confidence interval for the rate of hospitalizations, though this may not fully account for the uncertainty associated with the geographic variation in hospitalization practices.
  - *Patient age at baseline*. It was noted by the clinical expert consulted by CDR that the relevant subpopulation at study entry was, on average, about 10 years younger than the likely population in Canadian clinical practice. The impact of mean age at trial entry on the relative treatment effect observed in SHIfT is unclear.
  - *Baseline beta-blocker use*. As highlighted by the CDR clinical review, baseline usage of beta-blockers may alter the magnitude of effect experienced by adding ivabradine to SOC. The dose of beta-blockers used at the entry of the SHIfT study for the treatment-indicated population may vary in Canadian clinical practice. For instance, [redacted]% of SHIfT study patients who met the Health Canada indication criteria for ivabradine were receiving at least 50% of the guideline-recommended target dose of beta-blockers. However, the percentage of HF patients in Canadian clinical practice likely to receive this level of beta-blockers was estimated to be higher (likely between 50% and 75%) according to the clinical expert consulted by CDR. As noted in the CDR Clinical Report, SHIfT study results indicated a trend of reduced relative effect of ivabradine plus SOC when patients were close to or above 100% of the guideline-recommended target dose of a beta-blocker. The CDR reanalysis assessed subgroups of patients stratified by their baseline usage of beta-blockers.
- **Prediction of outcomes post-trial.** After the within-trial time horizon, the manufacturer extrapolated estimates for each outcome in the base-case analysis, assuming that the relative effects of treatment would be maintained up to 30 years following uninterrupted treatment until the end of the modelled time horizon. The majority of the incremental benefits associated with ivabradine were accrued after the 21-month within-trial period (~90% to 97%). CDR limited the analysis to 10 years.
- **Precision of the predictions for the indicated population based on predictive functions developed from other SHIfT patient populations.** The risk equations used to support the predictive modelling were based on SHIfT study populations that differed from the Health Canada–indicated population. While the justification by the manufacturer for using the full study population for risk equation derivation may be appropriate (to avoid breaking randomization and reducing the predictive power of the risk equations from a smaller sample size), it is unclear what impact this approach had on outcome prediction compared with using subgroup data relating to patients with a resting heart rate of ≥ 77 bpm to derive the risk equations. This impact could not be tested by CDR.
- **Modelling non-CV hospitalization is questionable.** The manufacturer modelled non-CV hospitalizations in addition to CV hospitalizations. A relative impact between comparators was not clearly demonstrated for non-CV hospitalization. Due to the convoluted nature of the way non-CV hospitalizations were modelled, CDR was unable to exclude non-CV hospitalizations, thus the CDR

base case reduced the length of hospitalization stay for non-CV hospitalizations from 9.2 days to 0.0001 days (zero could not be used due to modelling considerations).

- **Treatment benefit was overestimated.** The application of a utility increment for patients receiving ivabradine who are in the same health states as patients who received SOC was not justified and may overestimate the benefit associated with ivabradine. The CDR base case removed this increment.
- **Monthly treatment cost of ivabradine is uncertain.** As the two strengths of ivabradine have different costs, the manufacturer estimated a weighted average cost of treatment based on drug use data from the full SHIfT population ([redacted]% on 7.5 mg, [redacted]% on 5 mg, [redacted]% on 2.5 mg [half the 5 mg tablet]). As CDR previously highlighted, the generalizability of the SHIfT population to the Canadian setting may be limited, which may have underestimated the proportion of patients requiring 7.5 mg ivabradine. Additionally, when calculated for the relevant subpopulation (≥ 77 bpm), the weighted estimate calculated by the manufacturer underestimates the average dose of ivabradine observed in the SHIfT study for this subpopulation. To account for this uncertainty and the fact that manufacturer base case did not allow plausible increases of the ivabradine dose from 5 mg to 7.5 mg after the within-trial time horizon, the proportion of patients on ivabradine 7.5 mg was increased from [redacted].
- **The model lacks flexibility and transparency.** The submitted model lacks flexibility with pre-set subgroup and supplementary analyses, and its lack of transparency limits modifications necessary for model validation. The complex predictive statistical methodology was not fully presented in the submission, which did not permit closer inspection of the inner workings of the model. This ultimately renders the model results uncertain.

# 5. CADTH COMMON DRUG REVIEW REANALYSES

The CDR base case applied the following revisions to the submitted model:

- Sacubitril/valsartan was removed from SOC.
- The model's time horizon was reduced to 10 years, with treatment costs and benefits accrued up to this point, based on pre-programmed analyses included by the manufacturer.
- The lower 95% confidence interval for the rate of hospitalizations was used.
- The length of non-CV hospitalizations was reduced to 0.0001 days (zero could not be used due to modelling considerations).
- The utility increment associated with ivabradine treatment was removed.
- The proportion of patients receiving 7.5 mg ivabradine was increased from [redacted], while the proportion of patients receiving the 2.5 mg and 5 mg doses was reduced proportionally.
- The dispensing fees applied in the model were removed.

The probabilistic CDR base case reported that the ICUR for ivabradine plus SOC compared with SOC alone was $12,895 per QALY gained, based on an incremental cost of $3,355 and an incremental QALY gain of 0.2602 QALYs over a 10-year time horizon. This differed notably from the incremental results for the deterministic analysis, which resulted in an incremental cost of $2,016, an incremental gain of 0.1946 QALYs, and an ICUR of $10,362 per QALY gained (Table 14).

Additionally, stratified analyses of the CDR base case were performed according to beta-blocker use at baseline. Results of stratified analyses indicated that ICURs increased as patients received close to or more than the guideline-recommended target dose of a beta-blocker: $11,849 per QALY gained for patients receiving less than 50% of the target beta-blocker dose, $14,759 per QALY gained for patients

receiving between 50% and 100% of the target beta-blocker dose, and $16,729 per QALY gained for patients receiving 100% or more of the target beta-blocker dose.

Appendix V details the impact of independently varying each uncertain parameter on the results of the CDR base case and provides further details regarding all of the CDR reanalyses.

# 6. ISSUES FOR CONSIDERATION

**Potential off-label use of ivabradine.** Feedback from the clinical expert indicated that there is potential for clinicians to administer ivabradine to patients outside of the authorized indication, such as patients with a resting heart rate at or above 70 bpm.

**Patients on a target dose of a beta-blocker.** The Health Canada product monograph and Canadian and American treatment guidelines indicate that patients should up-titrate beta-blocker therapy to a maximally tolerated dose before initiating therapy with ivabradine.[1,5,6] However, the likelihood that a patient's HF symptoms are controlled with a guideline-recommended target dose of a beta-blocker at the time of initiation of ivabradine may be affected by the prescriber and their practice. For instance, larger specialist centres may be more willing to up-titrate a suboptimal beta-blocker dose toward the target beta-blocker dose than is likely the case in general clinical practice, based on the expertise of the treating physicians in managing any adverse events associated with beta-blockers. This may lead to more — or less — appropriate prescription of ivabradine when not by specialists.

**Measurement of heart rate may be challenging**. Feedback from the clinical expert suggested that the measurement of heart rate according to the SHIfT study (i.e., two consecutive electrocardiogram measurements following five minutes of rest) would be an ideal tool for ensuring that ivabradine is prescribed only to patients that meet the approved criteria.[7] The expert noted that proficiency in this measurement may occur at larger specialist centres, but that their ability to carry out this task in community care settings may be a barrier to prescribing ivabradine and lead to uncertainty in appropriate prescription.

# 7. PATIENT INPUT

The HeartLife Foundation and the Heart Failure Support Group of Manitoba provided input for the ivabradine submission. These patient groups noted that HF is a condition that restricts patients' functional capacity and the activities of daily living, leads to frequent hospitalization, and is often associated with a range of comorbid conditions, including depression and anxiety. While the effect of symptoms may vary depending on the stage and severity of disease, these factors ultimately contribute to a reduction in the quality of life of HF patients. These aspects were accounted for in the manufacturer's economic evaluation by the inclusion of utility weights reflective of disease severity and hospitalization.

Both patient groups also indicated that the burden of this disease is often felt by caregivers. Given that HF requires long-term, continuous daily monitoring and vigilance on the part of the caregiver, this is likely to negatively affect their daily life and result in increased physical and psychological caregiver distress as the patient's condition worsens. Information relating to the impact on caregivers was not provided by the manufacturer, and it was not considered in the economic analysis.

Although patients represented by the patient input groups did not report any experience with ivabradine, the groups noted that they hope that this new medication would lead to reduced hospital admissions and decreased mortality among HF patients and, by extension, an improvement in quality of life, especially among patients who are unable to tolerate or reach guideline-recommended target dosing of existing treatment regimens. Improvement in patient-reported quality of life was particularly emphasized by both patient groups. The manufacturer's economic evaluation accounted for hospitalization, quality of life, and mortality evidence captured in the SHIfT study.

# 8. CONCLUSIONS

CDR undertook several reanalyses of the manufacturer's submitted model to attempt to manage the identified limitations. The CDR base case result is highly uncertain due to differences in the patient populations used for predictive modelling compared with the target population of the analysis. As a result of the lack of transparency and flexibility of the submitted model, CDR was unable to further assess this issue. Other major factors that may affect the conclusions of the economic analysis also could not be sufficiently assessed.

# APPENDIX 1: COST COMPARISON

The treatments presented in the Table 3 have been deemed to be appropriate by clinical experts for the treatment of patients with New York Heart Association (NYHA) class II or III heart failure. Costs are manufacturer 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 3: CDR COST COMPARISON TABLE FOR IVABRADINE – TREATMENTS WITH HF INDICATION**

| Drug/Comparator | Strength | Dosage Form | Price[a] ($) | Recommended Daily Dosage[b] | Annual Cost ($) |
|---|---|---|---|---|---|
| **$I_f$ Current Inhibitor** | | | | | |
| **ivabradine (Lancora)** | **5 mg<br>7.5 mg** | **Tablet** | **$0.8506[c]<br>$1.5568[c]** | **5 mg to 7.5 mg twice daily[d]** | **621 to 1,136** |
| **Angiotensin Receptor-Neprilysin Inhibitor (ARNI)** | | | | | |
| sacubitril/valsartan (Entresto) | 24 mg/26 mg<br>49 mg/51 mg<br>97 mg/103 mg | Tablet | $3.6200[e] | 97 mg/103 mg twice daily[f] | 2,643 |
| **Angiotensin-Converting Enzyme Inhibitors (ACEIs)** | | | | | |
| captopril (generics) | 12.5 mg<br>25 mg<br>50 mg<br>100 mg | Tablet | 0.2120<br>0.3000<br>0.5590<br>1.0395 | 25 mg to 150 mg twice daily; or,<br>25 mg to 150 mg three times daily | 219 to 1,138<br><br>329 to 1,707 |
| cilazapril (generics) | 1 mg<br>2.5 mg<br>5 mg | Tablet | 0.1557<br>0.1795<br>0.2085 | 1 mg to 2.5 mg | 57 to 66 |
| enalapril (generics) | 2.5 mg<br>5 mg<br>10 mg<br>20mg | Tablet | 0.1863<br>0.2203<br>0.2647<br>0.3195 | 5 mg to 20 mg in one or two doses | 80 to 117 |
| fosinopril (generics) | 10 mg<br>20 mg | Tablet | 0.2178<br>0.2619 | 20 mg to 40 mg | 96 to 191 |
| lisinopril (generics) | 5 mg<br>10 mg<br>20 mg | Tablet | 0.1347<br>0.1619<br>0.1945 | 2.5 mg to 35 mg | 25 to 207 |
| perindopril (Coversyl) | 2 mg<br>4 mg<br>8 mg | Tablet | 0.6527<br>0.8168<br>1.1325 | 2 mg to 4 mg | 238 to 298 |
| quinapril (generics) | 5 mg<br>10 mg<br>20 mg<br>40 mg | Tablet | 0.2321 | 10 mg once daily to<br>20 mg twice daily | 85 to 169 |
| **Angiotensin Receptor Blockers (ARBs)** | | | | | |
| candesartan (generics) | 4 mg<br>8 mg<br>16 mg<br>32 mg | Tablet | 0.1700<br>0.2850<br>0.2850<br>0.2932 | 4 mg to 32 mg[g] | First year: 105<br>Subsequent years: 107 |
| valsartan (generics) | 80 mg<br>160 mg | Tablet | 0.2958<br>0.2958 | 80 mg to 160 mg twice daily | 216 |

| Drug/Comparator | Strength | Dosage Form | Price[a] ($) | Recommended Daily Dosage[b] | Annual Cost ($) |
|---|---|---|---|---|---|
| | 320 mg | | 0.2843 | | |
| **Aldosterone Antagonists** | | | | | |
| eplerenone (Inspra) | 25 mg<br>50 mg | Tablet | 2.7460 | 25 mg to 50 mg | 1,002 |
| spironolactone (generic) | 25 mg<br>100 mg | Tablet | 0.1057<br>0.2461 | 25 mg to 200 mg | 39 to 180 |
| **Beta-Blockers** | | | | | |
| carvedilol (generics) | 3.125 mg<br>6.25 mg<br>12.5 mg<br>25 mg | Tablet | 0.3377 | 3.125 mg to 25 mg<br>twice daily | 247 |

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

[a] All prices are from the Ontario Drug Benefit Formulary (accessed December 2016)[8] unless otherwise indicated and do not include dispensing fees.

[b] All dosage recommendations for treatments without a heart failure indication are based on hypertension indication, unless otherwise indicated.

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

[d] Target dosage is 7.5 mg twice daily with a recommended starting dosage of 5 mg twice daily for HF patients when heart rate is at or above 77 beats per minute (bpm). After two weeks of initial treatment at 5 mg twice daily, the dosage can be increased to 7.5 mg twice daily if resting heart rate is persistently above 60 bpm or decreased to 2.5 mg twice daily if resting heart rate is persistently below 50 bpm or in the case of symptoms related to bradycardia such as dizziness, fatigue, or hypotension. If heart rate is between 50 and 60 bpm, the dosage of 5 mg twice daily should be maintained.[1]

[e] DeltaPA, manufacturer's wholesale list price, accessed: January 2017.[9]

[f] Target dosage is 97 mg/103 mg twice daily with a recommended starting dosage of 49 mg/51 mg twice daily. A starting dosage of 24 mg/26 mg twice daily may be considered for certain patients such as patients at risk for hypotension or those on lower doses of ACE inhibitors or ARB prior to starting sacubitril/valsartan. The dose should be increased every 2-4 weeks to reach the target dose according to patient tolerance.[10]

[g] Target dosage is 32 mg daily with a recommended starting dose of 4 mg. Starting dose is doubled at approximately 2 week intervals to achieve target daily dosage, according to patient tolerance.[11]

### TABLE 4: CDR COST COMPARISON TABLE FOR TREATMENTS WITHOUT HF INDICATION

| Drug/Comparator | Strength | Dosage Form | Price[a] ($) | Recommended Daily Dosage[b] | Annual Cost ($) |
|---|---|---|---|---|---|
| **Angiotensin-Converting Enzyme Inhibitors (ACEIs)** | | | | | |
| benazepril (generics) | 5 mg<br>10 mg<br>20 mg | Tablet | 0.5577<br>0.6595<br>0.7567 | 20 mg to 40 mg | 276 to 552 |
| ramipril (generics) | 1.25 mg<br>2.5 mg<br>5 mg<br>10 mg | Capsule | 0.1274<br>0.1470<br>0.1470<br>0.1862 | 2.5 mg to 10 mg | 54 to 68 |
| trandolapril (Mavik) | 1 mg<br>2 mg<br>4 mg | Capsule | 0.6901<br>0.7931<br>0.9785 | 2 mg to 4 mg[c] | 289 to 357 |

| Drug/Comparator | Strength | Dosage Form | Price[a] ($) | Recommended Daily Dosage[b] | Annual Cost ($) |
|---|---|---|---|---|---|
| **Angiotensin Receptor Blockers (ARBs)** | | | | | |
| eprosartan (Teveten) | 400 mg<br>600 mg | Tablet | 0.7246<br>1.1079 | 600 mg | 404 |
| irbesartan (generics) | 75 mg<br>150 mg<br>300 mg | Tablet | 0.3025 | 150 mg to 300 mg | 110 |
| losartan (generics) | 25 mg<br>50 mg<br>100 mg | Tablet | 0.3147 | 50 mg to 100 mg | 115 |
| olmesartan (Olmetec) | 20 mg<br>40 mg | Tablet | 1.1500 | 20 mg to 40 mg | 420 |
| telmisartan (generics) | 40 mg<br>80 mg | Tablet | 0.2824 | 80 mg | 103 |
| **Beta-blockers** | | | | | |
| atenolol (generics) | 50 mg<br>100 mg | Tablet | 0.1437<br>0.2362 | 50 mg to 100 mg | 52 to 86 |
| bisoprolol (generics) | 5 mg<br>10 mg | Tablet | 0.0994<br>0.1450 | 10 mg[d] | 53 |
| labetalol (Trandate) | 100 mg<br>200 mg | Tablet | 0.3474<br>0.6141 | 200 mg to 400 mg twice daily | 448 to 897 |
| metoprolol (generics) | 50 mg<br>100 mg | Tablet | 0.0624<br>0.1361 | 50 mg to 100 mg twice daily | 46 to 99 |
| | 100 mg<br>200 mg | Sustained Release Tablet | 0.1415<br>0.2568 | 100 mg to 200 mg | 52 to 94 |
| nadolol (generic) | 40 mg<br>80 mg<br>160 mg | Tablet | 0.4512<br>0.3710<br>1.2046 | 80 mg to 320 mg | 135 to 879 |
| nebivolol (Bystolic) | 2.5 mg<br>5 mg<br>10 mg<br>20 mg | Tablet | 1.2670[e] | 5 mg to 20 mg | 462 |
| propranolol (generics) | 10 mg<br>20 mg<br>40 mg<br>80 mg | Tablet | 0.0689<br>0.1107<br>0.1225<br>0.2034 | 160 mg to 320 mg | 148 to 297 |
| sotalol (generics) | 80 mg<br>160 mg | Tablet | 0.2966[f]<br>0.1623 | 160 mg to 320 mg in two divided doses[g] | 59 to 118 |

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

[a] All prices are from the Ontario Drug Benefit Formulary (accessed December 2016)[8] unless otherwise indicated and do not include dispensing fees.

[b] All dosage recommendations for treatments without an HF indication are based on hypertension indication, unless otherwise indicated.

[c] Recommended dosage following acute myocardial infarction in patients with left ventricular dysfunction[12]

[d] Dosage based on off-label use in heart failure patients from the e-Therapeutics Heart Failure entry, last revised June 2015.

[e] DeltaPA, manufacturer's wholesale list price, accessed: January 2017.[9]

[f] Unit cost based on Saskatchewan Online Formulary Database (accessed December 2016).[13]

[g] Dosage based on ventricular arrhythmia indication.[14]

# APPENDIX 2: SUMMARY OF KEY OUTCOMES

**TABLE 5: WHEN CONSIDERING ONLY COSTS, OUTCOMES & QUALITY OF LIFE, HOW ATTRACTIVE IS IVABRADINE + SOC RELATIVE TO THE SOC*?**

| Ivabradine + SOC vs. SOC | Attractive | Slightly attractive | Equally attractive | Slightly unattractive | Unattractive | Unknown |
|---|---|---|---|---|---|---|
| Costs (total) | | | | X | | |
| Drug treatment costs alone | | | | X | | |
| Clinical outcomes | | X | | | | |
| Quality of life | | X | | | | |
| Incremental CE ratio or net benefit calculation | $12,895 per QALY | | | | | |

CE = cost-effectiveness; SOC = standard of care; QALY = quality-adjusted life-year.
* Based on the CDR base case.

# APPENDIX 3: ADDITIONAL INFORMATION

### TABLE 6: SUBMISSION QUALITY

| | Yes/ Good | Somewhat/ Average | No/ Poor |
|---|---|---|---|
| Are the methods and analysis clear and transparent? | | X | |
| *Comments* | Model lacks flexibility and transparency. There is a lack of information provided on the modelling approach. Description of the data and methods provided in the PE Report does not align with what appears to have occurred in the model in some cases. | | |
| Was the material included (content) sufficient? | | X | |
| *Comments* | There is a lack of information provided on the modelling approach. | | |
| Was the submission well organized and was information easy to locate? | | X | |
| *Comments* | None | | |

PE = pharmacoeconomic.

### TABLE 7: AUTHORS INFORMATION

| **Authors of the Pharmacoeconomic Evaluation Submitted to CDR** | | | |
|---|---|---|---|
| ☐ Adaptation of Global model/Canadian model done by the manufacturer<br>☒ Adaptation of Global model/Canadian model done by a private consultant contracted by the manufacturer<br>☐ Adaptation of Global model/Canadian model done by an academic consultant contracted by the manufacturer<br>☐ Other (please specify) | | | |
| | **Yes** | **No** | **Uncertain** |
| Authors included a statement 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: SUMMARY OF OTHER HTA REVIEWS OF IVABRADINE

The cost-effectiveness of ivabradine for the treatment of symptomatic systolic HF has been assessed by several international HTA organizations, including the Scottish Medicines Consortium (SMC)[15] and the National Institute for Health and Care Excellence (NICE)[16] in the UK, and (four times) by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia.[17,18] The SMC, NICE, and PBAC reviews are summarized in Table 8 and

Table 9.

Ivabradine was also assessed by the Haute Authorité de Santé in France for the treatment of chronic heart failure with systolic dysfunction. However, the review conducted by the Transparency Committee was based on an assessment of the product's clinical benefit and did not include consideration for health economic evidence. The Transparency Committee recommended ivabradine for the requested indication, with the reimbursement rate set at 65%.[19]

**TABLE 8: OTHER HTA FINDINGS (NICE AND SMC)**

| | NICE November 2012[16] | SMC September 2012[15] |
|---|---|---|
| Treatment | Ivabradine (Procoralan) tablet, 5 mg and 7.5 mg, in addition to standard care | |
| Indication/ Request | Treatment of CHF in patients with NYHA class II to IV stable CHF with systolic dysfunction; who are in sinus rhythm with heart rate ≥ 75 bpm; who are given ivabradine + standard therapy including BB therapy, ACEI and aldosterone antagonists, or when BB therapy is contraindicated or not tolerated; and, in patients with a LVEF of ≤ 35%. | Treatment of CHF NYHA class II to IV with systolic dysfunction, in patients with sinus rhythm and whose heart rate is ≥ 75 bpm, in combination with standard therapy including BB therapy or when BB therapy is contraindicated or not tolerated. SMC request for "initiation only in patients whose resting HR remains ≥ 75 bpm despite optimal standard therapy" |
| Comparator | Standard care, defined as treatment with BB therapy, ACEI and aldosterone antagonists. | |
| Price | £40.17 per 56-tablet pack<br>Average monthly cost = £42.10 | Cost per year = £522.00 |
| Similarities with CDR submission | • CUA<br>• Efficacy inputs from the SHIfT study<br>• Regression equations for mortality, NHYA class distribution, hospital admission, and quality of life from the entire SHIfT population rather than population covered by marketing authorization<br>• Model assumed effect of ivabradine continued after end of trial and equivalent to that in SHIfT | • CUA<br>• Efficacy inputs from SHIfT study<br>• Markov cohort model captured information relating to mortality, hospitalizations, quality of life, and NYHA functional class<br>• Model used risk equations estimated from entire SHIfT population, which differed from patient group specified in licence/market authorization<br>• Treatment effect of ivabradine + standard care assumed to continue beyond trial period to death |
| Differences with CDR submission | Population assessed by the model's base case included NYHA class II to IV patients with a resting heart rate of 75 bpm or more (in line with ivabradine's marketing authorization in the UK) | |

| | NICE November 2012[16] | SMC September 2012[15] |
|---|---|---|
| Manufacturer's results | ICER = £8,498 per QALY gained | ICER = £6,002 per QALY gained |
| Issues noted by the review group | • Manufacturer did not carry out analysis in patient population with disease severity reflective of UK population<br>• ERG considered the base case ICER may be biased against ivabradine<br>• QoL values assumed to remain same for NYHA class in post-trial period, which inflates utility values in later cycles and favours ivabradine | • Co-primary end point of reduction in CV death did not reach significance in whole population but numerical difference was used in economic model<br>• Inclusion of a utility gain for ivabradine treatment introduced a bias in favour of ivabradine<br>• Treatment effect of ivabradine + standard care assumed to continue beyond trial period until the patient dies |
| Review group reanalyses | None reported | None reported |
| Recommendation | NICE Appraisal Committee **recommended ivabradine for listing** and noted that ivabradine should only be initiated if patients are stabilized for 4 weeks on optimized doses of ACEI, BB, and aldosterone antagonists | Ivabradine was "accepted for restricted use within NHS Scotland." Specifically, ivabradine is restricted "for initiation only in patients whose resting HR remains ≥ 75 beats per minute despite optimal standard therapy" |

ACEI = angiotensin-converting enzyme inhibitor; BB = beta-blocker; bpm = beats per minute; CDR = CADTH Common Drug Review; CHF = chronic heart failure; CUA = cost-utility analysis; CV = cardiovascular; ERG = Evidence Review Group; HR = heart rate; ICER = incremental cost-effectiveness ratio; LVEF = left ventricular ejection fraction; NICE = National Institute for Health and Care Excellence; NYHA = New York Heart Association;
QALY = quality-adjusted life-year; QoL = quality of life; SMC = Scottish Medicines Consortium.

### TABLE 9: OTHER HTA FINDINGS (PBAC)

| | PBAC November 2011[17] | PBAC July 2012, November 2012, March 2013[18] |
|---|---|---|
| Treatment | Ivabradine (Coralan), tablet, 5 mg and 7.5 mg, in addition to standard medical management | |
| Indication/ Request | Request for "an Authority Required listing for initial and continuing treatment of symptomatic systolic HF in a patient in sinus rhythm, with HR ≥ 70 bpm stabilized on conventional therapy, which includes BB (unless intolerant or contraindicated) at a maximum tolerated dose" | Re-submission listing request for the treatment of "symptomatic systolic HF in patients with sinus rhythm, with HR ≥ 75 bpm, measured after 5 minutes rest, who are stabilized on optimal HF therapy, which must include an ACEI or angiotensin II antagonist and BB (unless intolerant or contraindicated)" |
| Comparator | Standard medical management (placebo): ACEI, or angiotensin II antagonist and BB, if tolerated | |
| Price | Price information was not reported. | |
| Similarities with CDR submission | • CUA<br>• Efficacy inputs from SHIfT study | • CUA<br>• Efficacy inputs from SHIfT study<br>• Results for pre-specified subgroup: HR ≥ 77 bpm |
| Differences with CDR submission | • Stepped economic evaluation for both ITT population and a subgroup of patients with a baseline HR ≥ 75 bpm<br>• Time horizon = 10 years | • Base case efficacy from post hoc subgroup analysis of patients at both HR ≥ 75 bpm and receiving ≥ 50% target BB dose<br>• Time horizon = 10 years |
| Manufacturer's | ICER = $15,000 to $45,000 per QALY gained | ICER < $15,000 to > $200,000 per QALY |

| | PBAC November 2011[17] | PBAC July 2012, November 2012, March 2013[18] |
|---|---|---|
| results | (ITT population) | (revised base case using 95% CIs from SHIfT Cox proportional hazards modelling results); ICER highly sensitive to small changes in RR of hospitalizations for worsening HF |
| Issues noted by the review group | • Not all patients in SHIfT were on optimized therapy<br>• Limited applicability of SHIfT to Australian setting given trial dominated by patients from Eastern Europe, likely to affect hospitalizations<br>• Australian population likely to be significantly older and have more comorbid conditions<br>• SHIfT did not test hypothesis that ivabradine provides additional benefit to patients on optimal HF treatment; based on a subgroup analysis in patients receiving a BB > 50% target dose, data suggest no additional benefit of ivabradine in this subgroup<br>• Role of ivabradine in patients whom BB contraindicated/not tolerated is unclear<br>• Restriction (limiting to patients with HR ≥ 70 bpm or 75 bpm) was deemed unworkable due to considerable variability in measurement<br>• Limitations with clinical trial data in economic evaluation making ICERs highly uncertain | • PBAC noted treatment with ivabradine may benefit small subgroup of patients in clinical practice; effect may be statistically significant in subgroup only and driven by hospitalization events<br>• No statistically significant difference noted for primary composite end point or CV death among post hoc patient subgroup with HR ≥ 75 bpm and receiving ≥ 50% target BB dose, which renders economic results highly uncertain<br>• PBAC remained concerned that statistical significance of composite end point was driven by clinician-decision component, which may differ in Australian clinical practice compared with Eastern European trial; PBAC noted it would be difficult to restrict use of ivabradine to patients with HR ≥ 77 bpm, even though it can be accurately measured, given HR can vary in individuals at any time |
| Review group reanalyses | None reported | None reported |
| Recommendation | PBAC "**rejected** the submission because of the high uncertainty around the clinical evidence to support the clinical claim and the resultant high uncertainty in the economic analysis" | July 2012: PBAC **deferred** the submission to verify revised ICERs, to clarify estimates of usage and cost, and to assess feasibility of the proposed restriction<br>November 2012: PBAC **rejected** the submission on the basis of uncertain clinical benefit and resulting uncertain cost-effectiveness<br>March 2013 (Minor submission)**:** PBAC **recommended listing** of ivabradine as an Authority Required benefit for patients with chronic HF (**NYHA class II or III; resting HR ≥ 77 bpm**) stabilized on optimal HF treatment |

ACEI = angiotensin-converting enzyme inhibitor; BB = beta-blocker; bpm = beats per minute; CDR = CADTH Common Drug Review; CUA = cost-utility analysis; CV = cardiovascular; HF = heart failure; HR = heart rate; HTA = health technology assessment; ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; NYHA = New York Heart Association; PBAC = Pharmaceutical Benefits Advisory Committee; QALY = quality-adjusted life-year; RR = relative risk.

# APPENDIX 5: REVIEWER WORKSHEETS

### Manufacturer's Model Structure

Ivabradine was submitted to the CADTH Common Drug Review (CDR) prior to receiving a Health Canada Notice of Compliance. Ivabradine received a Notice of Compliance with a slightly different indication to that which had been submitted to CDR and upon which the economic model was based.

The submitted economic model was based on a Markov cohort model originally submitted to the UK's National Institute for Health and Care Excellence (NICE) in 2012. The model is made up of two health states: alive and dead.

A series of multivariable risk equations were used to predict the risk of four outcomes of interest: mortality, hospitalization, health-related quality of life (QoL), and New York Heart Association (NYHA) class. Outcomes were modelled to vary according to treatment allocation and patient characteristics.

The risk of cardiovascular (CV) mortality was estimated using a Gompertz parametric survival regression based on data from a post hoc analysis of SHIfT study patients with a heart rate (HR) ≥ 75 bpm; the Gompertz model was chosen as it was reported to best fit the data, though there is some uncertainty associated with this assumption. The manufacturer noted that the relatively small number of deceased patients in the ivabradine arm at the close of the SHIfT study may not represent a sufficiently large data set to optimally extrapolate mortality within the trial period; thus, sensitivity analyses using external mortality data from the RAFT[20] and CARE-HF[21] trials were undertaken. These trials assessed the impact of cardiac resynchronization therapy in patients with and without implantable cardioverter-defibrillators.

NYHA class was used to classify heart failure (HF) severity. Patients' health-related QoL varied as a function of NYHA class and the proportions of patients in each NYHA class over time (NYHA distribution) reflected the observed SHIfT data for the model's within-trial time horizon. A generalized ordered logistic regression based on SHIfT data was used to predict the within-trial NYHA distribution, carrying forward the last observed NYHA class for each patient for the post-trial period.

The rate of all-cause hospitalizations per person-month was estimated from a Poisson regression model, based on SHIfT data. The rate of hospitalization did not appear to vary over time in SHIfT; thus, the Poisson model predicted hospitalizations to occur at a constant rate, although the predicted rate varies according to treatment allocation and patient baseline characteristics.

Health-related QoL data were collected from a representative sample of the SHIfT main trial population ([redacted] out of 6,505 patients; [redacted]%) using the EuroQoL 5-Dimension questionnaire (EQ-5D) to derive utility values. Regression techniques for repeated observations across individuals over time (multi-level regression model) were used to elicit utilities. The manufacturer indicated that the variables considered to be predictors of patient QoL were generally consistent with those used in the CV mortality and hospitalization risk equations, with the addition of two time-varying variables (hospitalization and NYHA class). Utility values were predicted to vary by treatment allocation, NYHA class, the occurrence of hospitalization events, and patient baseline characteristics.

Standard care treatments, their dosages, and ivabradine dosages were based on use patterns observed in the SHIfT study. As sacubitril/valsartan was not available at the time of the study, the manufacturer

assumed that approximately 10% of patients would receive this treatment as part of SOC, and that this treatment would not affect the clinical results. With regards to ivabradine dosing, the manufacturer assumed [redacted]% of patients would receive 2.5 mg twice daily, [redacted]% of patients would receive 5 mg twice daily, and [redacted]% of patients would receive 7.5 mg twice daily. This proportion was applied consistently over the model's time horizon. The manufacturer also included dispensing fees in the model's base-case analysis.[2]

Published literature informed the monthly cost of HF management, which was estimated at $617 per month ($144 for physician services, $384 for hospitalization, $36 for emergency department visits, $23 for same day surgery, and $31 for medications).[4] Excluding drug costs, hospitalization costs, and day surgery costs, the cost of managing HF in a stable disease state was about $180 per month ($144 for physician services and $36 for emergency department visits). This cost was inflated to 2016 Canadian dollars using the health care component of the Canadian Consumer Price Index to derive a monthly HF management cost of $203 per person, and was use in the submitted model.[4] Hospitalization costs were estimated based on a cohort of Ontario patients who were discharged from hospital with an HF diagnosis in 2005 (identified in the Canadian Institute for Health Information discharge abstract database), as well as data from the Ontario Case Costing Initiative.[4]

Due to a lack of transparency in the submitted model, CDR was unable to validate several model parameters.

**TABLE 10: DATA SOURCES**

| Data Input | Description of Data Source | Comment |
|---|---|---|
| Patient characteristics | The model reported baseline data for the entire SHIfT population in the simulation of patients.[2] As the model examined the ≥ 77 bpm subgroup, this population was stratified in the simulation. The population used to derive the regression equations was the full trial population or the ≥ 75 bpm subgroup population. | Feedback from the clinical expert noted some concern regarding the generalizability of the study results. Discordant mortality results have been seen in CV studies in [redacted] compared with North America.[3] |
| Efficacy: NYHA class | Baseline distribution was predicted in accordance with the observed data from the full population of the SHIfT study using generalized ordered logistic regression. For the probability of transitioning, data were extrapolated to be fixed post-trial (carry forward the last observed NYHA class for each patient). | The impact is unclear about the use of the full SHIfT population for producing predictive results for the indicated population. |
| Efficacy: Non-CV Mortality | The risk of non-cardiovascular death was estimated from age- and sex-adjusted Canadian life table data (Statistics Canada 2012) with cardiovascular death removed.[22,23] | Appropriate. |
| Efficacy: CV Mortality | The risk of CV mortality was derived from the SHIfT study using the patient population with a heart rate of 75 bpm or greater, adjusting based on baseline characteristics and covariates (e.g., treatment, age, sex, history of stroke, prior beta-blocker use, etc.). The mortality risk was extrapolated using a multivariable parametric (Gompertz) survival model. The manufacturer reported Gompertz was | The impact is unclear about the use of the 75 bpm subgroup data for producing predictive results for the indicated population.<br><br>The manufacturer did not justify the use of the 75 bpm subgroup to undertake this analysis. |

| Data Input | Description of Data Source | Comment |
|---|---|---|
| | chosen as the best statistical fit of observed data based on a comprehensive evaluation of six possible parametric functions which included exponential, Weibull, Gompertz, log-logistic, lognormal, and gamma. Data from external non-ivabradine trials (RAFT and CARE-HF) were used in sensitivity analyses.<br><br>The values were tested as HRs relative to the standard care arm. | The analyses lacked transparency and flexibility. |
| Efficacy: Hospitalizations | The probability of hospitalization was determined from the standard care arm of the SHIfT study; a rate ratio was then applied for ivabradine estimated using a Poisson regression model.<br><br>Hospitalization rates and probabilities were applied for hospitalization due to worsening HF, CV hospitalization, and all-cause hospitalization. | The inclusion of all-cause hospitalization is questionable. No rationale has been provided to support the assumption that any difference in all-cause hospitalization (exclusive of CV/HF hospitalization) would be expected between the two trial arms. |
| Utilities | Based on unpublished data from "a representative sample of the SHIfT main trial population."[2]<br><br>EQ-5D data were collected from [redacted]% of the SHIfT main trial population, though the manufacturer did not specify whether Canada-specific values were used to derive the utility values.<br><br>A multi-level regression model was developed to estimate utility values. The utility values were predicted to vary by NYHA class, occurrence of hospitalizations, and patient baseline characteristics.<br><br>The regression model was based on stratified patient populations, based on treatment and occurrence of hospitalization.<br><br>The regression model suggested ivabradine was associated with a statistically significant gain in utility, which was incorporated to model treatment effect, and assumed to continue beyond the trial period.<br><br>The model applied disutilities based on hospitalization events and multiple regression factors. | The pre-stratification of the population based on treatment and occurrence of hospitalization is associated with uncertainty.<br><br>The assumption of a treatment benefit for ivabradine exclusive of NYHA state is not justified.<br><br>CDR could not validate the regression model applied by the manufacturer. |
| Adverse events | Additional outpatient management costs were considered for two adverse events (symptomatic and asymptomatic bradycardia) reported in Swedberg et al. 2010.[24] | |

| Data Input | Description of Data Source | Comment |
|---|---|---|
| **Resource use** | | |
| Concomitant medications and ivabradine use | Estimated based on data from the SHIfT study and clinical expert opinion. Data from SHIfT were adjusted based on Canadian setting; 14% of anti-ischemic drugs reported in SHIfT are not used in Canada and were excluded from analysis, and treatments within class (e.g., ARB, BB, ACEI, etc.) were chosen based on availability in Canada.[2] | The manufacturer also assumed approximately 9% of patients received sacubitril/valsartan in the model, attributing a cost to this treatment and assuming no difference in treatment between the treatment arms. Due to the lack of data supporting this assumption, the cost of sacubitril/valsartan was excluded from SOC. |
| **Costs** | | |
| Ivabradine | Manufacturer | |
| SOC[a] | Ontario Drug Benefit Formulary | Acceptable |
| Other CV drugs | Ontario Drug Benefit Formulary<br><br>As Aspirin is available OTC, no cost attributed.<br><br>Price of sacubitril/valsartan was price submitted to CADTH. | Acceptable |
| Administration | Dispensing fee included based on ODB ($8.83 per prescription), assuming one script per 100-day supply | Excluded in CDR reanalysis |
| Ivabradine treatment costs (titration visit, ECG) | OHIP Schedule of benefits | Acceptable |
| Hospitalization costs | Based on Canadian costs from OCCI (HF hospitalization) and CIHI (CV and all-cause hospitalization) | Acceptable |
| HF management (e.g., physician visits, outpatient procedures, and diagnostic tests) | Based on Canadian cost-effectiveness study which estimated the costs (in 2008 Canadian dollars) and outcomes of HF patients who receives standard care[4] | Acceptable |
| Costs associated with AEs (bradycardia) | Based on Canadian costs from OCCI (ER visit) and OHIP Schedule of benefits (physician visit) | Acceptable |

ACEI = angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin II receptor blocker; BB = beta-blocker; bpm = beats per minute; CIHI = Canadian Institute for Health Information; CDR = CADTH Common Drug Review; CV = cardiovascular; ECG = electrocardiography;
EQ-5D = EuroQol 5-Dimensions questionnaire; ER = emergency room; HF = heart failure; HR = hazard ratio; OCCI = Ontario Case Costing Initiative; OHIP = Ontario Health Insurance Plan; NYHA = New York Heart Association; OTC = over the counter; SOC = standard care.
[a] SOC includes beta-blockers, ACEI, diuretics, mineralocorticoid receptor antagonists, ARBs, and cardiac glycoside.

**TABLE 11: MANUFACTURER'S KEY ASSUMPTIONS**

| Assumption | Comment |
|---|---|
| The modelled population (based on SHIfT) is representative of the Canadian population. | Questionable. Modelled population is based on the SHIfT study. [redacted], which may affect the applicability and generalizability of the trial results to the Canadian setting, given one of the trial outcomes of interest (HF hospitalization) was a clinical practice–dependent end point, which may differ between countries.<br>Approximately 10% of patients were not receiving a beta-blocker at treatment randomization in SHIfT, and less than 50% of the population was receiving at least 50% of the target dose of a beta-blocker. |
| The modelled population is representative of the Health Canada–indicated population. | Questionable. The modelled population was based on the SHIfT full population, which was undertaken in patients with a heart rate of ≥ 70 bpm, who had NYHA class II to IV HF. Many of the regression analyses were undertaken based on the ≥ 70 bpm population or the ≥ 75 bpm population (post hoc subgroup analysis). The Health Canada indication noted that patients should be on target doses of beta-blockers before moving on to ivabradine. In the trial, ~60% of patients were receiving less than 50% of the target beta-blocker dose. Subgroup analyses indicate that patients who were receiving at least 50% of the target beta-blocker dose did not achieve statistically significant benefits with ivabradine. |
| All appropriate comparators were considered. | Questionable. The manufacturer considered sacubitril/valsartan to be part of SOC, as opposed to a comparator option. Based on the product monographs for ivabradine and sacubitril/valsartan, and feedback from a clinical expert consulted by CDR, for the subset of patients for which ivabradine is intended for use, sacubitril/valsartan may also be used. |
| The modelling approach undertaken is appropriate and well justified. | Questionable. The modelling approach lacked transparency and flexibility based on the information provided to CDR, and on numerous occasions appeared to have questionable face validity. |
| Addition of a utility benefit for ivabradine. | Not justified. The application of a utility benefit associated with ivabradine within the same health state compared with the SOC alone is not justified. |
| Maintenance of effect after the trial time horizon. | Questionable and uncertain. This assumes a continued duration of benefit and may overestimate the incremental benefit of ivabradine over a longer time horizon. Only 3% of the incremental life-year benefit, and 11% of the incremental QALY benefit are seen during the trial period in the model. |
| Using data from the full population of the SHIfT study to determine the weighted average dose of ivabradine, and assuming this is a constant dose throughout the model. | This assumption is associated with uncertainty. [redacted] patients in the relevant subgroup (≥ 77 bpm) received the 7.5 mg dose of ivabradine than the full study population, and this subgroup received a [redacted] dose of ivabradine over the study period ([redacted]). The issues with the generalizability of the study have been highlighted earlier in this table and the report. Additionally, the assumption of a constant dose throughout the model may underestimate the dose over a longer duration. |

bpm = beats per minute; CDR = CADTH Common Drug Review; HF = heart failure; NYHA = New York Heart Association; QALY = quality-adjusted life-year; SOC = standard care.

## Manufacturer's Results

The manufacturer's base case was reported to be based on a probabilistic analysis of patients with a heart rate ≥ 77 beats per minute (bpm). The results were based on 1,000 iterations of 6,505 patients (the full SHIfT population). Subsequently, the relevant results for the subset of patients with a heart rate ≥ 77 bpm were derived.

The predicted mean discounted survival for ivabradine plus stand of care (SOC) patients was approximately 5.8 years compared with 5.4 years for patients receiving SOC alone. Ivabradine was therefore expected to improve patient survival by 0.34 years (approximately four months) compared with SOC alone. Overall, ivabradine plus SOC was associated with a gain of 0.35 quality-adjusted life-years (QALYs), or approximately four quality-adjusted life-months, versus SOC alone (Table 12).

The manufacturer's model predicted that, over a lifetime time horizon (approximately 30 years), ivabradine plus SOC would cost approximately $2,700 more per patient compared with SOC alone. The additional drug therapy and follow-up costs (approximately $6,700 per patient) were offset by a reduction in expected hospitalization costs (approximately $3,950 per patient). The resultant incremental cost per additional QALY gained for ivabradine plus SOC versus SOC alone was estimated to be $7,969 (Table 12).

**TABLE 12: RESULTS OF THE MANUFACTURER'S BASE CASE**

| | Ivabradine + SOC | SOC | Incremental Cost (Iva + SOC vs. SOC) |
|---|---|---|---|
| ***Total cost*** | ***$53,191*** | ***$50,445*** | ***$2,746*** |
| Drug cost | $8,829 | $3,048 | $5,882 |
| Hospitalization cost | $30,204 | $34,161 | –$3,957 |
| Follow-up costs | $14,057 | $13,237 | $821 |
| ***Total life-years*** | ***5.771*** | ***5.434*** | ***0.337*** |
| ***Total QALYs*** | ***4.170*** | ***3.826*** | ***0.345*** |
| **ICER (per LY)** | | | **$8,150** |
| **ICUR (per QALY)** | | | **$7,969** |

ICER = incremental cost-effectiveness ratio; ICUR = incremental cost-utility ratio; Iva = ivabradine; LY = life-year; QALY = quality-adjusted life-year; SOC = standard care.

## CADTH Common Drug Review Reanalyses

CDR undertook a series of one-way reanalyses on the manufacturer's base case (Table 13). The reanalyses that stemmed from the identified limitations included:

- **Consideration of sacubitril/valsartan in the economic analysis: Sacubitril**/valsartan was removed from standard care.
- **Baseline characteristics:** Patients were stratified by their baseline usage of beta-blockers in scenario analyses based on a pre-programmed analyses included by the manufacturer.
- **Prediction of outcomes post-trial:** The model time horizon was reduced to 10 years based on pre-programmed analyses included by the manufacturer. Treatment costs and benefits were accrued throughout the time horizon.
- **The modelling of hospitalization was questionable:** The lower 95% confidence interval for the rate of hospitalizations was used. Additionally, the length of hospitalization for non-CV hospitalizations was reduced to 0.0001 days (zero could not be used due to modelling considerations).
- **Treatment benefit was overestimated:** The utility increment associated with treatment with ivabradine was removed.
- **The monthly treatment cost of ivabradine is uncertain:** The proportion of patients on ivabradine 7.5 mg was increased from [redacted], while the proportion of patients on 2.5 mg and 5 mg was reduced proportionally.

The following reanalysis was also undertaken:

- Removal of dispensing fees applied in the submitted model.

CDR was unable to test the following limitations identified in the submitted economic model:

- Geographic variability in the clinical trial population.
- Precision of the predictions for the indicated population based on predictive functions developed from other SHIfT patient populations.
- The model lacks flexibility and transparency.

**TABLE 13: CDR ONE-WAY REANALYSES**

| Analysis | Incremental Cost | Incremental QALY | ICUR (per QALY) |
|---|---|---|---|
| **Manufacturer's base case** | **$2,746** | **0.3445** | **$7,969** |
| **CDR single parameter reanalysis** | | | |
| • Remove sacubitril/valsartan from standard care | $2,750 | 0.3417 | $8,050 |
| • Reduce time horizon to 10 years (pre-set analysis in the manufacturer's model) | $2,952 | 0.3430 | $8,608 |
| • Reduced duration of hospital stay for all-cause hospitalization (from 9.2 days to 0.0001 days) | $3,015 | 0.3503 | $8,607 |
| • Rate of hospitalization reduced to lower 95% confidence interval (pre-set analysis in the manufacturer's model) | $2,902 | 0.3420 | $8,245 |
| • Scenario analysis: < 50% TD BB (pre-set analysis in the manufacturer's model) | $2,391 | 0.3298 | $7,250 |
| • Scenario analysis: ≥ 50% TD BB use but <100% (pre-set analysis in the manufacturer's model) | $3,239 | 0.3486 | $9,289 |
| • Scenario analysis: ≥ 100% TD BB (pre-set analysis in the manufacturer's model) | $3,593 | 0.3502 | $10,262 |
| • Remove ivabradine utility increment | $2,880 | 0.2615 | $11,015 |
| • Revised ivabradine usage ([redacted]% use 7.5mg) | $3,649 | 0.3428 | $10,644 |
| • Remove dispensing fee | $2,763 | 0.3460 | $7,985 |

CDR = CADTH Common Drug Review; BB = beta-blocker; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TD = target dose.

The CDR base case was a multi-way reanalysis which considered the following revisions to the manufacturer's base-case analysis:

- Sacubitril/valsartan was removed from standard care.
- The model time horizon was reduced to 10 years based on pre-programmed analyses included by the manufacturer.
- The lower 95% confidence interval for the rate of hospitalizations was used.
- The length of hospitalization for non-CV hospitalizations was reduced to 0.0001 days (zero could not be used due to the modelling considerations).
- The utility increment associated with treatment with ivabradine was removed.
- The proportion of patients on ivabradine 7.5 mg was increased from [redacted], while the proportion of patients on 2.5 mg and 5 mg were reduced proportionally.
- The dispensing fees applied in the model were removed.

The results are presented in Table 14.

**TABLE 14: CDR BASE CASE**

| Analysis | | Costs | QALYs | Incremental Cost | Incremental QALY | ICUR (per QALY) |
|---|---|---|---|---|---|---|
| **Manufacturer** | **Ivabradine** | $53,191 | 4.170 | | | |
| **(probabilistic)** | **SOC** | $50,445 | 3.826 | $2,746 | 0.3445 | $7,969 |
| **CDR** | **Ivabradine** | $52,567 | 4.021 | | | |
| **(probabilistic)** | **SOC** | $49,212 | 3.761 | $3,355 | 0.2602 | $12,895 |
| **CDR** | **Ivabradine** | $48,386 | 3.752 | | | |
| **(deterministic)** | **SOC** | $46,369 | 3.557 | $2,016 | 0.1946 | $10,362 |

CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Scenario analyses of the CDR base case based on pre-stratified beta-blocker use were undertaken and the results are presented in Table 15.

**TABLE 15: SCENARIO ANALYSES ON THE CDR BASE CASE**

| Analysis | Incremental cost | Incremental QALY | ICUR (per QALY) |
|---|---|---|---|
| **Manufacturer's Base Case** | **$2,746** | **0.3445** | **$7,969** |
| **CDR Base Case** | **$3,355** | **0.2602** | **$12,895** |
| • Scenario analysis: < 50% TD BB (pre-set analysis in the manufacturer's model) | $2,982 | 0.2517 | $11,849 |
| • Scenario analysis: ≥ 50% TD BB use but <100% (pre-set analysis in the manufacturer's model) | $3,869 | 0.2621 | $14,759 |
| • Scenario analysis: ≥ 100% TD BB (pre-set analysis in the manufacturer's model) | $4,329 | 0.2588 | $16,729 |

BB = beta-blocker; CDR = CADTH Common Drug Review; ICUR = incremental cost-utility ratio; QALY = quality-adjusted life-year; TD = target dose.

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