Common Drug Review
Clinical Review Report

June 2017

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.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in cardiology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

ACEI	angiotensin-converting enzyme inhibitor
AE	adverse event
ARB	angiotensin receptor blocker
bpm	beats per minute
CDR	CADTH Common Drug Review
CI	confidence interval
CV	cardiovascular
ECG	electrocardiogram
HCN	hyperpolarization-activated cyclic nucleotide-gated
HF	heart failure
HFSGM	Heart Failure Support Group of Manitoba
HLF	HeartLife foundation
HR	hazard ratio
ITT	intention-to-treat
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonists
NYHA	New York Heart Association
PBAC	Pharmaceutical Benefits Advisory Committee
RCT	randomized controlled trial
SAE	serious adverse event
SHIfT	Systolic Heart Failure Treatment with the I_f inhibitor Ivabradine Trial
TEAE	treatment-emergent adverse events

EXECUTIVE SUMMARY

Introduction

Heart failure (HF) is a condition that results from the inability of the heart to meet the body's metabolic demands for oxygen because of structural or functional impairment of ventricular filling or ejection of blood. There are an estimated 600,000 Canadians with HF and roughly 50,000 new cases are diagnosed each year. Approximately half of HF patients have a reduced left ventricular ejection fraction (LVEF) (which may be defined as LVEF ≤ 40%); it is for this population that the evidence base regarding treatment is better established. The mortality rate for HF ranges from as low as 5% at year one to 50% at five years after diagnosis, depending on the severity of symptoms, heart function, age, and other factors. The primary symptoms of HF are dyspnea and fatigue, and may also include fluid retention. Patient group input submitted for this review reported that HF can have a substantial impact on patients' exercise tolerance and quality of life, limiting their ability to work, participate in recreational activities, and complete activities of daily living.

Ivabradine is a heart-rate-lowering drug utilizing a mechanism of action that differs from that of beta-blockers. It is available as film-coated tablets that contain ivabradine hydrochloride 5 mg and 7.5 mg.

Ivabradine is indicated for the treatment of stable chronic HF with reduced LVEF (≤ 35%) in adult patients with New York Heart Association (NYHA) class II or III HF 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 HF, administered in combination with standard chronic HF therapies. According to the Health Canada–approved product monograph for ivabradine, it should be used in clinically stable patients in conjunction with other HF treatments, such as beta-blockers and aldosterone antagonists, and angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) therapy. The recommended starting dosage is 5 mg twice daily orally; dosage adjustments are permitted following two weeks of treatment, depending on the resulting heart rate, to a maximum dose of 7.5 mg twice daily orally.

Indication under review
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 criteria requested by sponsor
As per indication

The objective of this review was to perform a systematic review of the beneficial and harmful effects of ivabradine 5 mg and 7.5 mg tablets for the treatment of stable chronic HF with LVEF (≤ 35%) in adult patients with NYHA class II or III HF who are in sinus rhythm with a resting heart rate ≥ 77 bpm, to reduce the incidence of cardiovascular mortality and hospitalizations for worsening HF, administered in combination with standard chronic HF therapies.

Results and Interpretation

Included Studies

One study met the inclusion criteria of the CADTH Common Drug Review (CDR) systematic review. The Systolic Heart Failure Treatment with the I_f inhibitor Ivabradine Trial (SHIfT, N = 6,558) was an event-driven, multi-centre (677 centres), multinational (37 countries), double-blind, placebo-controlled, phase III randomized trial designed to assess the superiority of ivabradine versus placebo. The SHIfT study, which was conducted mostly in Eastern European countries, enrolled patients with HF (NYHA class II to IV) suffering from left ventricular systolic dysfunction with LVEF of 35% or lower. Eligible patients were adults in sinus rhythm and with a resting heart rate ≥ 70 bpm, as measured with 12-lead electrocardiography after at least five minutes of rest on two consecutive visits before randomization.

Although the SHIfT study included patients with heart rates ≥ 70 bpm, the Health Canada–approved indication — and the manufacturer's reimbursement request — is for the treatment of patients with heart rates ≥ 77 bpm. Therefore, this CDR review focuses on a pre-specified subgroup of patients in the enrolled SHIfT population with heart rates ≥ 77 bpm (n = 3,357) who were derived from the randomized set and the safety set of the overall population. The interventions studied in SHIfT were ivabradine 2.5 mg (half of the 5 mg tablet), 5 mg, and 7.5 mg oral film-coated tablets twice daily in combination with standard chronic HF treatment (e.g., ACEI or ARB, beta-blockers, and mineralocorticoid receptor antagonists [MRAs]) compared with placebo. All concomitant treatments were permitted with few exceptions. The trial consisted of 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, respectively, for both treatment groups.

Patients in the heart rate ≥ 77 bpm subgroup of the SHIfT study had a mean age of [redacted] years (standard deviation [redacted]), of whom [redacted] were younger than 65 years of age and [redacted] were 75 years or older. The majority of patients were [redacted] and [redacted], with a history of [redacted]. Almost all patients were [redacted] and [redacted] of patients had underlying ischemic etiology. 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 majority of patients were being treated with [redacted] Approximately [redacted] of patients were receiving target daily doses of beta-blockers and nearly [redacted] were taking ≥ 50% of the target daily dose of beta-blockers. The primary end point of the SHIfT study was a composite of cardiovascular death or hospitalization for worsening HF. Secondary end points included all-cause mortality, death from cardiovascular causes, death from HF, all-cause hospitalizations, cardiovascular-related hospitalization, and hospitalization for worsening HF.

Key limitations of the trial include a lack of stratification by heart rate at randomization; a 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 study and what would be seen in a Canadian setting (for example, the mean age of patients and the use of optimal standard chronic HF treatment).

Efficacy

Based on the pre-specified subgroup of interest for this review (patients with a baseline heart rate ≥ 77 bpm), there were fewer primary composite end point events of cardiovascular mortality or hospitalization for worsening HF in the ivabradine treatment group compared with the placebo group

(27.4% versus 34.2%, respectively) which was associated with a statistically significant treatment effect in favour of ivabradine (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.67 to 0.85, *P* < 0.0001). The primary composite end point was statistically significant for both cardiovascular mortality (15.4% versus 18.4% [HR, 0.81; 95% CI, 0.69 to 0.96, *P* = 0.0137]) and for hospitalization for worsening HF (18.0% versus 24.6% [HR, 0.69; 95% CI, 0.59 to 0.80, *P* < 0.0001]). There were also statistically significant differences between treatment groups 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 HF (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 cardiovascular hospitalizations (32.2% versus 38.1% [HR, 0.79; 95% CI, 0.71 to 0.89, *P* < 0.0001]) in the ivabradine treatment group versus the placebo group, respectively. Other secondary cardiovascular outcomes, such as sudden cardiac death, fatal or non-fatal myocardial infarction and stroke, and new onset atrial fibrillation, were similar between treatment groups. It is important to note that these results are based on a pre-specified subgroup analysis with no control for multiple statistical testing. While the risk of type I error remains, the validity of the results for the subgroup of interest for this CDR review (i.e., heart rate ≥ 77 bpm) is strengthened by the pre-specified nature of the subgroup and the biological plausibility of the interaction effect.

The clinical expert consulted for this review noted that more than 50% (likely between 50% and 75%) of patients with chronic HF would be treated with ≥ 50% target daily beta-blocker doses in clinical practice. The patient population enrolled in the SHIfT study, within the heart rate ≥ 77 bpm subgroup, were receiving variable levels of optimal beta-blockers. The results of a post hoc subgroup analysis based on patients within four categories of per cent target daily beta-blocker dose (i.e., < 25%, ≥ 25% to < 50%, ≥ 50% to < 100%, and ≥ 100%), suggested that [redacted] Again, these results are based on a post hoc subgroup analysis with no control for multiple statistical testing. The observed trend, and the concordance of the results with the pre-specified subgroup analyses results based on ≥ 50% target daily beta-blocker dose, support these findings. Nonetheless, the risk of observing a chance effect remains. The pre-specified ≥ 50% target daily beta-blocker dose and the post hoc < 50% target daily beta-blocker dose subgroups demonstrated that there was [redacted] These results support the suggestion that the [redacted] demonstrated by the four categories of per cent target daily beta-blocker dose (i.e., < 25%, ≥ 25% to < 50%, ≥ 50% to < 100%, and ≥ 100%).

Harms

Treatment-emergent adverse events were experienced by [redacted] of patients in the ivabradine group and [redacted] of patients in the placebo group during the SHIfT study. The most common treatment-emergent adverse events were cardiac failure, bradycardia (symptomatic and asymptomatic), atrial fibrillation and inadequately controlled blood pressure. 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 cardiac failure and [redacted]. The percentage of patients who stopped treatment due to adverse events was similar between the ivabradine ([redacted]) and placebo ([redacted]) groups, for whom sudden death, [redacted] were the most commonly reported reasons for stopping treatment.

Notable harms that were more commonly reported in the ivabradine group compared with the placebo group included [redacted].

Potential Place in Therapy

According to the clinical expert consulted for this review, approximately 10% to 15% of patients with HF in Canada have heart rates ≥ 70 bpm despite recommended treatment. The patient population of interest for this CDR review (patients with a heart rate ≥ 77 bpm despite recommended treatment), would therefore be less than 10% to 15% of patients with HF in Canada. The mortality rate for HF ranges from as low as 5% at year one up to 50% at five years after diagnosis, depending on the severity of symptoms, heart function, age, and other factors. The all-cause mortality rate in the placebo group of the SHIfT study, for example, was 17% at 30 months. Prior to the introduction of MRAs and sacubitril/valsartan (Entresto), there was little progress in reducing the high mortality rate for patients with HF.

Both the Canadian Cardiovascular Society and the American Heart Association guidelines suggest potential benefits with the use of ivabradine in patients in sinus rhythm with symptomatic HF and reduced ejection fraction who have a heart rate ≥ 70 bpm and who are receiving an ACEI or ARB and a beta-blocker. The clinical expert consulted for this review, as well as Swedberg et al., noted that, in line with the conduct of the SHIfT study, ivabradine is considered an add-on treatment, and not a replacement for beta-blockers. Importantly, patients should be receiving guideline-directed evaluation and management (ACEIs or ARBs), including a beta-blocker at a maximum tolerated dose and MRAs.

Another available treatment option for patients who remain symptomatic despite optimal triple therapy is to switch the use of ACEI or ARB to sacubitril/valsartan, as was done in the PARADIGM-FH trial. The only difference is that in PARADIGM-FH, patients did not have to be on an MRA at the time of enrolment (only 50% of patients were on one). The clinical expert also indicated that an important advantage of ivabradine is that, unlike the combination of sacubitril/valsartan, it has little effect on blood pressure (and vasodilation), which often limits the therapeutic options in patients with HF.

Overall, the clinical expert consulted for this review indicated that ivabradine represents a viable option for the treatment of patients with HF, marginal blood pressure, and a heart rate ≥ 77 bpm. To ensure patients meet the heart rate criterion of the Health Canada–approved indication for ivabradine, the clinical expert indicated that heart rate should be documented by electrocardiogram, as was done in the SHIfT study.

Conclusions

The CDR systematic review included one double-blind, phase III, randomized placebo-controlled trial designed to assess the superiority of ivabradine versus placebo in patients with a heart rate ≥ 70 bpm. Given the reimbursement request and Health Canada–approved indication, this CDR review primarily focused on the results from a subgroup of patients in the SHIfT study (i.e., patients with a heart rate ≥ 77 bpm; N = 3,357). There was a statistically significant difference between ivabradine and placebo for the primary composite outcome of cardiovascular mortality and hospitalization for worsening HF (HR, 0.75; 95% CI, 0.67 to 0.85) based on the subgroup of patients with a heart rate ≥ 77 bpm. The primary composite end point was statistically significant for both cardiovascular mortality and for hospitalization for worsening HF. Although the results, which are based on subgroup analyses from the overall study population, are limited due to uncontrolled multiple statistical testing and the lack of stratification by

heart rate at randomization, the validity of the results are strengthened by the pre-specified nature of the subgroup, the biological plausibility of the relationship between heart rate and treatment effects, large sample sizes, and the consistency of the results between study outcomes. Further subgroup analyses based on the per cent target daily beta-blocker dose received by patients suggested that the treatment effects of ivabradine diminished with increasing per cent target daily beta-blocker dose received. However, these results were based on a post hoc subgroup analysis with no control for multiple statistical testing. The observed trend, and the concordance of the results with the pre-specified subgroup analyses results based on ≥ 50% target daily beta-blocker dose, support these findings. Nonetheless, the risk of observing a chance effect remains. The SHIfT study was conducted mainly in Eastern European centres with few North American centres; only 30 Canadian patients from 10 centres were included in the study when considering the overall population (i.e., heart rate ≥ 70 bpm). It is unclear how many Canadian patients were included in the subgroup of interest (i.e., heart rate ≥ 77 bpm). The differences in patient and practice characteristics (for example, patient age, the use of optimal standard chronic HF treatment, and the definition of hospitalization) between countries, may affect the generalizability of the results to patients in Canada.

Ivabradine was associated with an increased frequency of bradycardia (symptomatic and asymptomatic) and phosphenes compared with placebo; other adverse events were similar between groups. Additional data are required to determine the longer-term safety of this first-in-class therapy.

TABLE 1: SUMMARY OF RESULTS

	SHIfT (Subgroup ≥ 77 bpm)			
	Ivabradine (N = 1,657)	**Placebo (N = 1,700)**	**Treatment effect Ivabradine versus Placebo**	***P* value**
Primary Outcome	**n (%)**	**n (%)**	**HR (95% CI)**	
CV death or hospitalization due to worsening HF	454 (27.4)	581 (34.2)	0.75 (0.67 to 0.85)	< 0.0001
Mortality				
All-cause mortality	285 (17.2)	350 (20.6)	0.81 (0.69 to 0.94)	0.0074
CV mortality	255 (15.4)	312 (18.4)	0.81 (0.69 to 0.96)	0.0137
Death from HF	67 (4.0)	107 (6.3)	0.61 (0.45 to 0.83)	0.0017
Hospitalization				
All-cause hospitalization	667 (40.3)	778 (45.8)	0.82 (0.74 to 0.91)	0.0002
Hospitalization for worsening HF	298 (18.0)	418 (24.6)	0.69 (0.59 to 0.80)	< 0.0001
CV hospitalization	534 (32.2)	647 (38.1)	0.79 (0.71 to 0.89)	< 0.0001
SAEs				
[redacted]				
WDAEs				
[redacted]				
Notable Harms				
[redacted]				

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NR = not reported; SAE = serious adverse events; WDAE = withdrawal due to adverse events.

[a] SAE with an incidence of 2.5% or higher in one of the treatment groups.

[b] Asymptomatic bradycardia.

Source: Servier Canada Inc.[1]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Heart failure (HF) is a condition that results from the inability of the heart to meet the body's metabolic demands for oxygen because of structural or functional impairment of ventricular filling or ejection of blood.[2,3] The underlying etiologies include disorders of the pericardium, myocardium, endocardium, heart valves, and great vessels, or certain metabolic abnormalities.[2,3] The primary symptoms of HF are dyspnea and fatigue, and may also include fluid retention. Patient group input submitted for this review reported that HF can have a substantial impact on patients' exercise tolerance and quality of life, limiting their ability to work, participate in recreational activities, and complete activities of daily living.

There are an estimated 600,000 Canadians with HF and roughly 50,000 new cases are diagnosed each year.{119, 122} Approximately half of HF patients have a reduced left ventricular ejection fraction (LVEF) ≤ 40%; it is for this population that the evidence regarding treatment is better established.[2,3] The mortality rate for HF ranges between 5% at one year and 50% at five years after diagnosis, depending on the severity of symptoms, heart function, age, and other factors.[6] Among those with HF, the most common causes of death are arrhythmias, including sudden death and pump failure.[6] In the US, one in nine deaths are associated with HF, according to information from death certificates.[2,3] The economic burden due to HF is substantial, with costs associated with health care services, medications, and lost productivity. Hospitalizations due to HF are frequent, with 83% of patients hospitalized at least once, and 43% hospitalized four or more times after HF diagnosis.[2,3]

The New York Heart Association (NYHA) provides a means to classify patients with HF according to functional capacity, as described in Table 2.

TABLE 2: NEW YORK HEART ASSOCIATION FUNCTIONAL CLASSIFICATION

Class	Description
I	No limitations of physical activity
II	Slight limitation of physical activity, but no symptoms at rest
III	Marked limitation of physical activity, but no symptoms at rest
IV	Inability to perform any physical activity without discomfort; symptoms may be present at rest

Source: Heart failure guidelines.[2,3]

1.2 Standards of Therapy

Non-pharmacologic therapies for HF include sodium restriction, exercise programs, and education on disease management.[2,3] The key pharmacotherapies for patients with HF and reduced ejection fraction include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, and aldosterone antagonists (also known as mineralocorticoid receptor antagonists [MRAs]). Canadian and US guidelines recommend an ACEI plus a beta-blocker for all patients, unless contraindicated, as these therapies have been shown to reduce morbidity and mortality.[2,3,7] ARBs are usually recommended as second-line therapy, in patients who are intolerant to ACEIs. Aldosterone antagonists may also reduce morbidity and mortality, and are recommended as add-on therapy in select patients with NYHA class II to IV HF.[2,3,7] In addition, for patients in NYHA class II or III with reduced ejection fraction being treated with triple therapy (ACEI or ARB, beta-blocker, and MRA) but for whom HF remains inadequately controlled, the neprilysin inhibitor Entresto (combination sacubitril/valsartan), administered in combination with other HF therapies, is indicated in place of the ACEI or ARB. Diuretics

may provide symptomatic relief of dyspnea or edema in patients with fluid retention. A subset of patients may experience benefits from implantation of cardioverter-defibrillator, or cardiac resynchronization therapy devices.[2,3,7]

1.3 Drug

Ivabradine is a heart-rate-lowering drug utilizing a mechanism of action that differs from that of beta-blockers. It is available as a 5 mg and 7.5 mg film-coated tablet containing ivabradine hydrochloride.[8] Ivabradine is a first-in-class drug that selectively and specifically blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel, which is responsible for the cardiac pacemaker (I_f current), consequently lowering heart rate. A reduced heart rate permits more time for blood to flow to the myocardium.[8]

Ivabradine is indicated for the treatment of stable chronic HF with reduced LVEF (≤ 35%) in adult patients with NYHA class II or III HF 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 HF, administered in combination with standard chronic HF therapies.[8] According to the Health Canada–approved product monograph, ivabradine should be used in stable patients in conjunction with other HF treatments, such as beta-blockers and aldosterone antagonists, and ACEI or ARB therapy. Ivabradine should not be initiated in patients with heart rates < 70 bpm, unstable or acute HF, cardiogenic shock, prolonged QT intervals, acute myocardial infarction, severe hypotension, severe hepatic impairment, sick sinus syndrome, sino-atrial block, or third-degree atrioventricular block and pacemaker dependence, or in patients treated with concomitant strong cytochrome P450 3A4 inhibitors verapamil or diltiazem.[8] The recommended starting dosage is 5 mg twice daily orally; dose adjustments are permitted following two weeks of treatment depending on the resulting heart rate. For those with heart rate above 60 bpm, ivabradine should be up-titrated to a 7.5 mg twice-daily oral tablet, whereas those with resting heart rates below 50 bpm should be down-titrated to half of a 5 mg tablet (2.5 mg) twice daily orally. If the resting heart rate is between 50 and 60 bpm, the 5 mg twice-daily oral dose should be maintained. Dose adjustments are permitted at any time depending on patient tolerability. If patients receiving 2.5 mg of ivabradine exhibit heart rates below 50 bpm, treatment should be discontinued. The maximum dosage of ivabradine is 7.5 mg twice daily orally.[8]

Indication under review
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 criteria requested by sponsor
As per indication

The key characteristics of ivabradine and sacubitril/valsartan are listed in Table 3.

TABLE 3: KEY CHARACTERISTICS OF IVABRADINE AND SACUBITRIL/VALSARTAN FOR THE TREATMENT OF HF

	Ivabradine	Sacubitril/Valsartan
Mechanism of Action	Reduces heart rate by blocking the HCN channel, which is responsible I_f current	Inhibits the breakdown of peptides by neprilysin and blocks the binding of angiotensin II to the AT_1 receptor
Indication	Stable chronic HFrEF (≤ 35%) in patients with NYHA class II or III HF in sinus rhythm and heart rates ≥ 77 bpm in combination with optimal standard of treatment for HF	HFrEF in patients with NYHA class II or III HF
Route of Administration	Oral	Oral
Maximum Recommended Dosage	7.5 mg twice daily[a]	Sacubitril 24.3 mg/valsartan 25.7 mg to sacubitril 97.2 mg/valsartan 102.8 mg twice daily
Serious Side Effects and Safety Issues	Hypotension, renal impairment, eye disorders (phosphenes, visual disturbances), cardiac arrhythmias, bradycardia Contraindicated in patients with heart rates < 70 bpm prior to treatment, unstable or acute HF, cardiogenic shock, prolonged QT intervals, acute MI, severe hypotension, severe hepatic impairment, sick sinus syndrome, sino-atrial block, third-degree atrioventricular block, pacemaker dependence or pregnancy. Contraindicated with strong cytochrome P450 3A4 inhibitors, verapamil or diltiazem	Hypotension, renal dysfunction, hyperkalemia, angioedema Contraindicated with ACEI, ARB or aliskiren, and in patients with symptomatic hypotension, history of angioedema, or pregnancy Caution in patients with renal artery stenosis
Other	The 5 mg tablet can be broken in half for patients requiring a 2.5 mg dose twice daily orally	36-hour washout period required between ACEI and ARNI therapy

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; AT_1 = angiotensin type 1; bpm = beats per minute; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association.

[a] Recommended dosages when treated with 5 mg of ivabradine; patients with heart rate above 60 bpm should be up-titrated to a 7.5 mg twice-daily oral tablet; patients with heart rate below 50 bpm, down-titrated to half of a 5 mg tablet (2.5 mg) twice daily orally; for patients with heart rate between 50 and 60 bpm, a 5 mg twice-daily oral tablet dose should be maintained. Treatment should be discontinued in patients with heart rate below 50 bpm when treated with 2.5 mg of ivabradine.

Sources:[2,3,8,9]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of ivabradine 5 mg and 7.5 mg tablets, administered in combination with standard chronic HF therapies, for the treatment of stable chronic HF with reduced LVEF (≤ 35%) in adult patients with NYHA class II or III HF who are in sinus rhythm with a resting heart rate ≥ 77 bpm, to reduce the incidence of cardiovascular mortality and hospitalizations for worsening HF.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the criteria presented in Table 4.

TABLE 4: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with stable chronic heart failure of NYHA class II and III and with LVEF ≤ 35% in sinus rhythm and with heart rate ≥ 77 bpm, in combination with standard chronic heart failure therapies Subgroups: • Age • NYHA functional class • Ejection fraction • Heart rate • ICD/CRT • Ischemic cardiomyopathy • Background therapy • Target beta-blocker dose
Intervention	Ivabradine 5 mg and 7.5 mg twice daily in combination with standard chronic heart failure treatment
Comparators	Standard HF therapies (with or without placebo), including: • ACEI (or ARB) + BB + MRA (eplerenone, spironolactone) • Sacubitril/valsartan + BB + MRA (eplerenone, spironolactone)
Outcomes	**Key efficacy outcomes:** All-cause mortality Death from cardiovascular causes Death from heart failure All-cause hospitalizations HF-related hospitalization Cardiovascular-related hospitalization **Other efficacy outcomes:** Sudden cardiac death Fatal or non-fatal myocardial infarction Fatal or non-fatal stroke Development of new or worsening atrial fibrillation LVEF Health-related quality of life Symptom measures Change in NYHA class

	Harms outcomes: AEs, SAEs, WDAEs, notable harms (hypotension, renal impairment, eye disorders (phosphenes, visual disturbances), cardiac arrhythmias, bradycardia)
Study Design	Published and unpublished phase III RCTs

ACE I= angiotensin-converting enzyme inhibitor; AE = adverse event; ARB = angiotensin receptor blocker; BB = beta-blocker; CRT = cardiac resynchronization therapy; HF = heart failure; ICD = implantation of cardiac defibrillator; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonists; NYHA = New York Heart Association; RCT = randomized controlled trial; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was the drug name: Corlovan (ivabradine).

A methodological filter was applied to limit retrieval to randomized controlled trials (RCTs). Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on December 6, 2016. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee (CDEC) on April 19, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), Internet Search. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5; excluded studies (with reasons) are presented in 0.

3. RESULTS

3.1 Findings from the Literature

One study was identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5: Details of Included Studies and described in Section 3.2. A list of excluded studies is presented in 0.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

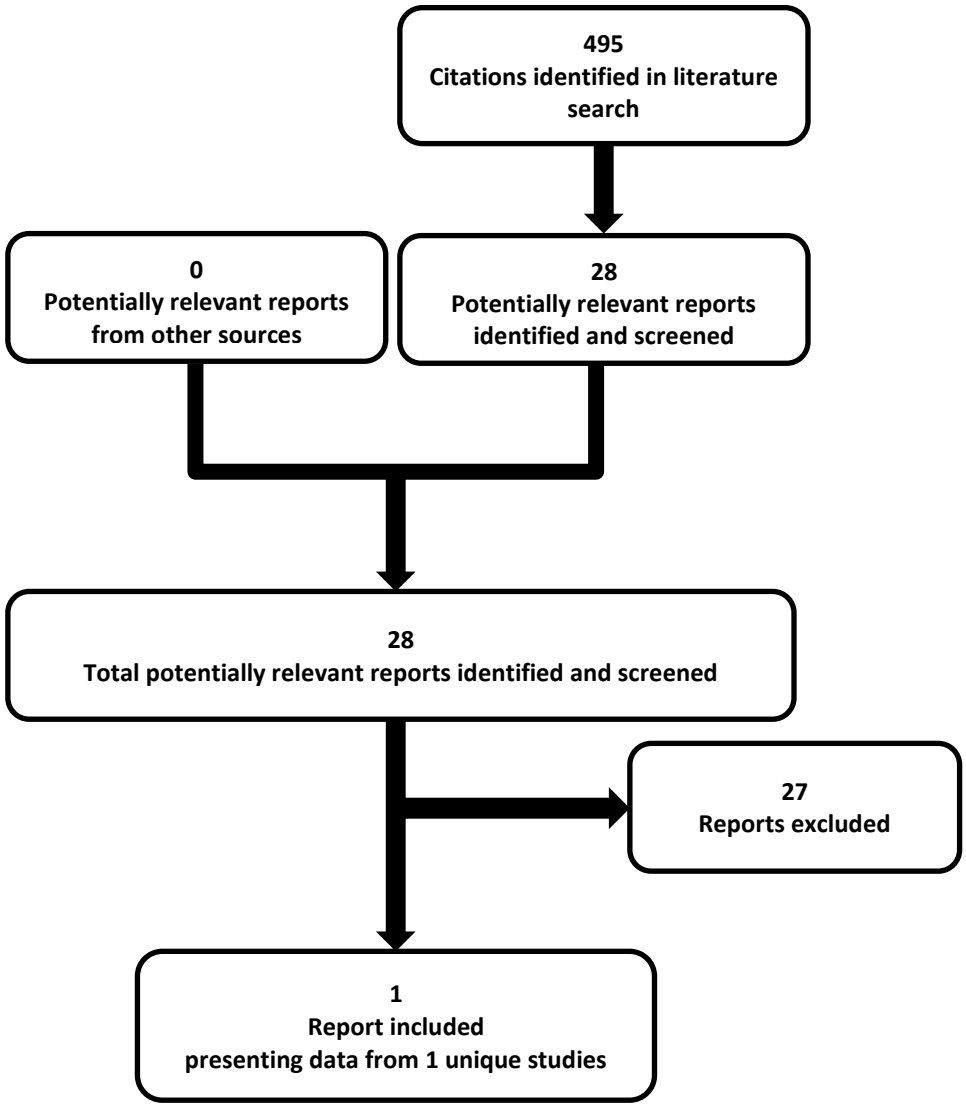

TABLE 5: DETAILS OF INCLUDED STUDIES

		SHIfT
Designs and Populations	**Study Design**	Multi-centre, DB, placebo-controlled phase III RCT
	Locations	North, South, and Central America; Europe; Asia
	Randomized (N)	6,558
	Inclusion Criteria	• ≥ 18 years with stable systolic CHF and EF ≤35% • NYHA class II, III or IV for ≥ 4 weeks prior to selection • Stable clinical condition for ≥ 4 weeks, with optimal and unchanged CHF medications and dosages • Electrocardiographic documentation of sinus rhythm at selection, with a resting heart rate ≥ 70 bpm on standard 12-lead ECG • Documented hospital admission for worsening heart failure within 12 months before selection
	Exclusion Criteria	• Recent (less than 2 months prior to selection) MI or coronary revascularization • Scheduled coronary revascularization, coronary artery bypass graft • Severe aortic or mitral stenosis, severe aortic regurgitation, severe primary mitral regurgitation, or active myocarditis or congenital heart diseases • Sitting SBP < 85 mm Hg or current symptomatic hypotension • Severe or uncontrolled hypertension (sitting SBP > 180 mm Hg or sitting DBP > 110 mm Hg • Moderate or severe liver disease (Child-Pugh score > 7) • Severe renal disease (serum creatinine > 220 µmol/L • Anemia (blood hemoglobin < 110 g/L) • ALAT or ASAT > 3 times ULN • Hepatitis B or C, or HIV • Familial history or congenital long QT syndrome or treated with selected QT prolonging products • Previous cardiac transplantation or on list for cardiac transplantation • CRT started within the previous 6 months • Pacemaker with atrial or ventricular pacing (except bi-ventricular pacing) > 40% of the time, or with a stimulation threshold at the atrial or ventricular level ≥ 60 bpm • Permanent atrial fibrillation or flutter • Sick sinus syndrome, sino-atrial block, second- and third-degree atrio-ventricular block • History of symptomatic or sustained (≥ 30 sec) ventricular arrhythmia unless a cardioverter-defibrillator was implanted • Any cardioverter-defibrillator shock experienced within the previous 6 months • Concomitant use of non-dihydropyridine calcium-channel blockers, Vaughan-Williams class I anti-arrhythmics, Strong cytochrome P450 3A4 (CYP3A4) inhibitors, cyclosporin, antiretroviral drugs, azole antifungal drugs administered by systemic route and nefazodone
Drugs	**Intervention**	Ivabradine 2.5 mg (half of the 5.0 mg tablet), 5.0 mg or 7.5 mg twice daily (oral tablet)
	Comparator(s)	Placebo

		SHIfT
Duration	**Phase**	
	Run-in	2 weeks
	Titration	4 weeks
	Double-blind	Event-driven (planned to be stopped once 1,600 primary outcome events occurred) up to a maximum of 52 months
	Follow-up	First visit at month 4, follow-up visits were planned every 4 months thereafter until the end of study
Outcomes	**Primary End Point**	Composite of cardiovascular death or first hospitalization due to worsening heart failure
	Other End Points	Efficacy: All-cause mortality, death from cardiovascular causes, death from heart failure, all-cause hospitalizations, HF-related hospitalization, cardiovascular-related hospitalization, sudden cardiac death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, development of new or worsening atrial fibrillation, change in LVEF, EQ-5D, KCCS, change in global assessment, change in NYHA class Harms: AEs, SAEs, WDAEs, notable harms
Notes	**Publications**	Swedberg 2010[10]

AE = adverse event; bpm = beats per minute; ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; CHF = chronic heart failure; CRT = cardiac resynchronization therapy; DB = double-blind; DBP = diastolic blood pressure; EF = ejection fraction; EQ-5D = EuroQol 5-Dimensions questionnaire; HF = heart failure; KCCS = Kansas City Cardiomyopathy Questionnaire; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; RCT = randomized controlled trial; SAE = serious adverse events; SHIfT = Systolic Heart Failure Treatment with the I_f inhibitor Ivabradine Trial; SBP = systolic blood pressure; ULN = upper limits of normal; WDAE = withdrawal due to adverse event.
Source: SHIfT Clinical Study Report.[11]

3.2 Included Studies

3.2.1 Description of Studies

One phase III randomized controlled trial (SHIfT) met the inclusion criteria for the CDR systematic review (Table 5).

The SHIfT study (N = 6,558) was an event-driven multi-centre (677 centres), multinational (37 countries), double-blind, placebo-controlled, phase III RCT conducted mostly in Eastern European countries to assess the superiority of ivabradine versus placebo. Randomization was stratified by beta-blocker intake (yes/no) and study centre using the Interactive Voice/Web Response System according to a 1:1 ratio to one of two treatment groups (ivabradine arm or placebo group) after the run-in period. Investigators and patients were blinded to the treatment group assignment.

The trial consisted of a two-week run-in period, a four-week titration period, and an event-driven (up to [redacted]) treatment follow-up period (Figure 2). No treatment was dispensed during the run-in period to confirm the eligibility and the stability of patients. Heart rate was measured twice during the run-in period to confirm the heart rate criteria of ≥ 70 bpm using 12-lead electrocardiography. The purpose of the titration period starting immediately after the run-in period (day 0) was to determine a successful dose for each patient ending at day 28. During the treatment period (initiated immediately after day 28), participants received the successful dose twice daily and attended follow-up visits at month 4 and every four months thereafter up to [redacted]([redacted]).

FIGURE 2: SHIFT STUDY DESIGN

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER

Source: SHIfT Clinical Study Report.[11]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The SHIfT study enrolled patients with HF (NYHA class II to IV) suffering from left ventricular systolic dysfunction with LVEF of 35% or lower. Eligible patients were adults in sinus rhythm and with a resting heart rate ≥ 70 bpm, as measured on 12-lead electrocardiography after at least five minutes of rest on two consecutive visits before randomization. Patients were also required to demonstrate stable symptomatic chronic HF for four or more weeks, and have a previous admission to hospital for worsening HF within the previous 12 months. HF of any etiology was permitted with the exception of primary severe valvular disease or congenital heart disease.

Patients were excluded for recent (within two months) myocardial infarction, atrial fibrillation or flutter, symptomatic hypotension, or ventricular or atrioventricular pacing operative for 40% or more of the day. Prohibited treatments included non-dihydropyridine calcium-channel blockers, strong inhibitors of cytochrome P450 3A4 and class I anti-arrhythmics.

Although the SHIfT study included patients with heart rates ≥ 70 bpm, the Health Canada–approved indication — and the manufacturer's reimbursement request — is for the treatment of patients with heart rates ≥ 77 bpm. Therefore, this CDR review focuses on a pre-specified subgroup of the enrolled SHIfT population with heart rates ≥ 77 bpm (n = 3,357), which was derived from the randomized set and the safety set of the overall population.

b) Baseline Characteristics

Patients in the heart rate ≥ 77 bpm subgroup of the SHIfT study had a mean age of [redacted], of whom [redacted] were younger than 65 years of age and [redacted] were 75 years or older. The majority of patients were [redacted], with a history of [redacted] and had been diagnosed with [redacted]. Almost all patients were [redacted], and [redacted] of patients had underlying ischemic etiology. 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 majority of patients were being treated [redacted] at baseline. In addition to standard of care, most patients were also taking diuretics [redacted]. Approximately [redacted] of patients were receiving target daily doses of beta-blockers and nearly [redacted] were taking ≥ 50% of the target daily dose of beta-blockers. [redacted]. Details of patients' baseline characteristics and concomitant treatment for the heart rate ≥ 77 bpm subgroup of the SHIfT population are presented in Table 6 Table 7.

Mean resting heart rates at baseline based on percentage of target beta-blocker dose were well balanced between the ivabradine and placebo treatment groups. However, patients treated with lower doses of beta-blockers typically had higher baseline resting heart rates. Details on heart rate based on beta-blocker use in the heart rate ≥ 77 bpm subgroup of the SHIfT population are provided in Table 18.

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS (HEART RATE ≥ 77 BPM SUBGROUP)

[redacted]	[redacted]	
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
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[redacted]	[redacted]	
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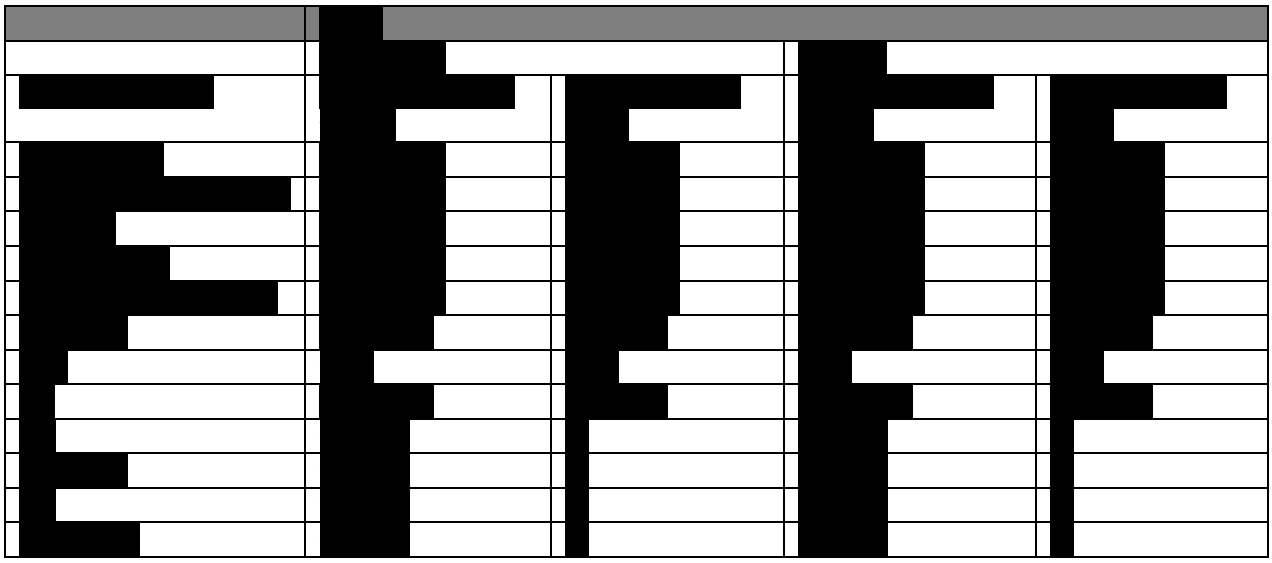
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; BP = blood pressure; bpm = beats per minute; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD= implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; SD = standard deviation.

[a] CADTH calculated values.

Source: Servier Canada Inc.[1]

TABLE 7: USE OF KEY CONCOMITANT TREATMENTS (HEART RATE ≥ 77 BPM SUBGROUP)



ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; NA = not available.
Source: Servier Canada Inc.[1]

3.2.3 Interventions

The interventions studied in SHIfT were ivabradine 2.5 mg (half of the 5 mg tablet), 5 mg, and 7.5 mg oral film-coated tablets twice daily in combination with standard chronic HF treatment (e.g., ACEIs or ARBs, beta-blockers, and MRAs) compared with placebo.

All concomitant treatments were permitted (defined as any treatment taken at the time of selection and any new and authorized treatments prescribed during the study) with the exception of non-dihydropyridine calcium-channel blockers, Vaughan-Williams class I anti-arrhythmics, strong cytochrome P450 3A4 (CYP3A4) inhibitors, cyclosporin, antiretroviral drugs, azole antifungal drugs administered by systemic route, and nefazodone.

In SHIfT, the purpose of the titration period was to determine a successful dose for each patient; the starting dosage for ivabradine (and matching placebo) was 5 mg twice daily for all patients. Doses were adjusted depending on the resulting heart rate. For those with heart rate above 60 bpm, ivabradine (or matching placebo) were up-titrated to 7.5 mg twice daily, whereas those with resting heart rates below 50 bpm were down-titrated to 2.5 mg twice daily. If the resting heart rate was between 50 and 60 bpm, the 5 mg twice-daily dosage was maintained. Dose adjustments were permitted throughout the trial. If patients dosed with 2.5 mg of ivabradine (or matching placebo) exhibited heart rates below 50 bpm, treatment was stopped. The dose identified in the titration period was the successful dose used throughout the double-blind follow-up period up to a maximum of 52 months.

3.2.4 Outcomes

All pre-specified end points were adjudicated by the Endpoint Validation Committee. This committee was blinded to the allocated study treatments as well as to patients' baseline heart rates (Figure 3).

a) Efficacy

All-cause mortality

All-cause mortality included cardiovascular death, non-cardiovascular death, and death of unknown cause.

Cardiovascular death

Cardiovascular death was defined as death due to HF, death due to myocardial infarction, arrhythmic death or presumed arrhythmic death, and other cardiovascular death (e.g., due to stroke, ruptured aneurysm, or pulmonary embolism). An amendment to the cardiovascular death definition was made after study unblinding. The definition was revised to include death of unknown cause.

Death from HF

Death from HF was defined as death occurring from worsening or uncontrolled HF with or without hospitalization, where HF is considered a major factor leading to death despite the presence of terminal arrhythmia, unless other causes of death are evident.

Myocardial infarction

Myocardial infarction was defined as:

Elevation of myocardial necrosis biomarkers (troponin, creatine kinase, creatine kinase MB, aspartate amino-transferase or myoglobin) exceeding thresholds as set by the hospital of admission, and at least one of the following:

- Ischemic symptoms such as cardiac ischemic pain lasting at least 20 minutes or pulmonary edema or cardiogenic shock not otherwise explained.
- At least two consecutive electrocardiograms (ECGs) indicating the development of pathologic Q waves (≥ 0.03 second in duration) following the event.
- Ischemia as indicated by changes in ECG (transient ST segment elevation or depression or new left bundle branch block).
- Coronary artery intervention (e.g., coronary angioplasty).

Death from myocardial infarction

Death from myocardial infarction was defined as death occurring up to 28 days after myocardial infarction with or without hospitalization despite the presence of terminal arrhythmia, unless other causes of death are evident.

Arrhythmic dearth or presumed arrhythmic death

An arrhythmic death or presumed arrhythmic death was defined as sudden death (instantaneous unexpected death witnessed within 24 hours after the onset of symptoms or unwitnessed unexpected death) with clinical evidence and/or electrical evidence for the occurrence of a ventricular arrhythmia, unless death is identified as death from HF or myocardial infarction.

Hospitalization

Hospitalization was defined as any admission to hospital requiring completion of the hospital admission procedures and/or at least an overnight stay (different date of entry and the date of discharge) or until death of the patient. Events extending an ongoing hospitalization (with or without patient transfer to a specialized hospital department) were considered hospitalization.

All-cause hospitalization
All-cause hospitalization included hospitalization for cardiovascular reason, hospitalization for undetermined cause, and hospitalization for non-cardiovascular reason.

Hospitalization for cardiovascular reason
Hospitalization for cardiovascular reason included hospitalization for worsening HF, hospitalization for myocardial infarction, and hospitalization for other cardiovascular reason (e.g., unstable angina, stroke, arrhythmia, hypotension, syncope, hypertensive emergency, or pulmonary embolism).

Hospitalization for worsening HF
Hospitalization for worsening HF was defined as, hospitalization for:

- New or increasing symptoms of HF (e.g., dyspnea or fatigue)
- New or increasing signs of HF, including signs of fluid retention (e.g., pulmonary rales, peripheral edema, raised jugular venous pressure, weight gain), or objective evidence of HF (e.g., pulmonary edema/congestion in chest X-ray)
- Significant change in HF treatment defined by initiation of intravenous diuretics or other intravenous medications (excluding cardiac glycosides) or mechanical ventilation or mechanical support (e.g., intra-aortic balloon pump or ventricular assist device)
- Cardiogenic shock

Heart failure will be adjudicated given the above criteria despite the presence of other causes for hospital admission, related or not with the episode of worsening HF (e.g., pneumonia, anemia or atrial fibrillation)

Death of unknown cause
Death of unknown cause consisted of non-violent or traumatic deaths for which it was not possible to specify whether the death was cardiovascular-related or not.

Change in NYHA functional class
Investigators evaluated HF by the functional capacity of the patient using the NYHA classification by questioning patients about their HF symptoms.

Global assessment questionnaires
Both patients and investigators were asked to complete the global assessment questionnaires during pre-specified visits to provide a patient and physician assessment. Patients and physicians were asked the following questions, “Since treatment started, please evaluate the change in your heart condition” and “According to your clinical evaluation, how do you find your patient today in comparison to before treatment started?” to assess their condition by selecting one of seven possible answers: “markedly improved,” “moderately improved,” “slightly improved,” “no change,” “slightly worsened,” “moderately worsened,” and “markedly worsened.” Patients and investigators were not to discuss the evaluation.

The primary end point was a composite of cardiovascular death and hospitalization for worsening HF. The most significant secondary end point was a composite of cardiovascular death or hospitalization for worsening HF in patients receiving at least 50% of the target daily dose of a beta-blocker at randomization.

Other secondary end points included all-cause mortality, death from cardiovascular causes, death from HF, all-cause hospitalizations, HF-related hospitalization, cardiovascular-related hospitalization, sudden cardiac death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, development of new or

worsening atrial fibrillation, and the composite of cardiovascular death, hospitalization for worsening HF, or hospitalization for non-fatal myocardial infarction. Changes in NYHA classification, LVEF, and heart rate, as well as by patient-reported and physician-reported global assessment were also evaluated.

FIGURE 3: DESCRIPTION OF THE ADJUDICATED TRIAL END POINTS IN SHIFT

FIGURE CONTAINED CONFIDENTIAL INFORMATION AND WAS REDACTED AT THE REQUEST OF THE MANUFACTURER

Source: SHIfT Clinical Study Report.[11]

b) Harms

The harms data collected in the SHIfT study included the occurrence of mortality, adverse events (AEs), serious adverse events (SAEs), withdrawal due to adverse events, and notable harms.

AEs were defined as any sign or symptom experienced by a patient, whether or not considered causally related to the product or study procedure. AE reporting began after a patient provided consent for involvement in the study, irrespective of the start of study medications.

SAEs were any AEs that were life-threatening, or resulted in death, required or prolonged hospitalization, resulted in persistent or significant disability, were congenital anomalies, or were deemed serious based on medical judgment.

Notable harms (bradycardia and atrial fibrillation) required additional measure. In addition to heart rate, details relating to how the bradycardia was documented (such as clinical examination, ECG tracing, Holter recording, and when it was observed) were also recorded. With respect to atrial fibrillation and supraventricular tachyarrhythmia, the diagnosis was to be documented by an ECG recording when possible.

3.2.5 Statistical Analysis

The objective of the SHIfT study was to assess the superiority of ivabradine compared with placebo using an intention-to-treat (ITT) analysis for the primary composite end point (cardiovascular death and hospitalization for worsening HF). If no pre-specified end point occurred during the study, censoring was applied for each patient according to the first occurrence of one of the following events: termination visit, date of death (not considered as the studied event), lost to follow-up date, date of withdrawal from the study, date of heart transplant or by study end date.

A total of three interim analyses were performed to detect the harmful and beneficial effects of ivabradine in the full SHIfT population (i.e., heart rate ≥ 70 bpm). Based on the Peto sequential procedure, the type I error was set at 0.1%, and therefore has no significant effect on the type I error used for the final analysis.

The sample size was estimated based on the accrual of the primary composite end point (cardiovascular death and hospitalization for worsening HF) to detect a difference between ivabradine and placebo using a log rank test and alpha of 0.05 (two-sided) in the full SHIfT population (i.e., heart rate ≥ 70 bpm). Originally, approximately [redacted] patients ([redacted] primary composite events) and an expected mean follow-up of two years were required to provide 90% power to detect a 17% relative risk reduction of the primary composite end point, assuming an annual incidence rate of the primary end point of [redacted] in the placebo group and an incidence rate of non-cardiovascular death of [redacted] in both the ivabradine and placebo groups. Two protocol amendments affecting the sample size were included. The

first was required to increase the power to detect a smaller relative risk reduction of the primary composite end point between ivabradine and placebo (15% versus 17%). Therefore the sample size increased to [redacted] patients (1,600 pre-specified primary composite events). A second modification to the protocol was included due to the number of pre-specified primary events observed. A new sample size of 6,500 patients (instead of 7,000) was required, considering an expected mean follow-up of 2.25 years and 90% power to detect a 15% relative risk reduction of the primary composite end point, and assuming an annual incidence rate of the primary end point of 14% in the placebo group and an incidence rate of non-cardiovascular death of [redacted] in both the ivabradine and placebo groups. Of note, there was no specific power calculation conducted for the pre-specified subgroup of interest for this CDR review (i.e., patients with a baseline heart rate ≥ 77 bpm). All end points assessed in the overall SHIfT population (i.e., heart rate ≥ 70 bpm) were also assessed in the heart rate ≥ 77 bpm subgroup using a *P* value threshold of 0.05 for statistical significance. Although randomization was not stratified for heart rate, baseline characteristics for the subgroup of patients with heart rate ≥ 77 bpm were reported and appeared to be relatively well balanced.

In SHIfT, treatment effects for all end points (primary, secondary, and exploratory) were analyzed using a Cox proportional-hazards model including factors for treatment (ivabradine versus placebo) and baseline beta-blocker intake with 95% confidence intervals and associated *P* value for all adjudicated end points. Proportional hazards were confirmed by evaluating the hazard interaction with log(time). Mean heart rates were summarized over time split by treatment group. Chi-square tests were used to compare changes in NYHA class and patient-reported and physician-reported global assessment. A number of pre-specified subgroup analyses based on age (< 65, ≥ 65), beta-blocker use, primary cause of HF (ischemic, non-ischemic), NYHA class (II, III or IV), and heart rate (< 77, ≥ 77 bpm) were conducted in a similar manner to the primary analysis, with the addition of the subgroup as a covariate (adjustment for beta-blocker intake at randomization was not applicable for the beta-blocker subgroups). Of note, only the ≥ 50% target daily beta-blocker dose and beta-blocker intake (yes/no) subgroups of the beta-blocker category were pre-specified. All other subgroup analyses were performed post hoc (ACEI and/or ARB intake, diuretic intake, digitalis intake, aldosterone antagonist intake, age ≥ 75 years, and all beta-blocker use with the exception of the ≥ 50% target daily beta-blocker dose and beta-blocker intake).

In addition to the adjusted (beta-blocker use and study centres as covariates) Cox proportional-hazards model used to evaluate treatment effect (on the primary composite and secondary end points), sensitivity analyses were performed using an unadjusted Cox proportional-hazards model as well as an analysis based on a model adjusted for baseline prognostic factors (beta-blocker intake at randomization, NYHA (II or III/IV), LVEF, primary cause of HF (ischemic or not), age, systolic blood pressure, heart rate, and creatinine clearance). It is unclear whether any sensitivity analyses were conducted on the subgroup of interest for this CDR review (i.e., heart rate ≥ 77 bpm).

A hierarchical testing procedure was applied to evaluate the superiority of ivabradine using only the primary composite end point in the randomized set and then on the ≥ 50% target daily beta-blocker dose randomized set. Treatment effects were evaluated based on two-sided statistical tests and 95% confidence intervals were estimated (alpha = 0.05) for all other outcomes that were not part of the hierarchical statistical testing procedure and for all subgroup analyses. No corrections for multiple statistical testing were applied to any of the end points or subgroups other than the primary composite end point in the randomized set and then on the ≥ 50% target daily beta-blocker dose randomized set.

a) Analysis Populations

The SHIfT study enrolled adults with stable chronic HF in NYHA class II to IV with LVEF ≤ 35% and with heart rate ≥ 70 bpm in sinus rhythm who are also treated with standard chronic HF therapies.
The randomized set, based on the ITT principle, included all randomized patients who received at least one dose of study medication (analyzed according to the randomized treatment).

The ≥ 50% target daily beta-blocker dose randomized set included all patients of the randomized set receiving at least half of target daily dose of beta-blockers at randomization. Half the target daily beta-blocker doses were defined by the European Society of Cardiology guidelines[12] with the exception of metoprolol tartrate:

- Carvedilol: 25 mg.
- Metoprolol succinate: 95 mg.
- Bisoprolol: 5 mg.
- Nebivolol: 5 mg.
- Metoprolol tartrate: 75 mg[13].

The safety set included all patients having received at least one dose of the study drug.

Although the SHIfT population enrolled patients with heart rates ≥ 70 bpm, the reimbursement request is limited to patients with heart rates ≥ 77 bpm as per the Health Canada indication. Therefore the focus of this CDR review is on a pre-specified subgroup of the enrolled SHIfT population, limited to the randomized set and safety set of patients with heart rates ≥ 77 bpm.

3.3 Patient Disposition

Of the 7,411 patients screened from the full SHIfT population, 6,558 were randomized (49.4% in the ivabradine and 49.7% in the placebo groups). Fifty-three patients were not included based on inclusion criteria or due to misconduct. Only 3,357 patients in the SHIfT population satisfied the Health Canada indication (heart rate ≥ 77 bpm at baseline), and of those, 1,657 (25.3%) had been randomized to the ivabradine treatment group and 1,700 (25.9%) to the placebo group. Approximately 19% of patients did not complete the study, and follow-up for the primary outcome was not available for the entire study period.

In general, patient disposition between the treatment groups was similar. A similar number of patients stopped treatment prematurely in the placebo (20.4%) and the ivabradine group (20.9%), and AEs and other reasons were the most commonly reported reasons for prematurely stopping treatment. The median duration of follow-up in the SHIfT study was approximately 22 months in both treatment groups. Details on patients' dispositions are provided in Table 8.

TABLE 8: PATIENT DISPOSITION

	SHIfT	
	Ivabradine	**Placebo**
Full SHIfT population ≥ 70 bpm		
Screened, N	7,411	
Randomized, N (%)	6,558[a]	
	3,241 (49.4)	3,264 (49.7)
SHIfT population subgroup ≥ 77 bpm		
Randomized patients meeting subgroup criteria, n (%)	1,657 (25.3)	1,700 (25.9)
Discontinued study, n (%)		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
RS, N	1,,657	1,700
[redacted]	[redacted]	[redacted]

b.i.d. = twice daily; bpm = beats per minute; HR = heart rate; IQR = interquartile range; NA = not available RS = randomized set.
[a] 53 patients were not included based on inclusion criteria or due to misconduct.
[b] Non-medical reasons were mostly consent withdrawals.
Source: Servier Canada Inc.[1]

3.4 Exposure to Study Treatments

A greater proportion of patients in the placebo group was treated with 7.5 mg compared with the ivabradine group and a greater proportion of patients in the ivabradine group was treated with doses below 7.5 mg compared with the placebo group. Of note, more patients were treated with other sequences of the study drug in the ivabradine group compared with the placebo group (no information on the other sequence of drug was provided for the ≥ 77 bpm subgroup). The median treatment exposure was approximately [redacted] in both groups and the mean dose was higher in the placebo group compared with the ivabradine group ([redacted]). Details on patients' treatment duration and exposure in the heart rate ≥ 77 bpm subgroup of the SHIfT population are provided in Table 9.

Close to [redacted] of patients with heart rate ≥ 77 bpm were taking ≥ 50% or more of daily target beta-blocker doses at randomization ([redacted] in the ivabradine and placebo groups, respectively). Beta-blocker use between treatment groups remained relatively similar for the duration of the trial. Details on beta-blocker use during the trial in the heart rate ≥ 77 bpm subgroup of the SHIfT population are provided in Table 17.

TABLE 9: TREATMENT DURATION AND EXPOSURE (HEART RATE ≥ 77 BPM SUBGROUP)

IQR = interquartile range; SD = standard deviation.
Source: Servier Canada Inc.[1]

3.5 Critical Appraisal

3.5.1 Internal Validity

The SHIfT study was a double-blind, placebo-controlled RCT that used accepted methods (Interactive Voice/Web Response System) to randomize patients. The baseline patient characteristics and use of background therapies of the heart rate ≥ 77 bpm subgroup of the SHIfT population appear to be similar between groups, therefore randomization appears to be successful. Matching placebo tablets looked and tasted identical to the ivabradine tablets. However, given that ivabradine is known to reduce heart rate, there was potential for unblinding the study investigators, who were aware of laboratory and clinical data throughout the trial. The adverse event profile was not likely to have significantly compromised blinding. Although those affected by bradycardia or phosphene events could have surmised that the allocated treatment was ivabradine, given that these events are known to occur with this treatment, the end points of the SHIfT study (e.g., mortality) are relatively objective, and the potential for bias is not of concern.

The SHIfT study assessed clinical outcomes such as mortality, morbidity, and quality of life. To avoid the risk of bias, the key outcomes (deaths or hospitalizations) were adjudicated by a blinded committee. The definition of cardiovascular death changed after study unblinding to include deaths of unknown cause. The potential effect of this is unknown. However, if imbalances in deaths of unknown cause differ in a systematic way between groups (e.g., more deaths of unknown cause in the placebo group compared with the ivabradine group), the treatment effect could be biased in either direction. Additionally, hospitalization for worsening HF was to be adjudicated according to the definition and specified criteria, despite the presence of other causes for hospital admission, related or not to the episode of worsening HF (e.g., pneumonia, anemia or atrial fibrillation). Misclassification of events (hospitalization for worsening HF and cardiovascular death) may not bias the study in favour of one treatment (assuming that blinding was maintained), but may overestimate or underestimate the true incidence of events.

The statistical methods used to test the superiority of the primary outcome in the SHIfT study were acceptable (two-sided test and 95% confidence interval). Furthermore, SHIfT used the ITT principal, which is considered most appropriate for a superiority trial.

SHIfT evaluated the effects of ivabradine versus placebo across a number of efficacy and safety outcomes in the full SHIfT population (heart rate ≥ 70 bpm). However, given the reimbursement request

and approved Health Canada indication, this CDR review was primarily focused on a subgroup analysis for the heart rate ≥ 77 bpm population. It should be noted that the SHIfT study was not designed to assess the benefits and harms of ivabradine in this subgroup and although baseline characteristics appear to be well distributed between treatment groups, randomization was not stratified by heart rate. As a result, the distribution of unknown confounders is unknown. Furthermore, the results for all outcomes other than the pre-specified primary composite end point in the full SHIfT population (heart rate ≥ 70 bpm) and the ≥ 50% target daily beta-blocker dose subgroup were not controlled for multiple statistical testing. Generally, any inferences or interpretations based on subgroups that were not part of the statistical testing hierarchy and that were not adjusted for multiplicity should be made with caution, given the increased risk of type I error. While the risk of type I error remains, the validity of the results for the subgroup of interest for this CDR review (i.e., heart rate ≥ 77 bpm) are strengthened by the pre-specified nature of the subgroup and the biological plausibility of the interaction effect. It has been suggested that ivabradine is most effective in blocking the HCN channel (which is responsible for the I_f current) when these channels are most frequently open (i.e., when heart rates are highest).[14,15] Therefore, ivabradine would be expected to show greater efficacy in the heart rate ≥ 77 bpm subgroup of the SHIfT study. In addition, the large sample size and the consistent direction of effect across outcomes, including the primary composite end point and its components (cardiovascular [CV] death and hospitalization due to worsening HF), alleviate some of the concerns associated with the increased risk of type I error. The subgroup analysis assessing the treatment effect of ivabradine according to per cent target daily beta-blocker dose (< 25%, ≥ 25% to < 50%, ≥ 50 to < 100%, and ≥ 100%) was one of several post hoc subgroup analyses conducted, increasing the risk of inflated type I error.

When considering overall patient disposition, withdrawals from the ivabradine and placebo groups were relatively similar and therefore present few threats to internal validity. Death was reported most often as the reason for withdrawal.

3.5.2 External Validity

The clinical expert consulted by CDR for this review highlighted that the generalizability of the findings of the SHIfT study is a concern. The SHIfT study mainly included Eastern European centres and patients, and included few North American centres and only 30 Canadian patients from 10 centres. The clinical expert consulted by CDR for this review indicated that the SHIfT patient population satisfying the heart rate ≥ 77 bpm subgroup was younger than the typical adult population in Canada with symptomatic stable chronic HF and reduced LVEF. This discrepancy in age was also noted by the Pharmaceutical Benefits Advisory Committee (PBAC), which suggested that those likely to be treated with ivabradine would be significantly older (mean age in the mid to high 70s).[16,17] Furthermore, not all patients included in the SHIfT study were on standard chronic HF therapy. According to the clinical expert consulted for this CDR review, standard chronic HF treatment consists of an ACEI or ARB added to beta-blockers as well as MRAs. Although the majority of patients were taking the suggested chronic HF treatments, a portion of the included patients were not treated with all three drugs (especially MRAs). The clinical expert also noted that more than 50% (likely between 50% and 75%) of patients with chronic HF would be treated with ≥ 50% target daily beta-blocker doses in clinical practice. The proportion of patients treated with ≥ 50% target daily beta-blocker doses included in the SHIfT study and meeting the heart rate ≥ 77 bpm criteria (46% of patients) was relatively similar to the lowest limit of the range provided by the clinical expert, and therefore may not be completely representative of the overall Canadian population. PBAC also noted this discrepancy and suggested that the trial did not truly assess the benefit of ivabradine to patients on optimal HF treatment.[16,17]

The time at which the SHIfT study was conducted (between 2006 and 2010) may also affect the generalizability of the trial results. The clinical expert consulted by CDR for this review indicated that new, more-selective MRAs have become available and are recommended as a part of standard of care for HF since the SHIfT study initiated. Additionally, Entresto has become available for the treatment of chronic HF since the SHIfT study was conducted. Given that Entresto's Health Canada indication encompasses a broader population suffering from HF (indication overlap) and that the standard treatment paradigm for HF has changed, it is unclear whether the population included in the SHIfT study is reflective of the population that would be eligible for treatment with ivabradine in current Canadian clinical practice.

The clinical expert consulted by CDR for this review also highlighted the discordant study results between regions of Europe and North America, such as those reported for the PLATO trial (Mahaffey et al.), albeit for a different drug and indication.[18] Eastern European clinical practice and criteria for hospital admission may vary from North American countries including Canada, and consequently may have an impact on the hospitalization component of the primary composite end point (first event among cardiovascular death and hospitalization due to worsening HF). This can be of particular concern when considering that the pre-specified primary composite end point is mostly driven by the hospitalization component. While this may not bias the study in favour of one treatment (assuming that blinding was maintained), it may underestimate or overestimate the true incidence of events compared with what would be expected in clinical practice in Canada. PBAC also highlighted that this was likely to affect the pre-specified primary composite end point.[16,17]

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 4). See *0 for detailed efficacy data.*

Details pertaining to key efficacy outcomes (mortality and hospitalization) in the heart rate ≥ 77 bpm subgroup of the SHIfT population are provided in Table 10.

3.6.1 Mortality

There was a statistically significant greater reduction in all-cause and cardiovascular mortality as well as death from HF for patients in the ivabradine treatment group compared with the placebo group in the heart rate ≥ 77 bpm subgroup of the SHIfT study with hazard ratios (HRs) of 0.81 (95% CI, 0.69 to 0.94), 0.81 (95% CI, 0.69 to 0.96) and 0.61 (95% CI, 0.45 to 0.83), respectively. However, when considering the < 77 bpm subgroup of the SHIfT study (Table 39), [redacted]

Mortality was analyzed in numerous subgroups in the heart rate ≥ 77 bpm population and those specified in the CDR review protocol have been presented in Appendix 4. [redacted]

3.6.2 Mortality or Hospitalization

A total of 454 (27.4%) and 581 (34.2%) of patients experienced the primary composite end point (cardiovascular mortality and hospitalization for worsening HF) in the ivabradine and placebo treatment groups, respectively, resulting in a statistically significant reduction in the primary composite outcome compared with placebo in the heart rate ≥ 77 bpm subgroup of the SHIfT study with an HR of 0.75 (95% CI, 0.67 to 0.85). However, when considering the < 77 bpm subgroup of the SHIfT study (Table 39), the primary composite outcome is no longer associated with a statistically significant reduction, with an HR of 0.93 (95% CI, 0.80 to 1.08).

When considering the post hoc subgroups based on per cent target daily beta-blocker dose (Table 11), it appears that the differences in treatment effects diminished with increasing per cent target daily beta-blocker doses. The differences in treatment effects based on the primary composite outcome only become statistically significant at the threshold of ≥ 25% to < 50% target daily beta-blocker dose [redacted]. However, statistical significance in this case is largely driven by hospitalization for worsening HF component [redacted] and not CV mortality [redacted]. Only at the < 25% target daily beta-blocker dose threshold does the difference in treatment effect between ivabradine and placebo become statistically significant in the primary outcome [redacted] and both its components [redacted]. The pre-specified ≥ 50% target daily beta-blocker dose and the post hoc < 50% target daily beta-blocker dose subgroups appear to indicate concordant results. Difference in treatment effect based on the primary composite end point and its CV mortality component are not statistically significant in the ≥ 50% target daily beta-blocker dose subgroup [redacted], whereas the treatment effect based on hospitalization for worsening HF component is statistically significant [redacted]. Contrarily, differences in treatment effect based on the primary composite end point and its hospitalization for worsening HF component are statistically significant in the < 50% target daily beta-blocker dose subgroup [redacted], whereas the treatment effect based on CV mortality component remains non-statistically significant [redacted].

The primary composite end point was also analyzed in numerous subgroups and those specified in the CDR review protocol have been presented in Appendix 4. [redacted]

3.6.3 Hospitalization

Statistically significant reductions in all-cause hospitalization, hospitalization for worsening HF, and cardiovascular hospitalization were also observed with ivabradine treatment when compared with placebo in the heart rate ≥ 77 bpm subgroup of the SHIfT study, with HRs of 0.82 (95% CI, 0.74 to 0.91), 0.69 (95% CI, 0.59 to 0.80) and 0.79 (95% CI, 0.71 to 0.89), respectively. However, when considering the < 77 bpm subgroup of the SHIfT study (Table 39), [redacted]

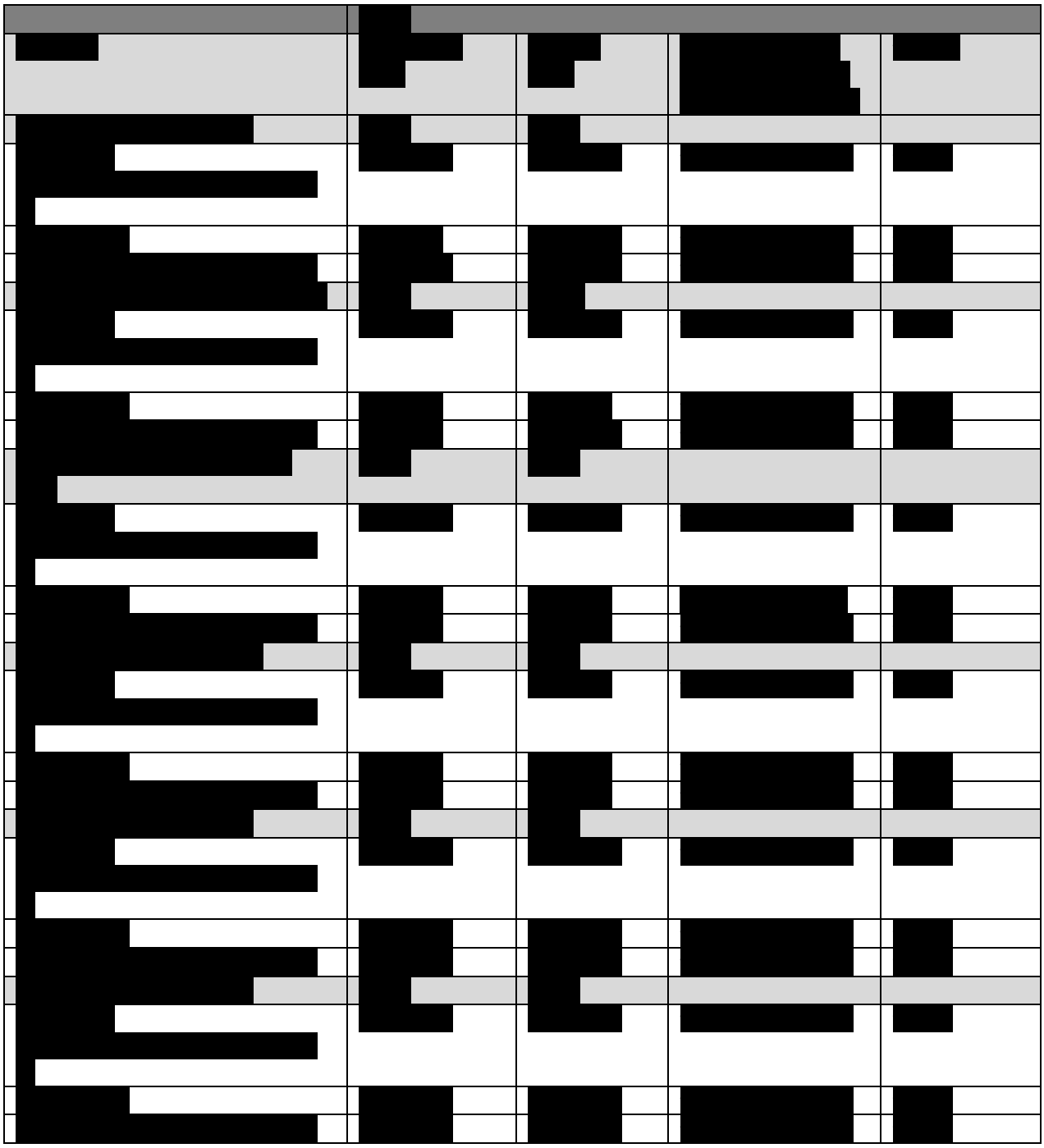
Hospitalization was analyzed in numerous subgroups and those specified in the CDR review protocol have been presented in Appendix 4. [redacted]

TABLE 10: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM SUBGROUP)

	SHIfT			
	Ivabradine (N = 1,657)	**Placebo (N = 1,700)**	**Treatment Effect Ivabradine Versus Placebo**	***P* value**
Primary Outcome	**n (%)**	**n (%)**	**HR (95% CI)**	
CV death or hospitalization due to worsening HF	454 (27.4)	581 (34.2)	0.75 (0.67 to 0.85)	< 0.0001
Mortality				
All-cause mortality	285 (17.2)	350 (20.6)	0.81 (0.69 to 0.94)	0.0074
CV mortality	255(15.4)	312 (18.4)	0.81 (0.69 to 0.96)	0.0137
Death from HF	67 (4.0)	107 (6.3)	0.61 (0.45 to 0.83)	0.0017
Hospitalization				
All-cause hospitalization	667(40.3)	778 (45.8)	0.82 (0.74 to 0.91)	0.0002
Hospitalization for worsening HF	298 (18.0)	418 (24.6)	0.69 (0.59 to 0.80)	< 0.0001
CV hospitalization	534 (32.2)	647 (38.1)	0.79 (0.71 to 0.89)	< 0.0001

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 11: KEY EFFICACY OUTCOMES BY PER CENT BETA-BLOCKER DOSE (HEART RATE ≥ 77 BPM SUBGROUP)



BB= beta-blocker; CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

3.6.4 Other Cardiovascular Outcomes

[redacted] Details pertaining to other cardiovascular outcomes in the heart rate ≥ 77 bpm subgroup of the SHIfT population are provided in Table 12.

TABLE 12: OTHER CARDIOVASCULAR OUTCOMES (HEART RATE ≥ 77 BPM SUBGROUP)

	SHIfT		
[redacted]			

AF = atrial fibrillation; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction; NA = not available.
[a]Data only provided for the safety analysis set (N = 1,652 ivabradine, N = 1,697 placebo)
Source: Servier Canada Inc.[1]

3.6.5 Change in New York Heart Association Functional Class

[redacted] Details on the change in NYHA function class in the heart rate ≥ 77 bpm subgroup of the SHIfT population are provided in Table 13.

TABLE 13: CHANGE IN NEW YORK HEART ASSOCIATION FUNCTIONAL CLASS (HEART RATE ≥ 77 BPM SUBGROUP)

[redacted]				

CI = confidence interval; HR = hazard ratio; NA = not available; NYHA = New York Heart Association.
Source: Servier Canada Inc.[1]

3.6.6 Change in Global Assessment

[redacted] Details on the change in both patient- and physician-reported global assessments in the heart rate ≥ 77 bpm subgroup of the SHIfT population are provided in Table 14.

TABLE 14: CHANGE IN GLOBAL ASSESSMENT (HEART RATE ≥ 77 BPM SUBGROUP)

[redacted]

CI = confidence interval; HR = hazard ratio; NA = not applicable.
Source: Servier Canada Inc.[1]

3.6.7 Change in Heart Rate

[redacted]

Details of the change in heart rate in the heart rate ≥ 77 bpm subgroup of the SHIfT population are provided in Table 15.

TABLE 15: CHANGE IN HEART RATE (HEART RATE ≥77 BPM SUBGROUP)

[redacted]

bpm = beats per minute; SD = standard deviation.
Source: Servier Canada Inc.[1]

3.6.8 Change in Health-Related Quality of Life

No data on the change in health-related quality of life were provided for the heart rate ≥ 77 bpm subgroup of the SHIfT population.

3.6.9 Change in Left Ventricular Ejection Fraction

No data on the change in LVEF were provided for the heart rate ≥ 77 bpm subgroup of the SHIfT population.

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2, Protocol). *See* APPENDIX 4: DETAILED OUTCOME DATA *for detailed harms data.*

Details pertaining to harms in the heart rate ≥ 77 bpm subgroup of the SHIfT population are provided in Table 16.

3.7.1 Adverse Events

A numerically greater percentage of patients in the placebo group experienced a treatment-emergent adverse event (TEAE) (emergent AEs that occurred after the first study drug intake and two days after the last study drug intake) when compared with the ivabradine group ( ). Cardiac failure , bradycardia , atrial fibrillation and inadequately controlled blood pressure were the most commonly reported TEAEs in the ivabradine treatment group.

3.7.2 Serious Adverse Events

A numerically greater percentage of patients in the placebo group experienced a serious TEAE (emergent SAEs that occurred after the first study drug intake and two days after the last study drug intake) when compared with the ivabradine group . Cardiac failure and atrial fibrillation were the most commonly reported serious TEAE in the ivabradine treatment group.

3.7.3 Withdrawal due to Adverse Events

A similar proportion of patients in the placebo group experienced a withdrawal due to TEAE (emergent adverse events occurred after the first study drug intake and two days after the last study drug intake) when compared with the ivabradine group . Sudden death , atrial fibrillation , unstable angina , pneumonia , cardiac failure , and sudden cardiac death were the most commonly reported reasons for stopping therapy in the ivabradine treatment group.

3.7.4 Notable Harms

For some of the notable harms, specifically bradycardia and phosphenes, a numerically greater percentage of patients experienced an event in the ivabradine group compared with the placebo group: bradycardia The occurrence of the remaining notable harms, specifically atrial fibrillation, hypotension, renal failure, and stroke (ischemic, haemorrhagic, and embolic), was approximately equal in both treatment groups.

TABLE 16: HARMS (HEART RATE ≥ 77 BPM SUBGROUP)

	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

SAE = serious adverse event; WDAE = withdrawal due to adverse events.
[a] Adverse events with an incidence of 2% or higher in one of the treatment groups. Italicized events were identified in the protocol as notable adverse events.
[b] Asymptomatic bradycardia.
[c] SAE with an incidence of 2.5% or higher in one of the treatment groups.
Source: Servier Canada Inc.[1]

4. DISCUSSION

4.1 Summary of Available Evidence

One randomized, double-blind, placebo-controlled trial met the inclusion criteria of the CDR systematic review. The SHIfT study (N = 6,558) compared the safety and efficacy of ivabradine 2.5 mg (half of the 5 mg tablet), 5 mg, or 7.5 mg twice daily with matching placebo in combination with standard chronic heart failure therapies in adult patients with stable chronic HF in sinus rhythm and reduced LVEF (≤ 35%) with NYHA functional class II to IV HF, and heart rate ≥ 70 bpm. Although the SHIfT population enrolled patients with heart rates ≥ 70 bpm, the manufacturer's reimbursement request is limited to patients with heart rates ≥ 77 bpm as per the Health Canada–approved indication. Therefore this CDR review is focused on the results from a pre-specified subgroup of the enrolled SHIfT population, limited to the randomized set and safety set of patients with heart rate ≥ 77 bpm (N = 3,357). The primary composite outcome was time to first cardiovascular death or hospitalization for worsening HF, and secondary outcomes included all-cause mortality, death from cardiovascular causes, death from HF, all-cause hospitalizations, HF-related hospitalization, cardiovascular-related hospitalization, sudden cardiac death, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, development of new or worsening atrial fibrillation, and the composite of cardiovascular death, hospitalization for worsening HF, or hospitalization for non-fatal myocardial infarction. Changes in NYHA classification, LVEF, and heart rate as well as patient-reported and physician-reported global assessment were also evaluated.

The SHIfT study had a number of limitations that could affect the internal and external validity of the results, such as the lack of control for type I error and the concerns raised regarding the generalizability of the results to patients with HF in Canada. Additionally, this CDR review is based on a subgroup analysis (i.e., heart rate ≥ 77 bpm) that was not part of statistical testing hierarchy and therefore not corrected for inflated type I error. While there is an increased risk of a statistically significant finding due to chance, the validity of these results are strengthened by the a priori specification of the subgroup of interest, the large sample size, and the biological plausibility of ivabradine's treatment effects being influenced by a patient's baseline heart rate.

4.2 Interpretation of Results

4.2.1 Efficacy

Based on the full SHIfT population (N = 6,505; heart rate ≥ 70 bpm), there was a statistically significant difference between the ivabradine and placebo treatment groups based on the primary composite end point (cardiovascular mortality and hospitalization for worsening HF) (HR, 0.82; 95% CI, 0.75 to 0.90). This result was driven by differences between groups for hospitalization for worsening HF component (HR, 0.74; 95% CI, 0.66 to 0.83); the cardiovascular mortality component of the composite end point was not statistically significant (HR, 0.91; 95% CI, 0.80 to 1.03).

The manufacturer's reimbursement request was limited to patients with heart rates ≥ 77 bpm as per the Health Canada–approved indication. Based on the pre-specified heart rate ≥ 77 bpm subgroup of the SHIfT study (N = 3,357), there were fewer primary composite events (first event among cardiovascular mortality or hospitalization for worsening HF) in the ivabradine treatment group compared with the placebo group (27.4% versus 34.2%). A statistically significant treatment effect in favour of ivabradine (HR, 0.75; 95% CI, 0.67 to 0.85) was reported. The statistical significance of the treatment effect for the primary composite end point was driven by both cardiovascular mortality and hospitalization for worsening HF (15.4% versus 18.4% [HR, 0.81; 95% CI, 0.69 to 0.96] and 18.0% versus 24.6% [HR, 0.69; 95% CI, 0.59 to 0.80], respectively). There were statistically significantly fewer all-cause deaths (17.2%

versus 20.6%) and deaths related to HF (4.0% versus 6.3%) in the ivabradine treatment group versus the placebo group, respectively. Other secondary cardiovascular outcomes, such as sudden cardiac death, fatal or non-fatal myocardial infarction and stroke, and new onset atrial fibrillation, [redacted] between treatment groups. Furthermore, there were fewer all-cause hospitalizations (40.3% versus 45.8%) and cardiovascular hospitalizations (32.2% versus 38.1%), in the ivabradine versus placebo groups, respectively, and the differences in treatment effect were all statistically significant.

When considering the pre-specified heart rate < 77 bpm subgroup of the SHIfT study (N = 3,144), there were no statistically significant reductions in all-cause and cardiovascular mortality, or death from HF, between the ivabradine and placebo treatment groups, with HRs of [redacted], respectively. In addition, there were no statistically significant differences in hospitalization for worsening HF between the ivabradine and placebo treatment groups, with an HR of [redacted]. Treatment effects in terms of all-cause hospitalization and cardiovascular hospitalization were not reported in < 77 bpm subgroup of the SHIfT study. Furthermore, there were no statistically significant differences between treatment groups for the primary composite outcome, with an HR of 0.93 (95% CI, 0.80 to 1.08). The concurrence and trend of the primary outcome and its components (CV death and hospitalization for worsening HF) suggest that ivabradine may not be effective compared with placebo in patients with heart rates < 77 bpm.

Only the evaluation of the primary composite end point in the randomized set of patients (i.e., the full SHIfT population with heart rate ≥ 70 bpm) and the primary composite end point in the ≥ 50% target daily beta-blocker dose subgroup of the randomized set were included in a statistical testing hierarchy. Generally, any inferences or interpretations based on subgroups that were not part of the statistical testing hierarchy and that were not adjusted for multiplicity should be made with caution, given the increased risk of type I error. While the risk of type I error remains, the validity of the results for the subgroup of interest for this CDR review (i.e., heart rate ≥ 77 bpm) is strengthened by the pre-specified nature of the subgroup and the biological plausibility of the interaction effect. It has been suggested that ivabradine is most effective in blocking the HCN channel (which is responsible for the I_f current) when these channels are most frequently open (i.e., when heart rates are highest).[14,15] Therefore, ivabradine would be expected to show greater efficacy in the heart rate ≥ 77 bpm subgroup of the SHIfT study. In addition, the large sample size and the consistent direction of effect across outcomes including the primary composite end point and its components (CV death and hospitalization due to worsening HF) alleviate some of the concerns associated with the increased risk of type I error.

The manufacturer's reimbursement request and the Health Canada–approved indication for ivabradine is for combination therapy with standard HF therapies. Not all patients included in the SHIfT study were on standard chronic HF therapy. According to the clinical expert consulted for this CDR review and Canadian Cardiovascular Society and American Heart Association guidelines,[2,3,7] standard chronic HF treatment consists of ACEIs or ARBs added to beta-blockers as well as MRAs. Although the majority of patients were taking the suggested chronic HF treatments, some patients were not treated with all three drugs (especially MRAs). The clinical expert noted that more than 50% (likely between 50% and 75%) of patients with chronic HF would be treated with ≥ 50% target daily beta-blocker doses. For patients in the SHIfT study with heart rate ≥ 77 bpm, [redacted] Therefore the proportion of patients treated with standard of care therapy for HF was not reflective of what would typically be seen in clinical practice. PBAC also noted

this discrepancy and suggested that the trial did not truly assess the benefit of ivabradine to patients on optimal HF treatment.[16,17]

The results of a post hoc subgroup analysis based on patients within four categories of per cent target daily beta-blocker dose (i.e., < 25%, ≥ 25% to < 50%, ≥ 50% to < 100%, and ≥ 100%), suggested that the differences in the treatment effects diminished with increasing per cent target daily beta-blocker doses received. Based on the primary composite end point, statistically significant results were demonstrated at the threshold of ≥ 25% to < 50% target daily beta-blocker dose [redacted] However, statistical significance in this case was largely driven by hospitalization for worsening HF component [redacted] and not CV mortality [redacted]. Only at the < 25% target daily beta-blocker dose [redacted] threshold does the difference in treatment effect between ivabradine and placebo become statistically significant in the primary composite outcome [redacted] and both of its components [redacted], suggesting that ivabradine may only be associated with a statistically significant difference in treatment effect when compared with placebo in patients treated with < 25% target daily beta-blocker doses or potentially those treated with ≥ 25% to < 50% target daily beta-blocker doses. These results are based on a post hoc subgroup analysis with no control for multiple statistical testing. However, the concordance of the results with the pre-specified subgroup analyses results based on ≥ 50% target daily beta-blocker dose support these findings. The difference in treatment effect based on the primary composite end point was not statistically significant in the ≥ 50% target daily beta-blocker dose subgroup [redacted], whereas the difference in treatment effect in the < 50% target daily beta-blocker dose post hoc subgroup was statistically significant [redacted]. These results support the suggestion that the differences in the treatment effects diminished with increasing per cent target daily beta-blocker doses received, as demonstrated by the four categories of per cent target daily beta-blocker dose (i.e., < 25%, ≥ 25% to < 50%, ≥ 50% to < 100%, and ≥ 100%).

Overall, a younger population (mean age 59 years) was included in the SHIfT study compared with patients who would be eligible for treatment with ivabradine in clinical practice. The age discrepancy was also noted by PBAC, which suggested that those likely to be treated with ivabradine would be significantly older (mean age in the mid to high 70s) and substantiated by the clinical expert consulted for this CDR review.[16,17] Moreover, the SHIfT study was conducted mainly in Eastern European centres with few North American centres; only 30 Canadian patients from 10 centres were included in the study when considering the overall population (i.e., heart rate ≥ 70 bpm). It is unclear how many Canadian patients were included in the subgroup of interest (i.e., heart rate ≥ 77 bpm). The origin and age of the patients in the SHIfT study further limit the generalizability of the results to patients in Canada as it is uncertain if results similar to the SHIfT study would be observed in the Canadian population given the potential differences in practice and patient characteristics.

The clinical expert consulted for this CDR review also highlighted discordant study results between regions of Europe and North America such as those reported for the PLATO trial (Mahaffey et al.), albeit for a different drug and indication.[18] Eastern European practice and criteria for hospital admission may vary from those used in North American countries, including Canada, and consequently may have an impact on the hospitalization component of the primary composite end point in the SHIfT study (first event among cardiovascular death and hospitalization due to worsening HF). This may be of particular concern when the primary composite end point is driven largely by the hospitalization component, such as in the case of the randomized set of the full SHIfT population (i.e., heart rate ≥ 70 bpm), where the treatment effect is associated with a statistically significant HR of 0.82 (95% CI, 0.75 to 0.90), largely

driven by hospitalization for worsening HF (HR, 0.74; 95% CI, 0.66 to 0.83; versus cardiovascular mortality (HR, 0.91; 95% CI, 0.80 to 1.03). This was also evident for the ≥ 25% to < 50% [redacted] While this may not bias the study in favour of one treatment (assuming that blinding was maintained), it may overestimate or underestimate the true incidence of events in both treatment groups, and influence the interpretation of the clinical significance of the results in the Canadian setting. PBAC also considered this was likely to affect the primary composite end point.[16,17]

4.2.2 Harms

At least [redacted] of patients experienced TEAEs during the SHIfT study in the ivabradine group compared with the [redacted] in the placebo group, the most common being cardiac failure, bradycardia (symptomatic and asymptomatic), atrial fibrillation and inadequately controlled blood pressure. Similarly, at least [redacted] of patients experienced SAEs during the SHIfT study in the ivabradine group compared with the [redacted] in the placebo group, the most common being cardiac failure and atrial fibrillation. The percentage of patients who stopped treatment due to AEs was similar in the ivabradine [redacted] and placebo groups [redacted], where sudden death, atrial fibrillation, unstable angina, pneumonia, cardiac failure, and sudden cardiac death were the most commonly reported reasons for stopping therapy.

Notable harms that were more commonly reported in the ivabradine group compared with the placebo group included bradycardia [redacted] as well as phosphenes [redacted] Although the Health Canada–approved product monograph for ivabradine states that atrial fibrillation, hypotension, and renal failure are of concern with ivabradine, the occurrence of these notable harms was similar in both treatment groups.[8]

The harms reported for the subgroup of interest for this CDR review (patients with heart rate ≥ 77 bpm) were similar to those observed for the full SHIfT population. Although the harms data were available for this specific subgroup of patients, the number of events that occurred according to dose of ivabradine received (i.e., 2.5 mg, 5 mg and 7.5 mg) was not available. Therefore, it is unclear if AE rates vary according to dose of ivabradine received. While the average treatment duration was 22 months, longer-term safety data are needed to determine the harms associated with this first-in-class pharmacotherapy.

4.3 Potential Place in Therapy

According to a draft report supplied by the clinical expert consulted by CDR for this review, approximately 10% to 15% of patients with HF in Canada have heart rates ≥ 70 bpm despite recommended treatment. The patient population of interest for this CDR review (patients with a heart rate ≥ 77 bpm despite recommended treatment) would therefore be less than 10% to 15% of patients with HF in Canada. The mortality rate for HF ranges as low as 5% at year one to 50% at five years after diagnosis, depending on the severity of symptoms, heart function, age, and other factors.[6] The all-cause mortality rate in the placebo group of the SHIfT study, for example, was 17% at 30 months.[8] Prior to the introduction of MRAs and sacubitril/valsartan (Entresto), there was little progress in reducing the high mortality rate for patients with HF.

Both Canadian Cardiovascular Society and American Heart Association guidelines suggest potential benefits with the use of ivabradine in patients in sinus rhythm with symptomatic HF and reduced ejection fraction who have a heart rate ≥ 70 bpm and who are receiving an ACEI or ARB and a beta-

blocker.[7,19] The clinical expert consulted for this review as well as Swedberg et al. noted that, in line with the conduct of the SHIfT study, ivabradine is considered an add-on treatment, and not a replacement for beta-blockers. Importantly, patients should be receiving guideline-directed evaluation and management (ACEIs or ARBs), including a beta-blocker at a maximum tolerated dose and MRAs.[7,19]

Another available treatment option for patients who remain symptomatic despite optimal triple therapy is to switch the use of ACEI or ARB to sacubitril/valsartan, as was done in the PARADIGM-FH trial. The only difference is that in PARADIGM-FH, patients did not have to be on an MRA at the time of enrolment (only 50% of patients were on one). The clinical expert also indicated that an important advantage of ivabradine is that, unlike the combination of sacubitril/valsartan, ivabradine has little effect on blood pressure (and vasodilation), which is often a limiting factor in the therapeutic options suitable for patients with HF.

Overall, the clinical expert consulted for this review indicated that ivabradine represents a viable option for the treatment of patients with symptomatic HF, marginal blood pressure, and heart rate ≥ 77 bpm. To ensure that patients meet the heart rate criterion of the Health Canada–approved indication for ivabradine, the clinical expert indicated that heart rate should be documented by ECG, as was done in the SHIfT study.

5. CONCLUSIONS

The CDR systematic review included one double-blind, phase III, randomized, placebo-controlled trial designed to assess the superiority of ivabradine compared with placebo in patients with a heart rate ≥ 70 bpm. Given the reimbursement request and Health Canada–approved indication, this CDR review focused primarily on the results from a subgroup of patients in the SHIfT study (i.e., patients with a heart rate ≥ 77 bpm; N = 3,357). There was a statistically significant difference between ivabradine and placebo for the primary composite outcome (cardiovascular mortality and hospitalization for worsening HF) (HR, 0.75; 95% CI, 0.67 to 0.85) based on the subgroup of patients with a heart rate ≥ 77 bpm. The primary composite end point was statistically significant for both cardiovascular mortality and for hospitalization for worsening HF. Although the results, which are based on subgroup analyses from the overall study population, are limited due to uncontrolled multiple statistical testing and the lack of stratification by heart rate at randomization, the validity of the results is strengthened by the pre-specified nature of the subgroup, the biological plausibility of the relationship between heart rate and treatment effects, large sample sizes, and the consistency of the results between study outcomes. [redacted] However, these results were based on a post hoc subgroup analysis with no control for multiple statistical testing. The observed trend, and the concordance of the results with the pre-specified subgroup analyses results based on ≥ 50% target daily beta-blocker dose support these findings. Nonetheless, the risk of observing a chance effect still remains. The SHIfT study was conducted mainly in Eastern European centres with few North American centres; only 30 Canadian patients from 10 centres were included in the study when considering the overall population (i.e., heart rate ≥ 70 bpm). It is unclear how many Canadian patients are included in the subgroup of interest (i.e., heart rate ≥ 77 bpm). The differences in patient and practice characteristics (for example, patient age, the use of optimal standard chronic HF treatment, and the definition of hospitalization) between countries may affect the generalizability of the results to patients in Canada.

Ivabradine was associated with an increased frequency of bradycardia (symptomatic and asymptomatic) and phosphenes compared with placebo; other AEs were similar between groups. Additional data are required to determine the longer-term safety of this first-in-class therapy.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patients groups responded to the call for patient input for this CADTH Common Drug Review (CDR) review.

The HeartLife Foundation (HLF) was founded in June 2016. Members of HLF are all patients along the heart failure (HF) continuum, including their families and caregivers. HLF aims to raise HF awareness, empower patient voices to stimulate dialogue, advance understanding, improve access to treatments and research, and improve patient care in Canada. HLF helps HF patients self-manage their condition, provide education and support for patients and families, and advocate for access to care and innovative treatments. The HLF has received grants and honorariums from Servier Canada, the Canadian Cardiovascular Society, and Novartis Canada. No conflict was declared in the preparation of this submission.

The Heart Failure Support Group of Manitoba (HFSGM) was established in 2011. Members are patients with a diagnosis of HF and their family members and caregivers. The purpose of the group is to provide support, education, and the opportunity for HF clients and their family members and caregivers to interact with others in similar situations. The group's activities include education sessions at which speakers discuss topics that are relevant to the care of those with HF or their caregivers. HFSGM received financial support from Servier Canada. One of the co-founders of HFSGM received honorariums from Novartis and Servier Canada, which was declared as a conflict of interest in respect of playing a significant role in the preparation of the submission.

2. Condition-Related Information

Information on the condition obtained by HLF was primarily gathered through the lived experiences of the co-founders of HLF, one-on-one conversations with medical experts, health care professionals, other patients with HF, family members, and caregivers. Information obtained by HFSGM was mainly gathered from discussions in various education sessions as well as during the annual public awareness on the management of HF education sessions.

HF is a serious health problem affecting an estimated 600,000 Canadians. Every year, 50,000 Canadians are newly diagnosed with HF. Patients with HF suffer from various symptoms, including shortness of breath, extreme fatigue, low blood pressure, dizziness, reduced appetite, reduced activity tolerance, difficulty sleeping at night due to breathing problems, edema and bloating, and sometimes confusion and impaired memory, to name a few. Many patients also have palpitations and arrhythmia as a result of the underlying etiology of their HF. Depending upon the stage and severity of the disease, the effect of the symptoms can vary.

Most patients who are diagnosed with HF quickly develop high levels of anxiety, coupled with bouts of depression, anger, and grief as they come to terms with the diagnosis and the immediate impact it has on their life. Medical teams often place a lot of emphasis on "restricting" aspects of a patient's life. Restrictions include constraints on fluid, sodium, alcohol, and caffeine, as well as food, and are often overwhelming, leading patients into prolonged states of depression and anxiety.

In patients with New York Health Association (NYHA) functional class I or II HF, sleep is often restless, and disturbed. However, if congestion is well controlled with medication, fluid restriction, and a low-sodium diet, rest is possible. Many patients are quick to catch seasonal colds and flus, which can easily

exacerbate and even worsen HF symptoms, potentially leading to hospitalization. Patients in NYHA class III are even more limited. Breathing at night is often congested, resulting in an increase of the patient's diuretic dose, thus increasing the frequency of urination, leading to even more interrupted, and often sleepless, nights. Standard treatment also dictates an increase in beta-blockers, which artificially slow the heart rate of patients, leading to further feelings of fatigue and resulting in an increased likelihood of depressive episodes. One patient in NYHA class III described it as follows: *"the condition has and continues to affect my day-to-day life. At present time, I am unable to work full-time, exercise regularly, travel to remote areas, and take part in many daily activities I once enjoyed."* Patients in NHYA class IV are very sick. Medical therapies are typically failing, their heart muscle has deteriorated to the point that severe edema in the legs and abdomen and congestion in the chest lead to many sleepless nights, often resulting in the patient sitting up in a chair to rest. Breathing in a horizontal position feels more like choking or gasping for air. Many have described it as feeling like they are drowning. Daily activities are difficult and exhausting, leaving most patients to spend the majority of their time resting at home, living increasingly isolated lives.

There are many activities in daily living that several patients are unable to accomplish due to HF symptoms. These include working a regular job, travelling, sports, and other outdoor activities, as well as participating in family events. It was reported that HF symptoms impair a patient's quality of life. It is important for patients to be able to control the symptoms of HF to help improve their quality of life, including that of their families. One patient group indicated that *"There is no cure for heart failure, and treatments serve only to manage symptoms and prolong survivability…."*

As HF progresses, patients become more reliant on their families and caregivers. Progression of illness means potential loss of income for family members as well, as they may need to miss work to help patients with their daily living activities. The caregiving process could have a negative effect on the caregiver's overall health and well-being. Many factors in caregiving could lead to stress, including the level of care, physical strain, financial hardship, emotional factors and lack of support from others. One patient group stated that *"The longer a caregiver provides caregiving activities, the more likely that the caregiver's physical and emotional health will worsen."*

3. Current Therapy-Related Information

Current treatments for HF include the use of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), beta-blockers, and mineralocorticoid receptor antagonists (MRAs) (triple therapy). In spite of advances in the treatment of HF, five-year mortality remains at 50%. However, some patients do not tolerate some of these medications and suffer side effects, including lowering of blood pressure, fatigue, or tiredness, increased potassium, and many others. Many patients remain intolerant to beta-blockers and in some cases to ACEIs, and there is a significant need for other treatment options.

4. Expectations About the Drug Being Reviewed

No patients had experience with ivabradine. It is expected that the quality of life of patients will be improved with the use of ivabradine. It is also expected that ivabradine would reduce hospitalization. The patient groups indicated that there are particular gaps or unmet patient needs in current therapy that ivabradine will help alleviate. Mainly, it is thought that ivabradine will benefit patients who cannot tolerate beta-blockers, such as those who suffer from increasing fatigue on beta-blockers, those with comorbidity, such as those with asthma or reactive airway problems, and those who have borderline blood pressure.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	December 6, 2016
Alerts:	Weekly search updates until April 19, 2017
Study Types:	Randomized controlled trials
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY
1.(ivabradin* or corlovan* or corabid* or corolan* or coraxan* or corlentor* or ivab or ivanor* or koraksan* or precorolan* OF siftus* or corlanor* or procorlan* or procoralan* or ivabad* or bradia* or coralan* or implicor* or s-16257* or s16257* or s16260* or s-16260 or amg998 or amg-998 or 3H48L0LPZQ or TP19837BZK).ti,ab,ot,kf,hw,rn,nm.
2. (155974-00-8 or 148849-67-6).rn,nm.
3. 1 or 2
4. 3 use ppez
5.*ivabradine/
6. (ivabradin* or corlovan* or corabid* or corolan* or coraxan* or corlentor* or ivab or ivanor* or koraksan* or precorolan* OF siftus* or corlanor* or procorlan* or procoralan* or ivabid* or bradia* or coralan* or implicor* or s-16257* or s16257* or s16260* or s-16260 or amg998 or amg-998 or 3H48L0LPZQ or TP19837BZK).ti,ab,kw,ot.
7. 5 or 6
8. 7 use oemezd
9. 4 or 8
10. conference abstract.pt.
11. exp animals/
12. exp animal experimentation/ or exp animal experiment/
13. exp models animal/
14. nonhuman/
15. exp vertebrate/ or exp vertebrates/
16. or/11-15
17. exp humans/
18. exp human experimentation/ or exp human experiment/
19. or/17-18
20. 16 not 19
21. 9 not 10
22. 21 not 20
23. Randomized Controlled Trial.pt.
24. Pragmatic Clinical Trial.pt.
25. exp Randomized Controlled Trials as Topic/
26. "Randomized Controlled Trial (topic)"/
27. Randomized Controlled Trial/
28. Randomization/
29. Random Allocation/
30. Double-Blind Method/
31. Double Blind Procedure/
32. Double-Blind Studies/
33. Single-Blind Method/
34. Single Blind Procedure/
35. Single-Blind Studies/
36. Placebos/
37. Placebo/

MULTI-DATABASE STRATEGY
38. (random* or sham or placebo*).ti,ab,hw,kf,kw.
39. ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
40. ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
41. or/23-40
42. 22 and 41
remove duplicates from 42

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	December 2016
Keywords:	Corlovan, Lancora, ivabradine
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
BOCCHI et al., 2015	Study population - irrelevant
BOHM et al., 2010	Study design - irrelevant
BOHM et al., 2013	Study population - irrelevant
BOHM et al., 2015	Study population - irrelevant
BOHM et al., 2016	Study population - irrelevant
BORER et al., 2012	Study population - irrelevant
BORER et al., 2014	Study population - irrelevant
EKMAN et al., 2011	Study population - irrelevant
KOLTOWSKI et al., 2010	Study population - irrelevant
KOMAJDA et al., 2014	Study population - irrelevant
KOMAJDA et al., 2015	Study population - irrelevant
KOMAJDA et al., 2016	Study population - irrelevant
MANSOUR et al., 2011	Study population - irrelevant
MANZANO et al., 2011	Study design - irrelevant
MARTIN et al., 2014	Study design - irrelevant
MIZZACI et al., 2016	Study design - irrelevant
ROGERS et al., 2015	Study population - irrelevant
SALLAM et al., 2016	Study population - irrelevant
SWEDBERG et al., 2012	Study population - irrelevant
TANBOGA et al., 2016	Study design - irrelevant
TARDIF et al., 2011	Study population - irrelevant
TAVAZZI et al., 2013	Study population - irrelevant
TAVAZZI et al., 2013	Study population - irrelevant
TSE et al., 2015	Study design - irrelevant
VITOVEC et al., 2012	Study population - irrelevant
VOORS et al., 2014	Study population - irrelevant

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 17: BETA-BLOCKER USE BASED ON PER CENT OF TARGET DAILY DOSE (HEART RATE ≥ 77 BPM SUBGROUP)

BB = beta-blocker.
Source: Servier Canada Inc.[1]

TABLE 18: MEAN RESTING HEART RATE BASED ON PERCENTAGE OF TARGET BETA-BLOCKER DOSE AT RANDOMIZATION (HEART RATE ≥ 77 BPM SUBGROUP)

bpm = beats per minute; SD = standard deviation.
Source: Servier Canada Inc.[1]

TABLE 19: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM [redacted] OF TARGET DAILY BETA-BLOCKER DOSE SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TABLE 20: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM [redacted] OF TARGET DAILY BETA-BLOCKER DOSE SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 21: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] OF TARGET DAILY BETA-BLOCKER DOSE SUBGROUP)

	[redacted]			
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 22: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] OF TARGET DAILY BETA-BLOCKER DOSE SUBGROUP)

	[redacted]			
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				
[redacted]				

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NA = not available.
Source: Servier Canada Inc.[1]

TABLE 23: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] OF TARGET DAILY BETA-BLOCKER DOSE SUBGROUP)

[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 24: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] OF TARGET DAILY BETA-BLOCKER DOSE SUBGROUP)

[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 25: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] OF TARGET DAILY BETA-BLOCKER DOSE SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NA = not available.
Source: Servier Canada Inc.[1]

TABLE 26: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] AT RANDOMIZATION SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NA = not available.
Source: Servier Canada Inc.[1]

TABLE 27: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] AT RANDOMIZATION SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NA = not available.
Source: Servier Canada Inc.[1]

TABLE 28: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] AT RANDOMIZATION SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NA = not available.
Source: Servier Canada Inc.[1]

TABLE 29: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] AT RANDOMIZATION SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NA = not available.
Source: Servier Canada Inc.[1]

TABLE 30: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 31: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 32: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 33: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 34: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 35: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 36: KEY EFFICACY OUTCOMES (HEART RATE ≥ 77 BPM AND [redacted] SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: Servier Canada Inc.[1]

TABLE 37: KEY EFFICACY OUTCOMES (FULL SHIFT POPULATION HEART RATE ≥ 70 BPM)

	SHIfT			
	Ivabradine (N = 3,241)	**Placebo (N = 3,264)**	**Treatment Effect Ivabradine Versus Placebo**	***P* value**
Primary outcome	**n (%)**	**n (%)**	**HR (95% CI)**	
CV death or hospitalization due to worsening HF	793 (24.5)	937 (28.7)	0.82 (0.75 to 0.90)	< 0.0001
Mortality				
All-cause mortality	503 (15.5)	552 (16.9)	0.90 (0.80 to 1.02)	0.092
CV mortality	449 (13.9)	491 (15.0)	0.91 (0.80 to 1.03)	0.128
Death from HF	113 (3.5)	151 (4.6)	0.74 (0.58 to 0.94)	0.014
Hospitalization				
All-cause hospitalization	1,231 (38.0)	1,356 (41.5)	0.89 (0.82 to 0.96)	0.0027
Hospitalization for worsening HF	514 (15.9)	672 (20.6)	0.74 (0.66 to 0.83)	< 0.0001
CV hospitalization	977 (30.0)	1122 (34.4)	0.85 (0.78 to 0.92)	0.0002

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: SHIfT Clinical Study Report.[11]

TABLE 38: KEY EFFICACY OUTCOMES (HEART RATE ≥ 70 BPM AND [redacted] TARGET DAILY BETA-BLOCKER DOSE SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio.
Source: SHIfT Clinical Study Report.[11]

TABLE 39: KEY EFFICACY OUTCOMES (HEART RATE [redacted] SUBGROUP)

	[redacted]			
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CV mortality	[redacted]	[redacted]	[redacted]	[redacted]
Death from HF	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalization				
All-cause hospitalization	[redacted]	[redacted]	[redacted]	[redacted]
Hospitalization for worsening HF	[redacted]	[redacted]	[redacted]	[redacted]
CV hospitalization	[redacted]	[redacted]	[redacted]	[redacted]

CI = confidence interval; CV = cardiovascular; HF = heart failure; HR = hazard ratio; NA = not available; NR = not reported.
Source: SHIfT Clinical Study Report,[11] Health Canada reviewer's report.[20]

TABLE 40: HARMS (FULL SHIFT POPULATION HEART RATE ≥ 70 BPM)

	SHIfT	
Adverse Events	**Ivavradine N = 3,232**	**Placebo N = 3,260**
Subjects with ≥ 1 adverse event, n (%)	[redacted]	[redacted]
Most common adverse events,[a] n (%)		
[redacted]	[redacted]	[redacted]
Atrial fibrillation	267 (8.3)	217 (6.7)
Blood pressure inadequately controlled	228 (7.1)	198 (6.1)
Heart rate decreased	181 (5.6)	45 (1.4)
Bradycardia	148 (4.6)	28 (0.9)
Ventricular extrasystoles	144 (4.5)	138 (4.2)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Phosphenes	89 (2.8)	16 (0.5)
Sudden cardiac death	73 (2.3)	68 (2.1)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

	SHIfT	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
SAEs		
Subjects with ≥ 1 SAE, n (%)	1,369 (42.4)	1,481 (45.4)
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
WDAEs		
Stopped treatment due to adverse events, n (%)[b]	467 (14.5)	416 (12.8)
Most common WDAEs, n (%)		
Atrial fibrillation	135 (4.2)	113 (3.5)
[redacted]	[redacted]	[redacted]

SAE = serious adverse event; WDAE = withdrawal due to adverse events.
[a] Adverse events with an incidence of 2% or higher in one of the treatment groups. Italicized events were identified in the protocol as notable adverse events.
[b] SAE with an incidence of 2.5% or higher in one of the treatment groups.
Source: SHIfT Clinical Study Report.[11]

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