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New Drug Evaluation: ivabradine tablet, oral

Date of Review: September 2015
Generic Name: ivabradine
PDL Class: not applicable

End Date of Literature Search: July 1, 2015
Brand Name (Manufacturer): CORLANOR® (Amgen, Inc.)
Dossier Received: yes

Research Questions:

1. What is the current evidence for the efficacy of ivabradine to reduce to reduce mortality and cardiovascular (CV) morbidities; and if available, how does the drug's efficacy compare to other drugs used to manage chronic heart failure with reduced ejection fraction (HFrEF)?
2. Based on the evidence available, does ivabradine have a clear place in therapy for management of chronic HFrEF?
3. How well is ivabradine tolerated in patients; and if available, how does the safety of ivabradine compare to other drugs used to manage chronic HFrEF?
4. Are there subgroups of patients in which ivabradine may be safer or more effective than other drugs used to manage chronic HFrEF?

Conclusions:

- Evidence for use of ivabradine is based on one 23-month clinical trial (n=6,505) with low overall risk bias.[1] The study was composed of patients with stable, mildly symptomatic HFrEF (New York Heart Association [NYHA] Classes II and III) with a mean ejection fraction (EF) of 32% in normal sinus rhythm with a minimum resting heart rate (HR) of 70 beats-per-minute (BPM).[1] Patients in the study remained on standard HF therapy, which typically included an ACE-inhibitor [ACE-I] or angiotensin-2 receptor blocker [ARB]), beta-blocker, diuretic(s), and an aldosterone antagonist.[1]
- There is low quality evidence, based on a secondary endpoint, that ivabradine 5-7.5 mg twice daily (BID) may reduce risk of hospitalizations for heart failure (HF) by 4.7% compared to placebo (15.9% vs. 20.6%, respectively; Hazard Ratio [HR]=0.74; 95% Confidence Interval [CI], 0.66-0.83; p<0.0001; number needed-to-treat [NNT] =22).[1] However, ivabradine does not appear to be any different from placebo in regards to ability to reduce all-cause or CV-related mortality in these patients.[1]
- Overall, studies that evaluated other populations provide moderate quality evidence that ivabradine does not reduce CV outcomes or mortality in patients with HFrEF in normal sinus rhythm when baseline resting HR is not considered,[2] or in CAD patients without HF.[3]
- There is moderate quality evidence ivabradine can cause asymptomatic and symptomatic bradycardia.[1–3] Negative chronotropic drugs such as non-dihydropyridine calcium channel blockers (i.e., diltiazem and verapamil), or amiodarone increases risk for adverse events with ivabradine.[4]
- There is moderate quality evidence ivabradine increases risk for development of atrial fibrillation.[1,3] Ivabradine should be avoided in patients with atrial fibrillation and should be discontinued if it develops after starting the drug.[4]

Recommendation:

- Restrict use of ivabradine to populations where it has demonstrated some efficacy. See **Appendix 2** for the proposed prior authorization criteria.

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Date: September 2015

Background:

The goals of management of HFrEF (ie, systolic HF) are to prevent hospital admission and improve survival, and to relieve signs (eg, edema) and symptoms (eg, dyspnea).[5] The cornerstone of drug therapy in chronic HFrEF is inhibition of the neurohormonal activation present in HFrEF that promotes cardiac remodeling.[5,6] The most well-studied system in the renin-angiotensin-aldosterone system (RAAS), and inhibition of RAAS has shown to have a significant impact on the pathophysiology and progression of HF.[5,6] Drugs that inhibit neurohormonal activation in HFrEF have consistently proven to reduce all-cause mortality in chronic HFrEF patients (NYHA class I-IV).[5,6] These drugs include an ACE-I (alternatively, an ARB if an ACE-I is not tolerated), a select beta-blocker (bisoprolol, carvedilol, or sustained-release metoprolol succinate), and for most patients, a mineralcorticoid (aldosterone) receptor antagonist (spironoloactone or eplerenone).[5,6]

An ACE-I can reduce mortality and hospitalizations, improve symptoms, exercise tolerance and performance, and improve quality of life in patients with HFrEF.[5,6] The benefits of ACE inhibition are seen in patients with mild, moderate or severe symptoms of HF and in patients with or without CAD.[6] The addition of a beta-blocker to an ACE-I further improves morbidity outcomes and mortality in these patients.[5] Long-term treatment with the aforementioned beta-blockers also improve symptoms of HF, improve functional status, and enhance the patient's overall sense of well-being.[5,6] However, these benefits should not be considered a class effect. Other beta-blockers, including metoprolol tartrate, were less effective in HF trials.[6] Nebivolol demonstrated a modest but non-significant reduction in the primary endpoint of all-cause mortality or CV hospitalization but did not affect mortality alone in an elderly population with both reduced and preserved EF.[7] Aldosterone antagonists are recommended to reduce morbidity and mortality in patients with NYHA class III-IV who have reduced EF (≤35%), though their benefits probably extend to all patients with HFrEF.[5,6] Patients with NYHA class II with reduced EF also benefit from an aldosterone antagonist if they have a history of previous CV hospitalization or have elevated plasma natriuretic peptide levels.[6] However, renal function and potassium should be routinely monitored because of risk for hyperkalemia in susceptible patients, such as those with renal insufficiency.

In most controlled clinical trials that were designed to evaluate mortality, the dose of the ACE-I/ARB, beta-blocker and aldosterone antagonist was not determined by the patient's therapeutic response but was increased until the predetermined target dose was reached. Current guidelines recommend clinicians use every effort to reach the study doses achieved in clinical trials that have demonstrated efficacy to reduce CV events (see Table 1).[5,6]

Table 1. Drugs Shown to Improve Mortality/Morbidity in Chronic Heart Failure with Reduced Ejection Fraction. Adapted from 2012 ESC Guidelines.[5]

ACE Inhibitors	Angiotensin-2 Receptor Blockers	Beta-Blockers	Aldosterone Antagonists
• Captopril 50 mg TID* • Enalapril 10-20 mg BID • Lisinopril 20-35 mg QDay^ • Ramipril 5 mg BID • Trandolapril 4 mg QDay*	• Candesartan 32 mg QDay • Losartan 150 mg QDay^ • Valsartan 160 mg BID	• Bisoprolol 10 mg Qday • Carvedilol 25-50 mg BID • Metoprolol succinate (XL/ER) 200 mg QDay	• Eplerenone 50 mg QDay • Spironolactone 25-50 mg QDay

Abbreviations: BID = twice daily; QDay = once daily; TID = three times daily; XL/ER = extended-release formulation

* Indicates an ACE inhibitor where the dosing target is derived from post-myocardial infarction trials.

^ Indicates drugs where a higher dose has been shown to reduce morbidity/mortality compared with a lower dose of the same drug, but there is no substantive placebo-controlled randomized controlled trial and the optimum dose is uncertain.

There are also other therapeutic options for management of HFrEF that do not inhibit RAAS or other components of neurohormonal activation. Hydralazine and isosorbide dinitrate has shown to decrease morbidity and mortality in self-identified African-Americans/Blacks with NYHA class III-IV and reduced EF.[6] Digoxin has no effect on survival, but it can have a modest effect on reducing hospitalizations regardless of the underlying rhythm or cause of HF (ischemic or non-ischemic cardiomyopathy).[6] Ivabradine inhibits I_f channels in the sinoatrial node of the heart, which acts as a pacemaker by slowing the heart rate; but unlike beta-blockers, ivabradine does not have an effect on myocardial contractility or intracardiac conduction.[4] In Europe, consideration for ivabradine is given to

reduce HF hospitalization in patients in normal sinus rhythm with HFrEF (EF ≤35%), a baseline resting HR of 70 BPM or more, and persistent symptoms (NYHA class II-IV) despite a recommended dose of a beta-blocker, an ACE-I/ARB and an aldosterone antagonist.[5] Ivabradine was recently approved by the U.S. Food and Drug Administration for a similar indication as that recommended in Europe.[4]

Previous evidence has shown increased HR, even at relatively low rates of 77-82 BPM, in patients with CAD is associated with higher higher CV mortality and CV complications.[8] In patients with HF with preserved EF (HFpEF), every increase in HR by 10 BPM was associated with a statistically significant 7% increased risk of all-cause mortality, and 8% increased risk of CV death or hospital admission for HF.[9] In patients with confirmed CAD and HFrEF, a baseline resting HR of 70 BPM or higher was associated with 34% higher risk for CV death, 53% increase in hospital admission for HF, and 46% increase in hospital admission for myocardial infarction (MI), which were statistically significant differences relative to a baseline resting HR lower than 70 BPM.[10] Patients with symptomatic HFrEF (NYHA Class II or higher) with high resting HR (≥87 BPM) were at a 3.5-fold higher risk for death from HF, and almost 2-fold higher risk for all-cause mortality and CV mortality than patients with a resting HR under 72 BPM.[11] However, decreasing HR may not necessarily improve CV risk. For example, sustained-release metoprolol succinate reduced mortality and hospitalizations independent of resting baseline HR, change in HR from baseline, or the HR achieved at the end of study follow-up.[12]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
The first large trial (median duration 19 months; n=10,917) of ivabradine was a fair-quality study called "morBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary artery disease and left-ventricULar dysfunction" (i.e., "BEAUTIFUL").[2] The study was a multi-centered, double-blind, randomized, controlled trial (RCT) that compared ivabradine 5 mg twice daily (BID), titrated up to 7.5 mg BID if tolerated, to placebo in mostly males with NYHA Class II HF. Most patients enrolled into the study were on appropriate concurrent HF therapies, including ACE-Is or ARBs (90%), beta-blockers (84%), aspirin or other antithrombotic agent (94%), and lipid lowering therapy (i.e., statins) (90%). Patients enrolled into the study had a mean left-ventricular ejection fraction (LVEF) of 32% and had stable CAD, defined as previous MI at least 6 months prior to enrollment, previous interventional coronary revascularization at least 6 months prior to enrollment, or patients with evidence of at least 1 major coronary artery with at least 50% occlusion. In addition, patients had to be in normal sinus rhythm with a resting HR of at least 60 BPM. The mean age in the study was 65 years and 82% were males. The primary endpoint was a composite of CV death, hospital admission for MI, or hospital admission for new-onset or worsening HF. CV death was defined as sudden cardiac death, death from a vascular procedure, death from arrhythmia, death from stroke, death from any vascular event, or sudden death from an unknown cause. The primary endpoint occurred in 15.4% of patients receiving ivabradine (mean dose 6.18 mg BID) and 15.3% of patients receiving placebo (hazard ratio [HR] =1.00 (95% confidence interval [CI], 0.91 to 1.10; p=0.94). In addition, there was a no significant difference in all secondary outcomes measured, including all-cause mortality, cardiac death, CV death (defined above), coronary revascularization, hospital admission for HF, and hospital admission for MI. The protocol was amended to evaluate a subgroup of patients with a resting HR of at least 70 BPM as data became available that ivabradine may be more beneficial in these patients. The subgroup analysis found a significant reduction in 2 secondary endpoints: hospital admission for MI, admission to hospital for MI or unstable angina, or coronary revascularization. There was no statistically significant difference between ivabradine and placebo for all other study endpoints, including the composite primary endpoint. Bradycardia was the most commonly associated adverse event (13%) attributed to ivabradine.[2]

The second trial (median duration 22.9 months) of ivabradine was a fair-quality study that evaluated the drug in patients (n=6505) with stable, symptomatic chronic HF (NYHA Classes II and III) with systolic dysfunction (LVEF ≤35%) and was titled the "Systolic Heart failure treatment with the If inhibitor ivabradine

Trial" (i.e., "SHIFT").[1] It was a multi-centered, double-blind, RCT that compared ivabradine 5 mg BID, titrated up to 7.5 mg BID if tolerated, to placebo in mostly White male subjects. Most patients enrolled into the study were on appropriate concurrent heart failure therapies, including ACE-I/ARBs (91%), and beta-blockers (89%); however, only 26% of the patients enrolled in the study were on target beta-blocker doses and under half (49%) were receiving 50% or more of the targeted beta-blocker dose, per the European Society of Cardiology (ESC).[5] No data were provided on the proportion of patients receiving target doses of ACE-Is or ARBs. Patients enrolled into the study had a LVEF of 29% and 84% regularly received diuretics. Only 2% were classified with NYHA Class IV HF. The mean age in the study was 60 years and 76% were males, mostly of Eastern European descent (no U.S. sites). The primary endpoint was a composite of CV death or hospital admission for worsening HF. CV death was defined as any sudden death unless an unequivocal non-CV cause of death was established. At 28 days, HR in patients on ivabradine fell by a mean 15.4 BPM compared to pre-treatment, which was a net reduction of 10.9 BPM (95% CI, 10.4-11.4) relative to placebo. The primary endpoint occurred in 24.5% of patients receiving ivabradine (mean dose 6.5 mg BID) and 28.7% of patients receiving placebo (absolute difference of 4.2%; HR =0.82 (95% CI, 0.75 to 0.90; p<0.0001; NNT=26 for 1 year). These data were driven by a reduction in the number of hospital admissions for worsening HF (15.9% vs. 20.6%; HR=0.74, 95% CI 0.66-0.83; p<0.0001) and not CV death (13.9% vs. 15.0%; HR=0.91, 95% CI 0.80-1.03; p=0.128). A sub-group analysis found that patients with a baseline resting HR of less than 77 BPM had a significant reduction in the composite primary endpoint, but there was no difference between the groups in patients with HR of 77 BPM or higher. Other secondary outcomes that demonstrated statistically significant reductions with ivabradine use included death attributed to HF (3.5% vs. 4.6%; HR=0.74, 95% CI 0.58-0.94; p=0.014), hospital admissions due to any CV reason (30.1% vs. 34.4%; HR=0.85, 95% CI 0.78-0.92; p=0.0002), and all-cause hospitalizations (38.0% vs. 41.5%; HR=0.89, 95% CI 0.75-0.90; p=0.003). However, there was no statistically significant difference in all-cause mortality between those receiving ivabradine (15.5%) and those receiving placebo (16.9%). In addition, there was no statistically significant difference in the primary endpoint in patients who were on at least 50% of the target beta-blocker dose as recommended by the ESC – a pre-specified secondary endpoint. A sub-group analysis of the study found there to be a direct association between HR achieved at 28 days and subsequent cardiac outcomes.[11] Patients with HRs lower than 60 BPM at 28 days on treatment had fewer primary composite endpoint events in the study (17.4%, 95% CI 15.3-19.6) than did patients with higher HRs.[11] However, there were statistically significant baseline differences in some confounding factors: patients enrolled into the study with lower baseline resting HRs were younger, had lower rates of current smoking status, had a higher LVEF, and lower NYHA classification status than patients with much higher baseline HRs.[11] Notable adverse events included symptomatic and asymptomatic bradycardia, which occurred at a statistically significantly greater extent with ivabradine.[1] More patients on ivabradine also experienced atrial fibrillation (9.5% vs. 7.7%), which occurred significantly more often than in patients receiving placebo (number needed to harm = 55 patients).[1]

The third trial (median duration 27.8 months) of ivabradine was a good-quality study that evaluated the drug in patients (n=19,102) with stable CAD but without any evidence of clinical HF and was titled "Study Assessing the Morbidity-Mortality Benefits of the I_f Inhibitor Ivabradine in Patients with Coronary Artery Disease" (i.e., "SIGNIFY").[3] The study was a multi-centered (no U.S. sites), double-blind, RCT that compared ivabradine 7.5 mg BID, adjusted to 5 mg, 7.5 mg or 10 mg BID if tolerated, to placebo in mostly White males without HF. Eligible patients had stable CAD, were in normal sinus rhythm, and a LVEF greater than 40% with a resting HR of 70 BPM or greater. However, patients had to have either activity-limiting angina pectoris (Canadian Cardiovascular Scale [CCS] class II or higher), a history of myocardial ischemia in the past year or were hospitalized for a coronary event in the past year. Otherwise, if patients did not meet one of the previous 3 criteria, they had to meet at least 2 other criteria put them at risk for a cardiac event, such as dyslipidemia, diabetes mellitus, current smoker, age 70 years or older, or peripheral artery disease. Most patients enrolled into the study were receiving ACE-I/ARBs (82.8%), beta-blockers (83.1%), aspirin or other antithrombotic agent (91.6%), and lipid lowering therapy (i.e., statins) (92.2%). Patients enrolled into the study had a mean age of 65 years and 72.4% were males. About 73% had a previous MI, 68% had a history of coronary revascularization, and 63% had activity-limiting angina. The primary endpoint was a composite of nonfatal MI and multiple outcomes under the umbrella term "cardiovascular death". CV death was defined as sudden cardiac death (from MI, coronary artery procedure, arrhythmia, HF or sudden death of unknown cause), death from a vascular procedure, fatal stroke, or non-sudden death from an unknown cause. The primary endpoint occurred in 6.8% of patients receiving ivabradine (mean dose 8.0 mg BID) and 6.4% of patients receiving placebo (HR =1.08; 95% CI, 0.96 to 1.20; p=0.20). In addition, there was a non-statistically significant difference in all secondary outcomes measured, including all-cause

mortality, cardiac death, CV death (defined above), fatal/non-fatal MI, coronary revascularization, and hospital admission for HF. Overall, the addition of ivabradine did not reduce CV events in patients with stable CAD without HF.[3]

Based on the evidence provided from these 3 trials, the FDA granted approval for the use of ivabradine to reduce risk of hospitalization for worsening HF in patients with stable, symptomatic chronic HF with a LVEF of 35% or less, who are in sinus rhythm with a resting HR of 70 BPM or more and either on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.[4] The approval was based on the efficacy demonstrated as a secondary endpoint in SHIFT, which showed a statistically significant 4.7% reduction in hospitalizations for worsening HF with ivabradine relative to placebo. Thus, 22 patients would need to be treated with ivabradine for nearly 2 years (22.9 months) to prevent 1 hospitalization for worsening HF. Based on the evidence available, patients that do not fit the criteria within the FDA approval will likely not benefit from ivabradine.

Clinical Safety:
A summary of the clinical safety of ivabradine will focus on the stable but symptomatic chronic HF population enrolled in SHIFT[1], which is the population for which the FDA has approved use of the drug. A summary of common adverse events associated with ivabradine is available in Table 2.

In SHIFT, symptomatic and asymptomatic bradycardia was more frequent in the ivabradine group than in patients taking placebo (both $p<0.001$).[1] The rate of bradycardia was 6.0% per patient-year in patients on ivabradine (2.7% symptomatic; 3.4% asymptomatic) and 1.3% per patient-year in patients treated with placebo. Bradycardia resulted in premature withdrawal from the study in 48 (1.5%) of patients on ivabradine and 10 (0.3%) of those on placebo.[1] Risk factors for bradycardia include sinus node dysfunction, conduction defects (e.g., 1st or 2nd degree atrioventricular block, bundle branch block), ventricular dyssynchrony, and use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, or amiodarone).[4] In addition, sinus arrest and heart block have occurred with use of ivabradine.[4] Therefore, patients on ivabradine should be monitored closely for signs and symptoms of bradycardia, especially early in therapy.

In SHIFT, the rate of atrial fibrillation was 5.0% per patient-year in patients on ivabradine and 3.9% per patient-year in patients treat with placebo. The manufacturer advises discontinuing ivabradine if atrial fibrillation develops.[4]

Table 2. Adverse Events with Rates ≥1% Higher with Ivabradine than Placebo Occurring in >1% of Patients Enrolled in SHIFT.[1,4]

Adverse Event	Ivabradine (n=3260)	Placebo (n=3278)
Bradycardia	10%	2.2%
Hypertension; Increased Blood Pressure	8.9%	7.8%
Atrial Fibrillation	8.3%	6.6%
Phosphenes, Visual Brightness	2.8%	0.5%

Phosphenes are phenomena described as a transiently enhanced brightness in a limited area of the visual field, halos, image decomposition, colored bright lights, or multiple images. Phosphenes are typically triggered by sudden variations in light intensity.[4]

According to the SHIFT investigators, there were no relevant between-group differences in laboratory parameters (unpublished data).[1]

Animal studies have shown ivabradine to result in embryo-fetal toxicity and cardiac teratogenic effects. It can therefore be assumed ivabradine may cause fetal toxicity when administered to pregnant women and it is advised females on ivabradine use effective contraception.[4]

Author: A. Gibler, Pharm.D. Date: September 2015

Look-alike / Sound-alike Error Risk Potential: The Institute for Safe Medication Practice (ISMP) has not updated their List of Confused Drug Names since approval of ivabradine.[13]

Pharmacology and Pharmacokinetic Properties:

Table 3. Basic Pharmacology and Pharmacokinetic Properties of Ivabradine.

Parameter	
Mechanism of Action	Specific inhibitor of the I_f current in the sinoatrial node, decreasing heart rate without affecting blood pressure, myocardial contractility, intracardiac conduction or ventricular repolarization.[4]
Oral Bioavailability	40% due to extensive first-pass metabolism and elimination in the gut and liver.[4]
Distribution and Protein Binding	Volume of distribution at steady state is about 100 L; approximately 70% of the drug in plasma is bound to protein.[4]
Elimination	Total clearance is 24 L/h, with renal clearance of about 4.2 L/h (4% unchanged in urine).[4]
Half-Life	Effective half-life is about 6 hours.[4]
Metabolism	Extensively metabolized in the liver and intestines by CYP 3A4-mediated oxidation.[4] The major metabolite is a N-desmethylated derivative that is as potent as ivabradine and circulates at about 40% that of ivabradine.[4]

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Mortality (all-cause, secondary to cardiovascular causes)
2) Hospitalizations (secondary to cardiovascular causes)
3) Symptom-relief (dyspnea on exertion, nocturnal dyspnea)
4) Quality-of-life

Primary Study Endpoints:
1) Composite (cardiovascular death*, hospital admission for MI, or hospital admission for HF)
2) Composite (cardiovascular death* or hospital admission for HF)
3) Composite (cardiovascular death* and nonfatal MI)

*Cardiovascular death was also a composite of several outcomes, which are defined individually in the Comparative Evidence Table.

Table 4. Comparative Evidence of Ivabradine.

Ref./ Study Design	Drug Regimens/ Median Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. BEAUTIFUL[2] MC, R, DB, PC PG	1. Ivabradine 5 mg BID x2 weeks, then 7.5 mg BID if resting HR ≥60 BPM (I) 2. Placebo (P) 19 months	Demographics: -Mean Age 64.6 y -82% Males -Mean HR 79.2 BPM -Mean LVEF 32% -NYHA I 14% -NYHA II 59% -NYHA III 27% -ACE-I/ARB 90% -Beta-blocker 84% Key Inclusion Criteria: -Age ≥55 y (or ≥18 years if have DM) -CAD (previous MI, previous coronary revascularization, or evidence ≥1 major coronary artery narrowed by ≥50%) -LVEF <40% -Normal sinus rhythm -Resting HR ≥60 BPM Key Exclusion Criteria: -MI or coronary revascularization previous 6 months -Stroke/TIA previous 3 months -Implanted pacemaker, cardioverter or defibrillator -Valvular disease -Sick sinus syndrome -Sinoatrial block -Congenital long QT -Complete AV block -Uncontrolled HTN -NYHA Class IV	ITT: I: n=5479 P: n=5438 Attrition: I: 28% P: 16%	Primary Endpoint: CV Death, Hospital Admission for MI, or Hospital Admission for HF: I: 15.4% vs. P: 15.3%; HR=1.00 (95% CI, 0.91-1.10; p=0.94) Secondary Endpoints: All-cause Mortality: I: 10.4% vs. P: 10.1%; HR=1.04 (95% CI, 0.92-1.16; p=0.55) Cardiac Death (death from MI, HF or cardiac surgery): I: 2.5% vs. P: 2.8%; HR=0.89 (95% CI, 0.71-1.12; p=0.33) CV Death (cardiac death, or death from vascular procedure, arrhythmia, stroke, other vascular event, or sudden death of unknown cause): I: 8.6% vs. P: 8.0%; HR=1.07 (95% CI, 0.94-1.22; p=0.32) Coronary Revascularization: I: 2.8% vs. P: 3.4%; HR=0.83 (95% CI, 0.67-1.02; p=0.078) Hospital Admission for HF: I: 7.8% vs. P: 7.9%; HR=0.99 (95% CI, 0.86-1.13; p=0.85) Hospital Admission for MI: I: 3.6% vs. P: 4.2%; HR=0.87 (95% CI, 0.72-1.06; p=0.16)	NS NS NS NS NS NS	Any Serious AE: I: 23% P: 23% P=NS Discontinuation due to AE: I: NR P: NR Bradycardia: I: 705 (13%) P: 79 (2%) P=NR Cardiac disorders: I: 18% P: 15% P<0.001	NS NR 11%/NR 3%/33	**Quality Rating**: FAIR **Internal Validity (Risk of Bias)**: Selection: (low) centralized, computer-generated randomization; demographic characteristics evenly matched. Performance: (mod) allocated by interactive web-response system to ensure allocation remained concealed; blinding not described. Detection: (mod) 2 major protocol amendments; power assumptions described; censoring rules appropriate; ITT analysis performed; assessors blinded. Attrition: (mod) high attrition, w/ 12% higher attrition w/ ivabradine but controlled w/ ITT. **Applicability**: Patient: patients w/ mild symptomatic HF; mostly male; unknown racial makeup; patients remained on appropriate HF therapies after enrollment (beta-blockers, ACE-Is, ARBs, statins, ASA, etc.). Intervention: mean dose of 6.18 mg BID; 40% remained on 7.5 mg BID. Comparator: placebo appropriate. Outcomes: composite primary outcome; clinically relevant individual outcomes; AEs only described by body system except for bradycardia. Setting: outpatient visits at 2 weeks, 1, 3 and 6 months; and every 6 months thereafter. **Analysis**: The drug sponsor used a subgroup analysis that found patients w/ HR ≥70 BPM may benefit from the following outcomes w/ ivabradine: hospital admission for MI, or hospital admission for coronary revascularization. The analysis was used to test the hypothesis in the SHIFT trial.

Author: A. Gibler, Pharm.D. Date: September 2015

2. SHIFT[1] MC, R, DB, PC PG	1. Ivabradine 5 mg BID x2 weeks, then 7.5 mg BID if resting HR >60 BPM; dose reduced by 2.5 mg if HR <50 BPM or symptomatic (I) 2. Placebo (P) 22.9 months	Demographics: -Mean Age 60.4 y -Male 76% -HR 79.9 BPM -LVEF 29% -NYHA II 48.7% -NYHA III 49.5% -NYHA IV 1.7% -Ischemic etiology 68% -Non-ischemic etiology 32% -Hypertension 67% -ACE-I/ARB 91% -Beta-blocker 89% -Diuretics 84% -Aldosterone antagonists 60% Key Inclusion Criteria: -Age ≥18 y -Stable, symptomatic HF ≥4 weeks -LVEF ≤35% -Normal sinus rhythm -Resting HR ≥70 BPM -Optimal and stable background HF therapy x ≥4 weeks -Previous hospitalization for HF in last 12 months Key Exclusion Criteria: -Recent MI <2 months -CVA/TIA <4 weeks -Ventricular or atrioventricular pacing operative ≥40% of day -Atrial fib/flutter -Symptomatic hypotension -HF from congenital disease or severe valvular disease -diltiazem/verapamil -Class I antiarrhythmic	mITT: I: n=3241 P: n=3264 Attrition: I: 21% P: 19%	Primary Endpoint: CV Death or Hospital Admission for HF: I: 24.5% vs. P: 28.7%; HR=0.82 (95% CI, 0.75-0.90; p<0.0001) Secondary Endpoints: CV Death or Hospital Admission for HF in Patients on ≥50% Target Beta-blocker Dose per the ESC*: I vs. P data NR; HR=0.90 (95% CI, 0.77-1.04; p=0.155) All-cause Mortality: I: 15.5% vs. P: 16.9%; HR=0.90 (95% CI, 0.80-1.02; p=0.092) Death from HF: I: 3.5% vs. P: 4.6%; HR=0.74 (95% CI, 0.58-0.94; p=0.014) CV Mortality: I: 13.9% vs. P: 15.0%; HR=0.91 (95% CI, 0.80-1.03; p=0.128) Hospital Admission for HF: I: 15.9% vs. P: 20.6%; HR=0.74 (95% CI, 0.66-0.83; p<0.0001) Hospital Admission for any CV reason: I: 30.1% vs. P: 34.4%; HR=0.85 (95% CI, 0.78-0.92; p=0.0002) All-cause Hospitalization: I: 38.0% vs. P: 41.5%; HR=0.89 (95% CI, 0.75-0.90; p=0.003)	 4.2%/24 NS 1.4%/NS 1.1%/91 1.1%/NS 4.7%/22 4.3%/24 3.5%/29	Serious AEs: I: 1450 (45%) P: 1553 (48%) p=0.025 Discontinuation due to AE: I: 467 (14%) P: 416 (13%) p=0.051 Symptomatic Bradycardia: I: 150 (4.6%) P: 32 (1.3%) p<0.0001 Asymptomatic Bradycardia: I: 184 (5.7%) P: 48 (1.5%) p<0.0001 Atrial Fibrillation: I: 306 (9.5%) P: 251 (7.7%) p=0.012 Phosphenes (transient enhanced brightness in a restricted area of the visual field): I: 89 (2.8%) P: 17 (0.5%) p<0.0001 Blurred Vision: I: 17 (1%) P: 7 (<1%) p=0.042	 NA NS 3.3%/30 4.2%/23 1.8%/55 2.3%/43 0.3%/333	**Quality Rating**: FAIR **Internal Validity (Risk of Bias)**: Selection: (low) centralized, computer-generated randomization with well-balanced demographics. Performance: (low) allocated by interactive web-response system to ensure allocation remained concealed; placebo identical in appearance, ensuring blinding maintained. Detection: (mod) power assumptions described; modified ITT analysis performed after 2 centers' data removed due to misconduct; imputation of missing data unclear; censoring rules unclear. Attrition: (low) 2% more patients on ivabradine (n=682) withdrew vs. placebo (n=605) (HR=1.14; 95% CI, 1.02-1.27; p=0.017). **Applicability**: Patient: majority White males w/ Class II or III NYHA HF; patients remained on appropriate HF therapies after enrollment (beta-blockers, ACE-Is, ARBs, statins, ASA, etc.), similar doses between groups; only 26% in each grp at target dose of beta-blocker. Intervention: mean dose 6.5 mg BID. Comparator: placebo appropriate. Outcomes: composite primary endpoint driven by decreased hospitalizations for HF; primary endpoint not significantly reduced in patients w/ baseline HR <77 BPM; primary endpoint also favors age <65 years; ivabradine resulted in a net HR reduction of 8.1 (95% CI, 8.5-9.7) BPM vs. placebo by end of study; all deaths categorized as CV deaths unless unequivocal non-CV cause established. Setting: no USA sites, mostly Eastern Europe (66%); outpatient clinic visits every 4 months. **Analysis**: Results of the trial were considered by the FDA to grant approval of the drug with specific criteria for use.

3. SIGNIFY[3] MC, R, DB, PC PG	1. Ivabradine 7.5 mg BID (5 mg BID if age ≥75 y). Dose adjusted to 5, 7.5 or 10 mg BID per HR (goal 55-60 BPM) and bradycardia symptoms (I) 2. Placebo (P) 27.8 months	Demographics: -Mean Age 65 y -72.4% Males -Mean HR 77.2 BPM -Mean LVEF 56.4% -73.3% previous MI -67.8% previous coronary revascularization -63.1% w/ activity-limiting angina (CCS class ≥II) Key Inclusion Criteria: -Age ≥55 y -Stable CAD w/o HF -LVEF >40% -Normal sinus rhythm -Resting HR ≥70 BPM And either: -≥1 major adverse prognostic factor: • angina pectoris (CCS class ≥2) • myocardial ischemia past 1 y • hospitalization for coronary event past 1 y -Or 2 minor adverse prognostic factors: • HDL <40 mg/dL or LDL >160 mg/dL (on meds) • T1DM or T2DM • PAD • Current smoking • Age ≥70 y Key Exclusion Criteria: -NYHA class II or higher -MI, coronary revascularization, stroke/TIA w/i 3 months	ITT: I: n=9550 P: n=9552 Attrition: I: 20.6% P: 14.5%	Primary Endpoint: Death from CV cause or nonfatal MI: I: 6.8% vs. P: 6.4%; HR=1.08 (95% CI, 0.96-1.20; p=0.20) Secondary Endpoints: All-cause mortality: I: 5.1% vs. P: 4.8%; HR=1.06 (95% CI, 0.94-1.21; p=0.35) Coronary Death (from MI, coronary artery procedure, arrhythmia, HF or sudden death of unknown cause): I: 2.8% vs. P: 2.6%; HR=1.06 (95% CI, 0.89-1.26; p=0.52) CV Death (coronary death; death from CV procedure; fatal stroke; non-sudden death of unknown cause): I: 3.4% vs. P: 3.2%; HR=1.10 (0.94-1.28; p=0.25) MI (fatal/non-fatal): I: 4.1% vs. P: 3.9%; HR=1.06 (95% CI, 0.92-1.22; p=0.43) Coronary Revascularization: I: 5.9% vs. P: 5.9%; HR=1.00 (95% CI, 0.89-1.12; p=0.98) Hospital Admission for HF: I: 2.3% vs. P:1.9%; HR=1.20 (95% CI, 0.99-1.46; p=0.07)	0.4%/NS 0.3%/NS NA/NS NA/NS NA/NS 0%/NS NA/NS	Serious AEs: I: 37.6% P: 35.4% p=0.001 Discontinuation due to AE: I: 13.2% P: 7.4% P<0.001 Symptomatic Bradycardia: I: 7.9% P: 1.2% p<0.001 Asymptomatic Bradycardia: I: 11.0% P: 1.3% p<0.001 Discontinuation due to Asymptomatic Bradycardia: I: 272 (2.8%) P: 17 (0.2%) p<0.001 Discontinuation due to Symptomatic Bradycardia: I: 194 (2.0%) P: 33 (0.3%) p<0.001 Atrial Fibrillation: I: 5.3% P: 3.8% p<0.001 Phosphenes: I: 5.4% P: 0.5% p<0.001	2.2%/45 5.8%/17 6.7%/14 9.7%/10 2.6%/38 1.7%/58 1.5%/66 4.9%/20	**Quality Rating**: GOOD **Internal Validity (Risk of Bias)**: Selection: (low) centralized, computer-generated randomization; demographics well-balanced between groups. Performance: (low) allocated by interactive voice/web-response system to ensure allocation remained concealed; matching placebo, ensuring blinding maintained. Detection: (mod) power assumptions described; true ITT analysis performed; data assessors remained blinded during study; censoring rules unclear. Attrition: (low) attrition high for ivabradine, w/ 6.1% more ivabradine patients who withdrew from study vs. placebo. **Applicability**: Patient: population studied different from previous trials (no HF); majority White males w/moderate angina but stable CAD; notable concurrent meds were beta-blockers (83.1%), ACE-I/ARB (82.8%), statins (92.2%), ASA (91.6%), diltiazem/verapamil (4.4%). Intervention: mean dose 8.2 mg BID. Comparator: placebo appropriate. Outcomes: composite primary outcome; ivabradine resulted in HR of 60.7 BPM at 3 months vs. 70.6 BPM w/ placebo; difference in HR maintained to end of study. Setting: no USA sites; outpatients visits at 1,2,3 and 6 months and every 6 months thereafter. **Analysis**: Well performed study confirmed lack of efficacy of ivabradine in CAD patients with preserved EF.

Abbreviations [alphabetical order]: ACE-I = ACE Inhibitors; AE = adverse events; ARB = angiotensin receptor blockers; ARR = absolute risk reduction; ASA = aspirin; AV = atrioventricular; BMI = body mass index; BPM = beats per minute; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society scale I-IV; CI = confidence interval; CV = cardiovascular; DB = double-blind; DM = diabetes mellitus; DF = ejection fraction; ESC = European Society of Cardiology; HDL = high-density lipoprotein cholesterol; HR = heart rate or hazard ratio; HTN = hypertension; ITT = intention to treat; LDL = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MC = multi-centered; MI = myocardial infarction; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; NYHA = New York Heart Association; PAD = peripheral artery disease; PC = placebo-controlled; PG = parallel-group; R = randomized; T1DM; type-1 diabetes mellitus; T2DM = type-2 diabetes mellitus; TIA = transient ischemic attack.

*Target doses: carvedilol: 25-50 mg BID; metoprolol succinate: 200 mg Qday; bisoprolol 10 mg Qday; nebivolol 10 mg Qday.[5]

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Appendix 1: Highlights of Prescribing Information[4]

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CORLANOR® safely and effectively. See full prescribing information for CORLANOR.

CORLANOR (ivabradine) tablets, for oral use
Initial U.S. Approval: 2015

---------- INDICATIONS AND USAGE----------

Corlanor (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use. (1)

----------DOSAGE AND ADMINISTRATION----------

- Starting dose is 5 mg twice daily. After 2 weeks of treatment, adjust dose based on heart rate. The maximum dose is 7.5 mg twice daily. (2)
- In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, initiate dosing at 2.5 mg twice daily. (2)

---------- DOSAGE FORMS AND STRENGTHS----------

Tablets: 5 mg, 7.5 mg (3)

---------- CONTRAINDICATIONS ----------

- Acute decompensated heart failure (4)
- Blood pressure less than 90/50 mmHg (4)
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present (4)
- Resting heart rate less than 60 bpm prior to treatment (4)
- Severe hepatic impairment (4)
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker) (4)
- In combination with strong cytochrome CYP3A4 inhibitors (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Fetal toxicity: Females should use effective contraception. (5.1)
- Monitor patients for atrial fibrillation. (5.2)
- Monitor heart rate decreases and bradycardia symptoms during treatment. (5.3)
- Not recommended in patients with 2nd degree AV block. (5.3)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions occurring in ≥ 1% of patients are bradycardia, hypertension, atrial fibrillation and luminous phenomena (phosphenes). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amgen Medical Information at 1-800-772-6436 (1-800-77-AMGEN) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

---------- DRUG INTERACTIONS----------

- CYP3A4 inhibitors increase Corlanor plasma concentrations and CYP3A4 inducers decrease Corlanor plasma concentrations. (7.1)
- Negative chronotropes: Increased risk of bradycardia, monitor heart rate. (7.2)
- Pacemakers: Not recommended for use with demand pacemakers set to rates ≥ 60 beats per minute. (7.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Breastfeeding not recommended. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2015

Ivabradine (Corlanor®)

Goals:

- Restrict use of ivabradine to populations in which the drug has demonstrated efficacy.
- Encourage use of ACE-inhibitors or angiotensin II receptor blockers (ARBs) with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.
- Encourage use of with demonstrated evidence of mortality reduction in heart failure with reduced ejection fraction.

Length of Authorization:

- 6 to 12 months

Requires PA:

- Ivabradine (Corlanor®)

Covered Alternatives:

- Preferred alternatives listed at http://www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for continuation of therapy (patient already on ivabradine)?	Yes: Go to Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code.	
3. Does the patient have current documentation of New York Heart Association Class II or III heart failure with reduced ejection fraction less than 40% (LVEF <40%)?	Yes: Go to #4	No: Pass to RPh. Deny for medical appropriateness
4. Is the patient in normal sinus rhythm with a resting heart rate of 70 beats per minute or greater (≥70 BPM)?	Yes: Go to #5	No: Pass to RPh. Deny for medical appropriateness

Approval Criteria		
5. Is the patient currently on a maximally tolerated dose of carvedilol, sustained-release metoprolol succinate, or bisoprolol; and if not, is there a documented intolerance or contraindication to each of these beta-blockers? *Note: the above listed beta-blockers have evidence for mortality reduction in chronic heart failure at these target doses and are recommended by national and international heart failure guidelines.[1,2] Carvedilol and metoprolol succinate are preferred agents on the PDL.*	Yes: Go to #6	No: Pass to RPh. Deny for medical appropriateness
6. Is the patient currently on a maximally tolerated dose of an ACE-inhibitor or an ARB; and if not, is there a documented intolerance or contraindication to both ACE-inhibitors and ARBs?	Yes: Approve for up to 6 months	No: Pass to RPh. Deny for medical appropriateness

Renewal Criteria		
1. Is the patient in normal sinus rhythm with no documented history of atrial fibrillation since ivabradine was initiated?	Yes: Approve for up to 12 months	No: Pass to RPh. Deny for medical appropriateness

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P&T / DUR Review: *9/15 (AG)*
Implementation: *TBD*

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