Ivabradine (CORLANOR®)

National Drug Monograph

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information[1]	
Description/Mechanism of Action	Ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel, reducing the cardiac pacemaker activity of the sinus node by selectively inhibiting the I_f–current (I_f), which decreases heart rate without an effect on ventricular repolarization or myocardial contractility.
Indication(s) Under Review in this document	Ivabradine is indicated to reduce the risk for hospitalization for worsening heart failure (HF) in patients with stable, symptomatic chronic HF with left ventricular ejection fraction (LVEF) ≤ 35%, who are in sinus rhythm with a resting heart rate ≥ 70 beats per minute (bpm), and either are on a maximally tolerated dose of a beta-blocker or have a contraindication to a beta-blocker.
Dosage Form(s) Under Review	Ivabradine is available in 5 mg and 7.5 mg tablets.
REMS	☐ REMS ☒ No REMS ☐ Post-marketing surveillance
Pregnancy Rating	Based on animal studies, ivabradine may cause fetal harm in pregnant women. Females receiving ivabradine should use effective contraception.

Executive Summary	
Efficacy[1-3]	• Results from the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) demonstrated a statistically significant reduction in the composite primary endpoint of cardiovascular death or hospital admission for worsening heart failure with ivabradine (24%) compared to placebo (29%) (HR 0.82, 95% CI 0.75 to 0.90; P<0.001; calculated NNT=24 over 22.9 months) in the 6505 patients analyzed. • Results were driven primarily by the reduction in hospitalizations for worsening HF with ivabradine (16%) compared to placebo (21%) (HR 0.74, 95% CI 0.66 to 0.83; P<0.001; calculated NNT=21 over 22.9 months). Cardiovascular death was not significantly reduced with ivabradine (P=0.128). • Patients enrolled in SHIFT had symptomatic HF and LVEF ≤ 35%, were in sinus rhythm with a resting heart rate ≥ 70 bpm, had a hospital admission for worsening HF in the past year, and were stable on guideline recommended therapy for HF including optimized treatment with a beta-blocker, as tolerated. • Median follow-up of the trial was 22.9 months.
Safety[1-3]	• Ivabradine is contraindicated in patients with: acute decompensated HF; blood pressure < 90/50 mm Hg; sick sinus syndrome, sinoatrial block or 3rd degree atrioventricular (AV) block, unless a functioning demand pacemaker is present; resting heart rate < 60 bpm prior to treatment; severe hepatic impairment; pacemaker dependence (heart rate maintained exclusively by the pacemaker); concomitant strong cytochrome CYP3A4 inhibitors. Ivabradine is also not recommended in patients with 2nd degree AV block. • It is also recommended to monitor for: a decrease in heart rate and symptoms of bradycardia, or atrial fibrillation, in patients receiving ivabradine. • Due to the potential for fetal toxicity, female patients taking ivabradine should use effective contraception. • The most common side effects with ivabradine include: bradycardia, hypertension,

	atrial fibrillation, luminous phenomena (in SHIFT, phosphenes reported in 3% on ivabradine vs. 1% on placebo; P<0.0001).
Other Considerations[1-3]	• At baseline, 56% of patients were at ≥ 50% of beta-blocker target dose; with only 26% of patients at target dose. It was noted that doses of the beta-blockers were maintained during the trial without a need to decrease the dose in order to titrate ivabradine. • Importantly, there was not a statistically significant difference in the primary endpoint with ivabradine compared to placebo in the subgroup of SHIFT patients who received ≥ 50% of beta-blocker target dose (HR 0.90, 95% CI 0.77 to 1.04; P=0.155); hospitalizations due to worsening HF was significantly reduced with ivabradine vs. placebo (HR 0.81, 95% CI 0.67 to 0.97; P=0.021) in this subgroup.
Projected Place in Therapy[1,2,4]	• Ivabradine may be considered in patients with stable and symptomatic chronic HF and LVEF ≤ 35%, who are in sinus rhythm, with a resting heart rate ≥ 70 bpm, on a maximally tolerated dose of a beta-blocker or with a contraindication to a beta-blocker. Patients should also be receiving optimal guideline directed medical therapy (e.g., ACEI or ARB, mineralocorticoid receptor antagonist, in addition to optimal doses of a beta-blocker, as indicated and tolerated).

Background

Purpose for review	Recent FDA approval. Issues to be determined: ✔ Does the evidence show that ivabradine reduces long-term outcomes in patients with heart failure with reduced ejection fraction in addition to standard therapy? ✔ Determine the most appropriate patients for treatment with ivabradine? ✔ What additional safety issues need to be considered with the use of ivabradine? ✔ Does ivabradine have specific characteristics best managed by the non-formulary process or criteria for use?
Other therapeutic options	Ivabradine is a new drug entity that reduces heart rate, and is being recommended in a specific patient population with HF with reduced ejection fraction with an elevated heart rate despite maximally tolerated doses of a beta-blocker or who have a contraindication to a beta-blocker.[1,2]

Efficacy (FDA Approved Indication)[1-3,5]

Literature Search Summary

A literature search was performed on PubMed/Medline (1996 to July 2015) using the search term ivabradine. The search was limited to studies performed in humans and published in the English language. Reference lists of review articles were searched for relevant clinical trials. Randomized controlled Phase 3 trials published in peer-reviewed journals evaluating the FDA approved indication were included.

Review of Efficacy[1-3,5]

- FDA approval of ivabradine was based on the pivotal Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT).
- Patients enrolled in SHIFT had stable symptomatic HF and LVEF ≤ 35%, were in sinus rhythm with a resting heart rate ≥ 70 bpm, had a hospital admission for worsening HF in the past year, and were stable on guideline recommended therapy for HF including optimized treatment with a beta-blocker, as tolerated. Results from SHIFT demonstrated a statistically significant reduction in the composite primary endpoint of cardiovascular death or hospital admission for worsening HF with ivabradine (24%) compared to placebo (29%) (HR 0.82, 95% CI 0.75 to 0.90; P<0.001). Results were driven primarily by the reduction in hospitalizations for worsening

HF with ivabradine (16%) compared to placebo (21%) (HR 0.74, 95% CI 0.66 to 0.83; P<0.001). Cardiovascular death was not significantly reduced with ivabradine (P=0.128).[2]

- Overall, there is moderate quality of evidence (Refer to Appendix A) for the use of ivabradine to reduce the risk for hospitalization for worsening HF, or composite cardiovascular death or HF hospitalization, in patients with symptomatic HF and LVEF ≤ 35%, who are in sinus rhythm with a resting heart rate ≥ 70 bpm, and were hospitalized for worsening HF in the past year, and are currently stable on guideline recommended therapy for HF including optimized treatment with a beta-blocker.[1,2]

SHIFT

- SHIFT was a Phase 3 multicenter, multinational, double-blind, parallel group, placebo-controlled trial in patients with symptomatic chronic HF (New York Heart Association [NYHA] class II-IV) and LVEF ≤ 35%, who had been hospitalized for worsening HF in the past 12 months. It is noted that no patients from the North American continent were enrolled or studied in the trial, and therefore the relevance of findings from this study to the VA population is unknown. Study patients were in sinus rhythm with a resting heart rate ≥ 70 bpm, and were stable on guideline recommended therapy for HF, including optimal doses of a beta-blocker, as tolerated. Median follow-up was 22.9 months.[2,3]
- Select main exclusion criteria: recent (within past 2 months) myocardial infarction (MI); ventricular or AV pacing operative for ≥ 40% of the day; atrial fibrillation or flutter; sick sinus syndrome, sinoatrial block, 2nd and 3rd degree AV block; symptomatic hypotension or sitting systolic blood pressure (SBP) < 85 mm Hg. Treatment with non-dihydropyridine (non-DHP) calcium channel blockers (CCBs), class I anti-arrhythmic agents, or strong CYP3A4 inhibitors were not allowed.[2,3]
- Patients were randomized to ivabradine (N=3268) or placebo (N=3290). Patients assigned to ivabradine were started on 5 mg twice daily, with heart rate assessed at 14 days. If at 14 days the patient's resting heart rate was > 60 bpm, the dose of ivabradine (or corresponding placebo) was increased to 7.5 mg twice daily. The patient was maintained on 5 mg twice daily if their resting heart rate was between 50 and 60 bpm; or decreased to 2.5 mg twice daily if the resting heart rate was < 50 bpm or the patient was experiencing signs and symptoms related to bradycardia. Starting at day 28, patients were seen every 4 months for dose adjustment based on resting heart rate as above. The mean dose of ivabradine was 6.4 mg twice daily at 28 days, and 6.5 mg twice daily at one year. The mean reduction in heart rate with ivabradine was 15.4 bpm at day 28 (placebo corrected 10.9 bpm), and 9.1 bpm (placebo corrected 8.1 bpm) at one year.[2,3]
- There were 3241 patients in the ivabradine group and 3264 patients in the placebo group that were analyzed, accounting for the 7 patients that did not have the study drug dispensed and the 46 patients that were from the removed treatment centers due to misconduct. There were 682 withdrawals (21%) in the ivabradine treatment group compared to 605 (19%) on placebo (HR 1.14, 95% CI 1.02 to 1.27; P=0.017). Adverse events leading to treatment withdrawal occurred in 467 (14%) patients on ivabradine and 416 (13%) of patients on placebo (P=0.051).[2]
- At baseline, 56% of patients were at ≥ 50% of beta-blocker target dose; with 26% of patients at target dose. Mean daily doses of the evidence-based beta-blockers at baseline were approximately: bisoprolol 6 mg; carvedilol 25 mg; metoprolol succinate 90 mg. Hypotension, fatigue, dyspnea, dizziness and bradycardia were reported as reasons for not achieving target dose. It was noted that doses of the beta-blockers were maintained during the trial without a need to decrease the dose in order to titrate ivabradine.[2,5]
- In those patients not receiving beta-blockers at baseline (ivabradine 11%; placebo 10%), chronic obstructive pulmonary disease, hypotension, asthma, cardiac decompensation, dizziness or bradycardia, fatigue, Raynaud or peripheral arterial disease, were each reported in ≥ 5% of these patients as reasons for not receiving treatment with a beta-blocker.[2]
- Select baseline characteristics are included in the table below.

SHIFT Select Baseline Characteristics[2]

Characteristic	Ivabradine (N=3241)	Placebo (N=3264)
Age	60.7	60.1
Male	76%	77%
Race/ethnicity		
White	89%	89%
Asian	8%	8%
Other	3%	3%
Cardiac		
Heart rate (bpm)	79.7	80.1
Systolic blood pressure (mm Hg)	122.0	121.4
Diastolic blood pressure (mm Hg)	75.7	75.6
Left ventricular ejection fraction	29.0%	29.0%
Primary cause of HF - ischemic	68%	67%
History of myocardial infarction	56%	56%
History of atrial fibrillation/flutter	8%	8%
New York Heart Association functional class		
II	49%	49%
III	50%	50%
IV	2%	2%
Treatment at randomization		
Beta-blocker	89%	89%
Angiotensin-converting enzyme inhibitor	79%	78%
Angiotensin II receptor antagonist	14%	14%
Diuretic	84%	83%
Mineralocorticoid antagonist	61%	59%
Cardiac glycoside	22%	22%
Devices		
Cardiac resynchronization therapy	1%	1%
Implantable cardiac defibrillator	3%	4%

- Patients treated with ivabradine experienced a significant reduction in the composite primary endpoint of cardiovascular death or hospital admission for worsening heart failure compared to placebo. Results were driven primarily by the reduction in hospitalizations for worsening HF with ivabradine, which was significant compared to placebo; however, the difference in cardiovascular death as an outcome was not statistically significant. There was also no significant difference in all-cause mortality between treatment groups. Results of the other endpoints reported in the trial are noted in the table below.[2]

SHIFT Primary and Other Outcome Results[2]

Outcome[a]	Ivabradine (N=3241)	Placebo (N=3264)	HR (95% CI)	P
	Number (%)			
Composite primary endpoint	793 (24)	937 (29)	0.82 (0.75-0.90)[b]	<0.0001
Mortality outcomes				
All-cause mortality	503 (16)	552 (17)	0.90 (0.80-1.02)	0.092
Cardiovascular mortality	449 (14)	491 (15)	0.91 (0.80-1.03)	0.128
Death from HF	113 (3)	151 (5)	0.74 (0.58-0.94)	0.014
Other outcomes				
All-cause hospital admission	1231 (38)	1356 (42)	0.89 (0.82-0.96)	0.003
Hospitalization for worsening HF	514 (16)	672 (21)	0.74 (0.66-0.83)	<0.0001
Any cardiovascular hospital admission	977 (30)	1122 (34)	0.85 (0.78-0.92)	0.0002
Cardiovascular death, or hospital admission for worsening HF, or hospital admission for non-fatal MI	852 (25)	979 (30)	0.82 (0.74-0.89)	<0.0001

Composite primary endpoint=Cardiovascular mortality or hospitalization for worsening HF; AF=atrial fibrillation; CI=confidence interval; HF=heart failure; HR=hazard ratio; MI=myocardial infarction

[a] Number of first events; [b] NNT (calculated number needed to treat for 22.9 months to prevent one cardiovascular death or one hospitalization for worsening HF)=24

- According to pre-specified subgroup analyses, there was a significant treatment effect in patients with a baseline heart rate ≥ 77 bpm, but not in the subgroup of patients with < 77 bpm at baseline (P for interaction 0.029). There was not a statistically significant difference in the primary endpoint with ivabradine compared to placebo in the subgroup of SHIFT patients who received ≥ 50% of beta-blocker target dose (HR 0.90, 95% CI 0.77 to 1.04; P=0.155); hospitalizations due to worsening HF was significantly reduced with ivabradine vs. placebo (HR 0.81, 95% CI 0.67 to 0.97; P=0.021) in this subgroup.[2]
- In a subgroup analyses based on baseline heart rate in the patients receiving placebo, it was noted that patients with a higher heart rate were at an increased risk compared to patients with lower baseline heart rate (e.g., pulse ≥ 87 vs. 70 to < 72: HR 2.34, 95% CI 1.84 to 2.98; P < 0.0001) for the composite primary endpoint. In addition, the greatest treatment effect with ivabradine appeared to be in those patients with the highest heart rates at baseline (e.g., ivabradine vs. placebo in patients with baseline pulse ≥ 87: HR 0.69, 95% CI 0.58 to 0.83; P value not provided) as well as in patients who achieved the lowest heart rate (< 60 bpm) compared to higher heart rates.[5]
- It was reported that 28% of patients had an improvement in NYHA functional class with ivabradine compared to 24% on placebo (P=0.001). Patient-reported global assessment improved in 72% on ivabradine vs. 68% of patients on placebo (P=0.0005), with an improvement in 61% on ivabradine compared to 57% of patients on placebo (P=0.0011) for the physician-reported global assessment.[2]
- The SHIFT study was sponsored by the pharmaceutical company Servier, France.[3] The investigators note that the sponsor was responsible for data management and final data analyses.[2]

Potential Off-Label Use[6-16]

- Ivabradine is approved outside the U.S. for the symptomatic treatment of long-term stable angina in patients with coronary artery disease who are in normal sinus rhythm. It is recommended in patients unable to be treated with a beta-blocker, or in combination with a beta-blocker in patients with symptoms despite treatment with a beta-blocker and who have a heart rate ≥ 70 bpm.[6] Ivabradine was found to have similar efficacy (exercise endpoints; N=939) compared to atenolol at 4 months, and compared to amlodipine at 3 months (exercise endpoints; N=1,195), in patients with chronic stable angina.[7,8] In patients with chronic stable angina treated with atenolol, the addition of ivabradine was more effective than placebo (exercise endpoints; N=889) at 4 months.[9]
- Ivabradine has also been studied in patients with coronary artery disease with or without stable HF.[10,11] In one trial (BEAUTIFUL) evaluating 10,917 patients with coronary artery disease, LVEF < 40%, and resting heart rate ≥ 60 bpm (without a specific requirement for treatment with a beta-blocker or dose), there was no significant difference in the primary composite endpoint of time to first cardiovascular death, hospitalization for acute myocardial infarction, or hospitalization for new-onset or worsening HF with ivabradine compared to placebo (HR 1.00, 95% CI 0.91 to 1.10). According to a pre-specified subgroup analysis of patients with a heart rate ≥ 70 bpm, there was no significant difference in the above endpoints with ivabradine, except for hospitalization for myocardial infarction (ivabradine 3.1% vs. placebo 4.9%).[10]
- In another trial (SIGNIFY), 19,102 patients with coronary artery disease without symptomatic HF (i.e., NYHA class I), ivabradine titrated to a heart rate of 55 to 60 bpm (beta-blocker not required) did not have a significant impact on the primary endpoint of first occurrence of cardiovascular death or myocardial infarction (HR 1.08, 95% CI 0.96 to 1.20; P=0.20). Patients with activity-limiting angina (Canadian Cardiovascular Society class II or higher) had a significant increased risk for the primary endpoint with ivabradine (7.6%) compared to placebo (6.5%); although, it was noted that patients could be titrated to a higher dose of ivabradine (i.e., 10 mg twice daily) than is FDA approved.[11]
- Ivabradine has been found to be effective in reducing symptoms in small short-term studies in patients with inappropriate sinus tachycardia,[12-15] and in a small retrospective case series of patients with postural orthostatic tachycardia syndrome (POTS).[15,16]

Safety[1,2]

(for more detailed information refer to the product package insert)

	Comments
Contraindications[1]	• Acute decompensated HF • Blood pressure < 90/50 mm Hg • Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present • Resting heart rate < 60 bpm prior to treatment • Severe hepatic impairment (Child-Pugh C) • Pacemaker dependence (heart rate maintained exclusively by the pacemaker) • Concomitant strong cytochrome CYP3A4 inhibitors
Warnings/Precautions[1,2]	• Fetal toxicity: based on animal studies, ivabradine may cause fetal toxicity if administered to pregnant women. Refer to product information for additional details. Females should be advised to use effective contraception when taking ivabradine. • Atrial fibrillation: ivabradine increases the risk for atrial fibrillation (5.0% vs. 3.9% per patient-year for ivabradine compared to placebo, respectively);[2] it is recommended to regularly monitor cardiac rhythm, and to discontinue ivabradine if atrial fibrillation occurs. • Bradycardia and conduction disturbances: bradycardia, sinus arrest, and heart block have occurred with ivabradine. Bradycardia has been reported to occur in 6.0% (2.7% symptomatic; 3.4% asymptomatic) per patient-year on ivabradine compared to 1.3% with placebo. According to the product information, risk factors for bradycardia include: sinus node dysfunction, conduction defects (e.g., 1st or 2nd degree AV block, bundle branch block), ventricular dyssynchrony, use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, amiodarone). It is noted that diltiazem or verapamil may result in lowering of the HR, as well as increase exposure to ivabradine with concomitant use; therefore, use of these medications with ivabradine should be avoided. It is recommended that ivabradine be avoided in patients with 2nd degree AV block unless a functioning demand pacemaker is present.

Safety Considerations[1,17]

- Clinically significant adverse reactions include: fetal toxicity; atrial fibrillation; bradycardia and conduction disturbances.
- According to a meta-analysis of 21,571 patients, the risk of atrial fibrillation with ivabradine treatment was 1.15 (95% CI 1.07 to 1.24; P=0.0027), with an estimated number needed to harm (NNH) of 208 per year of treatment (95% CI 122 to 667).[17]

Adverse Reactions[1,2]

Common adverse reactions[1,2]	In SHIFT, the following adverse events were reported (ivabradine vs. placebo, respectively): all adverse events (75% vs. 74%; P=0.303); heart failure (25% vs. 29%; P=0.0005); symptomatic bradycardia (5% vs. 1%; P<0.0001); asymptomatic bradycardia (6% vs. 1%; P<0.0001); atrial fibrillation (9% vs. 8%; P=0.012); phosphenes (3% vs. 1%; P<0.0001); blurred vision (1% vs. < 1%; P=0.042).[2] The most common adverse drug reactions (≥ 1.0% higher with ivabradine vs. placebo, and in > 1% of patients on ivabradine) reported in the product information include (ivabradine vs. placebo, respectively): bradycardia (10.0% vs. 2.2%); hypertension, blood pressure increase (8.9% vs. 7.8%); atrial fibrillation (8.3% vs. 6.6%); phosphenes, visual brightness (2.8% vs. 0.5%).[1] Phosphenes, or luminous phenomena, are described in the ivabradine product information as "transiently enhanced brightness in a limited area of the visual

	field, halos, image decomposition (stroboscopic or kaleidoscopic effects), colored bright lights, or multiple images (retinal persistency)" that are typically triggered by sudden variations in the intensity of light. The effect of ivabradine on retinal photoreceptors is thought to be the result of the phenomena. Ivabradine inhibits the retinal current I_h, which is involved in limiting the retinal response to bright light stimuli. The onset is reported to be within the first 2 months of treatment, with the possibility of symptoms continuing to repeatedly occur. It is also reported that symptoms were mild to moderate intensity, with < 1% of patients discontinuing therapy, and most resolving during or after treatment.[1]
Death/Serious adverse reactions[2]	In SHIFT, 45% of patients treated with ivabradine experienced a serious adverse event (SAE) compared to 48% of patients in the placebo group (P=0.025). Cardiac disorders were reported as the most common SAE occurring in 28% of patients in the ivabradine treatment group and 30% on placebo. Other select SAEs that were reported more frequently with ivabradine vs. placebo, respectively, included: renal and urinary disorders (2% vs. 1%; P=0.685); eye disorders (1% vs. < 1%; P=0.374).[2] Deaths were reported in the context of all-cause mortality, with 503 (16%) deaths in the ivabradine treatment group compared to 552 (17%) on placebo (HR 0.90, 95% CI 0.80 to 1.02; P=0.092).[2]
Discontinuations due to adverse reactions[2]	Ivabradine vs. placebo, respectively: overall (14% vs. 13%; P=0.051); heart failure (2% vs. 3%; P=0.367); symptomatic bradycardia (1% vs. < 1%; P<0.002); asymptomatic bradycardia (1% vs. < 1%; P<0.0001); atrial fibrillation (4% vs. 3%; P=0.137); phosphenes (< 1% vs. < 1%; P=0.224); blurred vision (< 1% vs. < 1%; P=1.000).[2]

Drug Interactions[1]

Drug-Drug Interactions[1]

- **Cytochrome P450 interactions:** ivabradine is primarily metabolized by CYP3A4; therefore, concomitant use of strong CYP3A4 inhibitors including azole antifungals (e.g., itraconazole, ketoconazole), macrolide antibiotics (e.g., clarithromycin, telithromycin), HIV protease inhibitors (e.g., nelfinavir), and nefazodone are contraindicated due to the potential for increased plasma concentrations of ivabradine that may result in exacerbation of bradycardia and conduction disturbances. Concomitant use of moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, grapefruit juice), or CYP3A4 inducers (e.g., St. John's wort, rifampicin, barbiturates, phenytoin) should be avoided.
- **Negative chronotropes:** The majority of patients treated with ivabradine will also be receiving treatment with a beta-blocker. There is an increased risk for bradycardia in patients who are receiving medications that also slow heart rate (e.g., amiodarone, beta-blockers, digoxin). Heart rate should be monitored in patients receiving ivabradine in addition to other agents that are negative chronotropes.
- **Pacemakers:** ivabradine is not recommended in patients with a demand pacemaker set to a rate of $\geq$ 60 bpm as these patients were not studied in the clinical trials and these patients are unable to achieve a target heart rate of < 60 bpm (and the use of ivabradine is to a target heart rate of 50 to 60 bpm).

Drug-Food Interactions[1]

- With food, the absorption of ivabradine is delayed approximately 1 hour and plasma exposure is increased by 20 to 40%. It is recommended that ivabradine be administered with meals.

Risk Evaluation

As of July 1, 2015

	Comments
Sentinel event advisories	• None
Look-alike/sound-alike error potentials	Look-alike/sound-alike error potentials NME Drug Name: Ivabradine 5mg, 7.5 mg tab — Lexi-Comp: None — First DataBank: None — ISMP: None — Clinical Judgment: Isradipine NME Drug Name: CORLANOR — Lexi-Comp: None — First DataBank: None — ISMP: None — Clinical Judgment: Corlopam, Cortalone, Cangrelor • Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations[2,18-21]

- At baseline, 56% of patients were at ≥ 50% of beta-blocker target dose; with only 26% of patients at target dose. It was noted that doses of the beta-blockers were maintained during the trial without a need to decrease the dose in order to titrate ivabradine.[2] There was not a statistically significant difference in the primary endpoint with ivabradine compared to placebo in the subgroup of SHIFT patients who received ≥ 50% of beta-blocker target dose (HR 0.90, 95% CI 0.77 to 1.04; P=0.155); hospitalizations due to worsening HF was significantly reduced with ivabradine vs. placebo (HR 0.81, 95% CI 0.67 to 0.97; P=0.021) in this subgroup.[2] In another subgroup analysis of the SHIFT data, it was suggested that the extent of heart rate reduction with beta-blocker therapy in addition to ivabradine was of greater influence than the dose of beta-blocker.[18]
- Per request of the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use, the manufacturer evaluated the SHIFT data based on baseline heart rate to determine a threshold for providing mortality benefit. A post hoc subgroup analysis of patients with a baseline resting heart rate of ≥ 75 bpm demonstrated a statistically significant reduction in all-cause mortality as well as the primary and all secondary endpoints.[19] In patients with a heart rate ≥ 75 bpm, ivabradine decreased the primary endpoint (HR 0.76, 95%CI 0.68 to 0.85; P<0.0001); as well as all-cause mortality (HR 0.83, 95% CI 0.72 to 0.96; P=0.0109) and cardiovascular mortality (HR 0.83, 95% CI 0.72 to 0.96; P=0.0109), the latter two which were not statistically significant with ivabradine in the overall analysis of SHIFT data.[2,20] It was also noted that the optimal reduction based on heart rate was < 60 bpm or reduction of > 10 bpm. In this subgroup analysis, there were no significant reductions in the outcomes in patients with baseline heart rate < 75 bpm.[19] Marketing approval by the EMA for ivabradine in heart failure is in patients with NYHA class II to IV with systolic dysfunction, in patients with sinus rhythm with a heart rate ≥ 75 bpm, in addition to standard therapy that includes a beta-blocker or when a beta-blocker is contraindicated or not tolerated.[19,20]
- The European Society of Cardiology HF Guidelines (2012) include considerations for use of ivabradine to reduce the risk for HF hospitalization in patients in sinus rhythm with LVEF ≤ 35% and heart rate ≥ 70 bpm and persistent NYHA Class II to IV symptoms despite treatment with an evidence-based, or maximally tolerated, dose of a beta-blocker, in addition to an ACEI (or ARB), and mineralocorticoid receptor antagonist (Class IIa Recommendation; Level of Evidence B). These guidelines also suggest that ivabradine may be considered in patients who fit the criteria as stated above, and who are unable to tolerate a beta-blocker (Class IIb Recommendation; Level of Evidence C).[21]

Dosing and Administration[1]

- The recommended starting dose of ivabradine is 5 mg twice daily, to be administered with meals (with food, the absorption of ivabradine is delayed approximately 1 hour and plasma exposure is increased by 20 to 40%).
- After 2 weeks, the patient should be assessed, with dose adjustments based on heart rate (refer to table below):

Heart Rate	Dose Adjustment
> 60 bpm	Increase by 2.5 mg (given twice daily), up to a maximum dose of 7.5 mg twice daily
50 to 60 bpm	No change in dose
< 50 bpm or signs & symptoms of bradycardia	Decrease by 2.5 mg (given twice daily); if the current dose is 2.5 mg twice daily, discontinue therapy

Special Populations (Adults)[1]

	Comments
Elderly	• There was no difference in the pharmacokinetics of ivabradine in patients ≥ 65 years of age or in patients ≥ 75 years of age compared to the general population. It is noted that data with ivabradine in patients ≥ 75 years of age are limited.
Pregnancy	• Based on animal studies, ivabradine may cause fetal harm in pregnant women. Females receiving ivabradine should use effective contraception.
Lactation	• There is no information on ivabradine in human breast milk; however, breastfeeding is not recommended with ivabradine due to the potential risk to the infant based on animal studies.
Renal Impairment	• No dosage adjustment is needed in patients with renal impairment with a creatinine clearance (CrCl) 15 to 60 ml/min. There are no data available in patients with CrCl < 15 ml/min.
Hepatic Impairment	• No dosage adjustment is required for patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment. Ivabradine is contraindicated in patients with severe (Child-Pugh C) hepatic impairment, as it has not been studied in this patient population and it is anticipated that there would be an increase in systemic exposure of the drug.
Pharmacogenetics/genomics	• No data identified.

Projected Place in Therapy

- Approximately 5.7 million patients in the U.S. have heart failure, with > 850,000 new cases diagnosed each year.[22] Heart failure increases with age, and it is estimated that over 5% of patients who receive care from the VA have a primary diagnosis of HF.[23] Mortality rates are high, at approximately 50% within 5 years of being diagnosed with HF.[4,22] Risk for rehospitalization is also high, with patients hospitalized for HF having a one month readmission rate of 25%.[4]
- Several pharmacologic treatments have been shown to reduce mortality and hospitalizations in patients with HF.[4] Evidence-based guideline directed medical therapy includes an ACEI (or ARB, if ACEI intolerant) and a beta-blocker (i.e., bisoprolol, carvedilol, or metoprolol succinate) for most patients. Treatment with a mineralocorticoid receptor antagonist has also been shown to reduce morbidity and mortality in patients with HF, and is recommended where appropriate and in patients where safety can be monitored.[4] The majority of patients in SHIFT were receiving treatment with these medications at baseline (e.g., beta-blockers 90%; ACEI 79% or ARB 14%; mineralocorticoid receptor antagonist 60%).[2] The combination of hydralazine and isosorbide dinitrate was found to reduce mortality and hospitalization and is recommended in African American patients who remain symptomatic despite treatment with an ACEI, beta-blocker and mineralocorticoid receptor antagonist.[4] It is noted that black patients did not represent a large proportion of the population studied in SHIFT.[2] Sacubitril/valsartan, a combination therapy that was not available during SHIFT, is another therapy for select patients with HF and reduced ejection fraction that demonstrated a significant reduction in death from cardiovascular causes or HF hospitalization compared to an ACEI.[24]

- Digoxin may be considered in patients with persistent symptoms despite guideline directed medical therapy, to reduce HF hospitalizations.[4,25] This recommendation is based on the Digitalis Investigators Group (DIG) trial, that evaluated the benefit of digoxin in 6,800 patients with HF and LVEF ≤ 45%, in addition to a diuretic and ACEI, on survival. Although there was no significant difference in the primary outcome of all-cause mortality, or in cardiovascular mortality, treatment with digoxin significantly decreased the risk for hospitalization due to worsening HF by 28% (digoxin 26.8% vs. placebo 34.7%; Risk Ratio 0.72; 95% CI 0.66 to 0.79; P<0.001; calculated NNT=13 over 37 months).[25] It is noted that only 22% of patients were receiving digoxin at baseline in SHIFT.[2]
- Results from SHIFT demonstrated a statistically significant reduction in the composite primary outcome of cardiovascular death or hospital admission for worsening heart failure with ivabradine (24%) compared to placebo (29%) (HR 0.82, 95% CI 0.75 to 0.90; P<0.001; calculated NNT=24 over 22.9 months) in the 6505 patients analyzed. Results were driven primarily by the reduction in hospitalizations for worsening HF with ivabradine (16%) compared to placebo (21%) (HR 0.74, 95% CI 0.66 to 0.83; P<0.001; calculated NNT=21 over 22.9 months; adjusted NNT=13 over 37 months [for comparison to DIG trial]). Cardiovascular death was not significantly reduced with ivabradine (P=0.128).[2]
- According to a survey of 824 patients with HF presenting for a clinic visit, 25% of patients had a LVEF ≤ 35%, and of these patients, 142 (70%) were in sinus rhythm. Of 58 patients with LVEF ≤ 35%, heart rate ≥ 70 bpm, and in sinus rhythm, it was estimated that 43% of these patients might be eligible for ivabradine (according to European Society of Cardiology guidelines).[26]
- Treatment with ivabradine may be considered in patients with HF and LVEF ≤ 35%, who are in sinus rhythm, with a resting heart rate ≥ 70 bpm, on a maximally tolerated dose of a beta-blocker or with a contraindication to a beta-blocker. It was noted that the benefit of ivabradine in patients receiving ≥ 50% target dose of beta-blocker was not as robust. Every effort should be made to implement maximally tolerated doses of guideline directed medical therapy as discussed above, prior to considering ivabradine. Although different treatment populations in the trials,[2,25] given the similar benefit in reducing HF hospitalizations, place in therapy of digoxin vs. ivabradine should be determined on a case by case basis, taking into consideration patient specific factors, as well as price for the medication.
- Overall, there is moderate quality of evidence (Refer to Appendix A) for the use of ivabradine in a non-U.S. population to reduce the risk for hospitalization for worsening HF, or composite cardiovascular death or HF hospitalization, in patients with symptomatic HF and LVEF ≤ 35%, who are in sinus rhythm with a resting heart rate ≥ 70 bpm, and were hospitalized for worsening HF in the past year, and are currently stable on guideline directed medical therapy for HF including optimized treatment with a beta-blocker.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199.