New Drug Overview
Corlanor® (Ivabradine)

Overview/Summary: Corlanor® (ivabradine) is a novel medication that received priority review designation from the Food and Drug Administration (FDA) and was granted fast track designation for patients with systolic heart failure (HF) who receive standard therapy and who have an elevated heart rate of 70 beats per minute (bpm) or greater.[1] It was approved to reduce the risk of hospitalization for worsening HF in adult patients who are either on maximally tolerated doses of β-blockers or have a contraindication to β-blocker use. This agent works by blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker I_f, which regulates heart rate. This results in heart rate reduction with no effect on ventricular repolarization or myocardial contractility.[2]

Heart failure affects more than five million adults in the U.S. and its prevalence is projected to increase by 25% by 2030.[3] The presence of multiple comorbidities poses significant challenges in the treatment and management of patients with HF. Atherosclerotic disease, diabetes, metabolic syndrome, obesity and uncontrolled hypertension are some of the predisposing risk factors for HF. Heart failure is a clinical syndrome caused by the inability of the heart to pump sufficient blood to meet the demands of the body. It can result from a number of cardiac diseases including those that reduce ventricular filling (diastolic dysfunction) and or myocardial contractility (systolic dysfunction). The cardinal manifestations of HF are dyspnea, fatigue and fluid retention.[4] Goals of HF therapy are clinical improvement of symptoms and ultimately a reduction in the risk of morbidity (including the rate of hospitalization) and mortality. Generally, loop diuretics are initiated first in individuals with overt HF to assist with fluid control. A β-blocker, an angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), and an aldosterone antagonist are the preferred antihypertensive agents as they have been shown to improve survival in patients with HF. For those who cannot tolerate these drugs, appropriate alternative agents include nitrates, some vasoselective calcium channel blockers (e.g., amlodipine and felodipine), and hydralazine.[5] Resting heart rate is a significant independent predictor of poor outcomes in patients with chronic symptomatic HF. Evidence suggests that cardiovascular (CV) risk associated with heart rate rises steeply at resting heart rates of 70 bpm and greater.[6] There are currently limited treatment options for those individuals with chronic HF whose symptoms are not controlled with guideline-recommended treatment leading to frequent hospitalizations.[7]

Table 1. Dosing and Administration

Generic Name (Trade Name)	FDA-Approved Indications	Pediatric Dose	Availability
Ivabradine	Chronic heart failure: Tablet: Initial, 5 to 60 mg QD with food*; maintenance, use lowest dosage that will maintain an adequate clinical response; maximum, undefined†	Safety and efficacy in children have not been established.	Tablet: 5 mg 7.5 mg

Evidence-based Medicine

- The approval of ivabradine was based mainly on global clinical data from a phase III, multicenter, randomized, double-blind, parallel-group, placebo-controlled SHIFT trial in 6,558 clinically stable patients in sinus rhythm with reduced left ventricular ejection fraction (LVEF) ≤ 35%, heart rate (HR) ≥ 70 bpm, and with a hospitalization for HF within the past 12 months.
    - Ivabradine significantly reduced the risk of hospitalization or cardiovascular death for worsening HF, with 672 (21%) of patients on placebo compared to 514 (16%) of those on ivabradine experiencing a hospital admission (hazard ration [HR], 0.74; 95% confidence interval [CI], 0.66 to 0.83; P<0.0001).
    - There was no favorable effect on the mortality component of the primary endpoint.

- CV deaths in the overall treatment group were not significantly reduced by ivabradine (P=0.128), but deaths due to HF did decrease significantly (HR, 0.74; 95% CI, 0.58 to 0.94; P=0.014).[9]

· Two additional double-blind, multi-center, placebo-controlled phase III trials evaluated the use of ivabradine compared to placebo in individuals with coronary artery disease (CAD).
  - The BEAUTIFUL study that ivabradine did not affect CV death or admission to hospital for MI or new-onset or worsening HF (HR, 1.00; 95% CI, 0.91 to 1.10; P=0.94) and there was no statistical significance seen with the ivabradine group compared to placebo for any of the mortality endpoints.[10]
  - The third phase III trial, SIGNIFY, evaluated the use of ivabradine compared to placebo in individuals with stable coronary artery disease but without clinically significant HF. There was no significant effect of ivabradine on the composite of death from CV causes or nonfatal MI or secondary endpoint of death from CV causes, nonfatal MI and death from any cause.[11]

Key Points

· According to Current Clinical Guidelines:
  - Consensus guidelines in the U.S. have not been updated to address this medication's place in therapy. However, the European Society of Cardiology (ESC) and the National Institute for Health Care Excellence (NICE) guidelines have both provided recommendations for the use of this agent in chronic HF.[7]
  - The 2013 guidelines from the American College of Cardiology Foundation/American Heart Association continue to recommend that all individuals with hypertension and lipid disorders should be controlled according to contemporary guidelines to lower the risk of HF.[8]
  - Specifically in Stage B-D HF with reduced ejection fraction, individuals should be given an ACE inhibitor to prevent symptomatic HF and reduce mortality (or an ARB if ACE inhibitor is contraindicated).[8]
  - In patients with a recent or remote history of myocardial infarction (MI) or acute coronary syndrome (ACS) and reduced ejection fraction (EF), a β-blocker such as bisoprolol, carvedilol or sustained-release metoprolol succinate, is recommended for all patients.[8]
  - In the case of volume overload, in New York Heart Association (NYHA) class II-IV patients, it is recommended to add a diuretic, unless contraindicated, to improve symptoms (loop diuretics are preferred).[8]
  - Other alternatives such as the combination of hydralazine and isosorbide dinitrate can be considered for those who cannot be given an ACEI or ARB because of drug intolerance, hypotension or renal insufficiency, unless contraindicated.[8]
  - Aldosterone receptor antagonists are also recommended to reduce morbidity and mortality following an acute MI in patients with a LVEF ≤ 40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.[8]

· Other Key Facts:
  - Ivabradine has a novel mechanism of action.
  - Ivabradine provides an alternative treatment option for individuals with chronic HF who cannot take β-blockers as part of their SOC regimen or as an adjunct treatment for those individuals not adequately treated with maximally tolerated doses of β-blockers and other SOC medications.
  - Ivabradine is only approved for a small subset of chronic HF individuals.
  - Ivabradine has not shown to provide a decreased risk of cardiovascular mortality.[9]
  - As noted in the product dossier, the results from the SIGNIFY Study are not directly applicable to the evaluation of benefit-risk in the chronic HF population as this study did not enroll any individuals with NYHA class II or greater.

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New Drug Review
Corlanor® (Ivabradine)

Overview/Summary

Corlanor® (ivabradine) is a novel medication that received priority review designation from the Food and Drug Administration (FDA) and was granted fast track designation for patients with systolic heart failure (HF) who receive standard therapy and who have an elevated heart rate of 70 beats per minute (bpm) or greater.[1] It was approved to reduce the risk of hospitalization for worsening HF in adult patients who are either on maximally tolerated doses of β-blockers or have a contraindication to β-blocker use. This agent works by blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac pacemaker I_f, which regulates heart rate. This results in heart rate reduction with no effect on ventricular repolarization or myocardial contractility.[2]

Heart failure affects more than five million adults in the U.S. and its prevalence is projected to increase by 25% by 2030.[3] The presence of multiple comorbidities poses significant challenges in the treatment and management of patients with HF. Atherosclerotic disease, diabetes, metabolic syndrome, obesity and uncontrolled hypertension are some of the predisposing risk factors for HF. Heart failure is a clinical syndrome caused by the inability of the heart to pump sufficient blood to meet the demands of the body. It can result from a number of cardiac diseases including those that reduce ventricular filling (diastolic dysfunction) and or myocardial contractility (systolic dysfunction). The cardinal manifestations of HF are dyspnea, fatigue and fluid retention.[4] Goals of HF therapy are clinical improvement of symptoms and ultimately a reduction in the risk of morbidity (including the rate of hospitalization) and mortality. Generally, loop diuretics are initiated first in individuals with overt HF to assist with fluid control. A β-blocker, an angiotensin converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB), and an aldosterone antagonist are the preferred antihypertensive agents as they have been shown to improve survival in patients with HF. For those who cannot tolerate these drugs, appropriate alternative agents include nitrates, some vasoselective calcium channel blockers (e.g., amlodipine and felodipine), and hydralazine.[5]

Resting heart rate is a significant independent predictor of poor outcomes in patients with chronic symptomatic HF. Evidence suggests that cardiovascular (CV) risk associated with heart rate rises steeply at resting heart rates of 70 bpm and greater.[6] There are currently limited treatment options for those individuals with chronic HF whose symptoms are not controlled with guideline-recommended treatment leading to frequent hospitalizations.[7]

Indications

Ivabradine is FDA-approved 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.

Pharmacokinetics

Table 1. Pharmacokinetics[2]

Generic Name	Onset (hours)	Renal Excretion (%)	Metabolism	Plasma Protein Bound (%)	Active Metabolites	Serum Half-Life (hours)
Ivabradine	1	4	CYP3A4; extensive	70	N-desmethylated derivative (S 18982)	6

Clinical Trials

The approval of ivabradine was based mainly on global clinical data from a phase III, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial named SHIFT (Systolic Heart Failure treatment with the I_f inhibitor ivabradine Trial). This trial compared the use of ivabradine to placebo in addition to standard of care (SOC) therapies in 6,558 clinically stable patients in sinus rhythm with reduced left ventricular ejection fraction (LVEF) ≤ 35%, heart rate (HR) ≥ 70 bpm, and with a hospitalization for HF within the past 12 months. The SOC generally included a β-blocker (89%), ACEI and/or ARB (91%), diuretics (83%) and an aldosterone antagonist (60%).[9]

The primary endpoint that was evaluated was the composite of CV death or hospital admission for worsening heart failure. For secondary endpoints, the composite of CV death or hospital admission for worsening heart failure in patients receiving ≥ 50% of the target daily dose of a β-blocker at randomization was evaluated as well as numerous others. Results showed that ivabradine significantly reduced the risk of hospitalization or cardiovascular death for worsening HF, with 672 (21%) of patients on placebo compared to 514 (16%) of those on ivabradine experiencing a hospital admission (hazard ration [HR], 0.74; 95% confidence interval [CI], 0.66 to 0.83; P<0.0001). The treatment effect, however, only reflected this reduction in the risk of hospitalization for worsening HF; there was no favorable effect on the mortality component of the primary endpoint. CV deaths in the overall treatment group were not significantly reduced by ivabradine (P=0.128), but deaths due to HF did decrease significantly (HR, 0.74; 95% CI, 0.58 to 0.94; P=0.014).[9]

Two additional double-blind, multi-center, placebo-controlled phase III trials evaluated the use of ivabradine compared to placebo in individuals with coronary artery disease (CAD). In the first, BEAUTIFUL, adults patients with impaired left ventricular systolic function and resting heart rate of ≥ 60 bpm with stable symptoms of heart failure and/or angina being treated with conventional cardiovascular medications for at least one month were enrolled. This outcomes study compared the effects of ivabradine compared to placebo in reducing cardiovascular events in 10,917 patients. The primary endpoint was the composite of time to first cardiovascular death, hospitalization for acute myocardial infarction, or hospitalization for new-onset worsening heart failure. Results from this trial showed that ivabradine did not affect CV death or admission to hospital for MI or new-onset or worsening HF (HR, 1.00; 95% CI, 0.91 to 1.10; P=0.94) and there was no statistical significance seen with the ivabradine group compared to placebo for any of the mortality endpoints.[10]

The third phase III trial, SIGNIFY, evaluated the use of ivabradine compared to placebo in individuals with stable coronary artery disease but without clinically significant HF. The dose of ivabradine in this study was initiated at a slightly higher dose of 7.5 mg twice daily and could be titrated up to 10 mg twice daily if necessary or down to 5 mg twice daily to achieve a target heart rate of 55 to 60 bpm. Results from this trial showed no significant effect of ivabradine on the primary endpoint of composite of death from CV causes or nonfatal MI or secondary endpoint of death from CV causes, nonfatal MI and death from any cause.[11] As noted in the product dossier, the results from the SIGNIFY Study are not directly applicable to the evaluation of benefit-risk in the chronic HF population as this study did not enroll any individuals with NYHA class II or greater.

Table 2. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Swedberg et al[9] SHIFT Ivabradine 5 mg BID vs placebo Following the 14–day titration period, doses were either increased to 7.5 mg BID (or corresponding placebo) if resting HR was > 60 bpm; continued on 5 mg BID if resting HR was 50 to 60 bpm; or decreased to 2.5 mg BID if resting HR < 50 bpm or patient had signs or symptoms related to bradycardia.	DB, MC, PC, PG, RCT Patients ≥ 18 years of age with symptomatic systolic HF in sinus rhythm with resting heart rate ≥ 70 bpm, a LVEF ≤ 35%, receiving maximally tolerated doses of β-blockers and other guidelines-based HF therapies and hospitalized for HF within 12 months prior to study entry	N=6,558 22.9 months	Primary: Composite of CV death or hospital admission for worsening HF Secondary: Composite of CV death or hospital admission for worsening HFin patients receiving ≥ 50% of the target daily dose of a β -blocker (as defined by ESC guidelines) at randomization; all-cause death, any CV death; death from HF; all-cause admission to hospital; any CV admission and the composite of CV, hospital admission for worsening HF or hospital admission for non-fatal MI	Primary: Compared to placebo, Ivabradine reduced the risk of the combined endpoint of hospitalization for worsening HF or cardiovascular death based on a time-to-event analysis (HR, 0.82; 95% CI, 0.75 to 0.90; P<0.0001). Secondary: The composite of cardiovascular death, or hospital admission for worsening HF or hospital admission for non-fatal MI was reduced for the ivabradine group compared to placebo (HR, 0.82; 95% CI, 0.74 to 0.89; P<0.0001). Hospital admissions for worsening HF occurred in 672 (21%) of patients on placebo versus 514 (16%) of those on ivabradine (HR, 0.74; 95% CI, 0.66 to 0.83; P<0.0001). All cause hospital admission was reduced in the ivabradine group compared to placebo (HR, 0.89; 95% CI, 0.82 to 0.96; P=0.003). Any CV hospital admission was also reduced in the ivabradine group compared to placebo (HR, 0.85; 95% CI, 0.78 to 0.92; P=0.0002). CV mortality was not significantly reduced in ivabradine group (P=0.128), but deaths due to HF did fall significantly (HR, 0.74; 95% CI, 0.58 to 0.94; P=0.014). Serious adverse events occurred at a lower rate in ivabradine group than in placebo (P=0.025). The incidence of symptomatic and asymptomatic bradycardia was more frequent in ivabradine group than in patients taking placebo (both P<0.0001). Reported visual symptoms occurred in 89 (3%) of patients taking ivabradine compared to < 1% in those taking placebo (P<0.0001).
Fox et al[10]	DB, MC, PC, RCT	N=10,917	Primary: Composite of CV	Primary: There was no significant difference between the ivabradine-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BEAUTIFUL Ivabradine 5 mg BID vs placebo Following the 14–day titration period, doses were increased to 7.5 mg BID if resting HR was ≥ 60 bpm; dose reduced from 7.5 mg to 5 mg BID if resting heart rate was < 50 bpm, or if they had signs or symptoms related to bradycardia; study drug was discontinued in patients given 5 mg BID if resting HR was < 50 bpm, or if they had signs or symptoms related to bradycardia.	Patients ≥ 55 years of age (18 years of age if diabetic) with documented CAD, LVEF < 40%, end-diastolic short-axis internal dimension > 56 mm by echocardiography, in normal sinus rhythm with resting heart rate ≥ 60 bpm, stable angina and/or HF symptoms for ≥3 months, and receiving optimal conventional cardiovascular medication on appropriate and stable doses for ≥1 month	Median duration of follow-up was 19 months with a maximum of 35 months	death or hospitalization for acute MI or new onset or worsening HF Secondary: Composite of hospitalization for acute coronary syndrome, for new onset or worsening HF, or coronary revascularization; mortality due to coronary artery disease; all-cause mortality; the individual components of the composite primary and secondary endpoints	and placebo-treated patients in CV death or admission to hospital for MI or new-onset or worsening HF (HR, 1.00; 95% CI, 0.91 to 1.10; P=0.94). A total of 1,119 patients died during the study, 572 (10%) in the ivabradine group and 547 (10%) in the placebo group (HR, 1.04; 95% CI, 0.92 to 1.16; P=0.55). Secondary: Ivabradine reduced secondary endpoints of admission to hospital for fatal or non-fatal MI in a prespecified subgroup of individuals with HR of ≥ 70 bpm (HR, 0.64; 95% CI, 0.49 to 0.84; P=0.001) and coronary revascularization (HR, 0.70; 95% CI, 0.52 to 0.93; P=0.016). This was not seen in the total study population. There was no statistical significance seen with the ivabradine group compared to placebo for any of the mortality endpoints (all-cause death: [HR, 1.04; 95% CI, 0.92 to 1.16; P=0.55]; cardiovascular death: [HR, 1.07; 95% CI, 0.94 to 1.22; P=0.32]; cardiac death: [HR, 0.89; 95% CI, 0.71 to 1.12; P=0.33]).
Fox et al[11] SIGNIFY Ivabradine 7.5 mg BID	DB, MC, PC, RCT Patients ≥ 55 years of age with documented and treated stable CAD with no evidence of	N=19,102 Median follow-up 27.8 months	Primary: Composite of death from CV causes or nonfatal MI Secondary:	Primary: There was no significant difference between the ivabradine group and the placebo group in the incidence of death from CV causes or nonfatal MI (6.8% and 6.4%, respectively; HR, 1.08; 95% CI, 0.96 to 1.20; P=0.20). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo ivabradine dose was titrated up to 10 mg BID or down to 5 mg BID to achieve a target HR of 55 to 60 bpm	clinical HF, in sinus rhythm with a resting HR of ≥ 70 bpm on two consecutive electrocardiographic readings and at least one major adverse prognostic factor, or two minor adverse prognostic factors or a LDL cholesterol level > 160 mg per deciliter		Death from CV causes, nonfatal MI and death from any cause	There was no significant difference between the ivabradine group and the placebo group in the incidence of death from CV causes (3.4% and 3.2%, respectively; HR, 1.10; 95% CI, 0.94 to 1.28; P=0.25), nonfatal MI (2.8% and 2.6%, respectively; HR, 1.06; 95% CI, 0.89 to 1.26; P=0.52) or death from any cause (5.1% and 4.8%, respectively; HR, 1.06; 95% CI, 0.94 to 1.21; P=0.35). The incidence of bradycardia was higher with ivabradine compared to placebo (18.0% vs. 2.3%; P<0.001).

*Study grading according to Agency for Healthcare Research and Quality (AHRQ) (See Appendix I for definition of ratings). Studies falling outside of the grading criteria defined by AHRQ will be noted as "Not Applicable". This indicates that the grading criteria did not appropriately fit the design of the included study, but that it was included due to the potential value of the presented data
Drug regimen abbreviations: BID=twice daily
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
BPM=beats per minute, CAD=coronary artery disease, CV=cardiovascular, ESC=European Society of Cardiology, HF=heart failure, HR=heart rate, LDL=low density lipoprotein cholesterol level, LVEF=left ventricular ejection fraction, MI=myocardial infarction

Special Populations

Table 3. Special Populations[2]

Special Population	Recommendations
Elderly	No pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population. However, ivabradine has only been studied in a limited number of patients ≥ 75 years of age.
Children	Safety and efficacy in children have not been established.*
Renal Dysfunction	No dosage adjustment is required for patients with creatinine clearance 15 to 60 mL/min. No data are available for patients with creatinine clearance below 15 mL/min.
Hepatic Dysfunction	No dosage adjustment required in patients with mild to moderate hepatic impairment. Contraindicated in severe hepatic impairment.
Pregnancy	Based on findings in animals, ivabradine may cause fetal harm when administered to a pregnant woman. Fetal and infant risk cannot be ruled out.
Nursing Mothers	Animal studies have shown that ivabradine is present in rat milk. Because of the potential risk to breastfed infants from exposure to ivabradine, breastfeeding is not recommended.*

*No adequate or well-controlled trials.

Adverse Drug Events

The most common adverse drug reactions in the SHIFT trial were bradycardia, hypertension, atrial fibrillation and temporary vision disturbances. The 6,558 participants had a median duration of ivabradine use of 21.5 months. Results are shown below in Table 4.

Table 4. Adverse Events With Rates ≥ 1.0% Higher on Ivabradine than Placebo Occurring in > 1% on Ivabradine in SHIFT[2]

Adverse Event	Reported Frequency	
	Ivabradine %, N=3,260	Placebo %, N=3,278
Atrial fibrillation	8.3	6.6
Bradycardia	10	2.2
Hypertension	8.9	7.8
Phosphenes, visual brightness	2.8	0.5

Contraindications

Ivabradine is contraindicated in individuals with acute decompensated heart failure; blood pressure less than 90/50 mmHg; sick sinus syndrome, sinoatrial block or third degree AV block, unless a functioning demand pacemaker is present; resting heart rate < 60 beats per minute prior to treatment; severe hepatic impairment; pacemaker dependence (if heart rate maintained exclusively by pacemaker); and concomitant use of strong cytochrome P450 (CYP) 3A4 inhibitors.[2]

Warnings/Precautions

Table 5. Warnings and Precautions[2]

Warning/Precaution	Prednisone delayed-release
Atrial fibrillation; ivabradine increases the risk of atrial fibrillation. In the SHIFT trial, the rate of atrial fibrillation was 5.0% per patient-year in patients treated with ivabradine and 3.9% per patient-year in patients treated with. Regularly monitor cardiac rhythm and discontinue medication if atrial fibrillation develops.	a
Bradycardia and conductance disturbances; Bradycardia, sinus arrest, and heart block have occurred with ivabradine. The rate of bradycardia was 6.0% per patient-year in patients treated with ivabradine (2.7% symptomatic; 3.4%	a

Warning/Precaution	Prednisone delayed-release
asymptomatic) and 1.3% per patient-year in patients treated with placebo. 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, amiodarone). Concurrent use of verapamil or diltiazem will increase ivabradine exposure, may themselves contribute to heart rate lowering, and should be avoided. Avoid use of ivabradine in patients with 2nd degree atrioventricular block, unless a functioning demand pacemaker is present.	
Fetal toxicity; ivabradine may cause fetal toxicity when administered to a pregnant woman based on findings in animal studies. It is advised to have females use effective contraception when taking this medication.	a

Drug Interactions

Table 6. Drug Interactions[2]

Interacting Medication or Disease	Potential Result
CYP3A4 inhibitors	Concomitant use of ivabradine and CYP3A4 inhibitors increases ivabradine plasma concentrations. Concomitant use with strong CYP3A4 inhibitors is contraindicated. It is also suggested to avoid concomitant use of moderate CYP3A4 inhibitors if possible.
CYP3A4 inducers	Concomitant use of ivabradine and CYP3A4 inducers decreases ivabradine plasma concentrations. Avoid concomitant use if possible.
Negative inotropes (digoxin, amiodarone, beta-blockers, etc.)	Concomitant use of these agents with ivabradine increases the risk of bradycardia. Monitor heart rate closely.
Pacemakers	The use of ivabradine is not recommended in patients with demand pacemakers set to rates ≥ 60 beats per minute.

CYP=cytochrome P-450

Dosage and Administration

Table 7. Dosing and Administration[2]

Generic Name	Adult Dose	Pediatric Dose	Availability
Ivabradine	Chronic heart failure: Tablet: initial, 5 mg BID; maintenance, 2.5 to 7.5 mg BID; maximum, 7.5 mg BID	Safety and efficacy in children have not been established.	Tablet: 5 mg 7.5 mg

BID=twice daily

Clinical Guidelines

The 2013 guidelines from the American College of Cardiology Foundation/American Heart Association continue to recommend that all individuals with hypertension and lipid disorders should be controlled according to contemporary guidelines to lower the risk of HF. In addition, other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use, etc. should be controlled or avoided. Specifically in Stage B-D HF with reduced ejection fraction, individuals should be given an ACEI to prevent symptomatic HF and reduce mortality. If individuals have a contraindication or are intolerant to ACEIs then the use of an ARB is an appropriate alternative. In patients with a recent or remote history of myocardial infarction (MI) or acute coronary syndrome (ACS) and reduced ejection fraction (EF), a β-blocker such as

bisoprolol, carvedilol or sustained-release metoprolol succinate, is recommended for all patients. In the case of volume overload, in New York Heart Association (NYHA) class II-IV patients, it is recommended to add a diuretic, unless contraindicated, to improve symptoms. The loop diuretics are currently the preferred diuretics. Other alternatives such as the combination of hydralazine and isosorbide dinitrate can be considered for those who cannot be given an ACEI or ARB because of drug intolerance, hypotension or renal insufficiency, unless contraindicated. Aldosterone receptor antagonists are also recommended to reduce morbidity and mortality following an acute MI in patients with a LVEF ≤ 40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated.[8]

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
American College of Cardiology Foundation/American Heart Association: **Guideline for the Management of Heart Failure (2013)**[8]	Pharmacologic treatment for Stage A HFrEF: · Hypertension and lipid disorders should be controlled in accordance with contemporary guidelines to lower the risk of HF. · Other conditions that may lead to or contribute to HF, such as obesity, diabetes mellitus, tobacco use and known cardiotoxic agents, should be controlled or avoided. Pharmacologic treatment for Stage B HFrEF (NYHA Class I): · All patients with a recent or remote history of MI or ACS and reduced EF, ACEI should be used to prevent symptomatic HF and reduce mortality. In patients intolerant of ACEI, ARBs are appropriate unless contraindicated. · In all patients with a recent or remote history of MI or ACS and reduced EF, evidence–based β-blockers should be used to reduce mortality. · In all patients with a recent or remote history of MI or ACS, statins should be used to prevent symptomatic HF and cardiovascular events. · In patients with structural cardiac abnormalities, including LV hypertrophy, in the absence of a history of MI or ACS, blood pressure should be controlled in accordance with clinical practice guidelines for hypertension to prevent symptomatic HF. · ACEIs should be used in all patients with a reduced EF to prevent symptomatic HF, even if they do not have a history of MI. · β-blockers should be used in all patients with a reduce EF to prevent symptomatic HF, even if they do not have a history of MI. Pharmacologic treatment for Stage C HFrEF (NYHA Class I-IV): · It is recommended to provide treatment with an ACEI or ARB and a β-blocker, unless contraindicated, to reduce morbidity and mortality. · ACEI have shown benefits in patients with mild, moderate or severe symptoms of HF and in patients with or without CAD. · There are no differences between available ACEI in their effects on symptoms or survival. · Treatment with an ACEI should be initiated at low doses followed by gradual dose increments if lower doses have been well tolerated. Clinicians should attempt to use doses that have been shown to reduce the risk of cardiovascular events in clinical trials. If these target doses of an ACE inhibitor cannot be used or are poorly tolerated, intermediate doses should be used. · ARBs are recommended for individuals who are ACEI intolerant or can be considered as reasonable alternatives to ACEI for first-line therapy for

Clinical Guideline	Recommendations
	patients with HFrEF. · ARBs may also be considered in persistently symptomatic patients with HFrEF who are already being treated with an ACEI and a beta-blocker in whom an aldosterone antagonist is not indicated or tolerated. · Use of bisoprolol, carvedilol or sustained-release metoprolol succinate is recommended for all patients with current or prior symptoms of HFrEF, unless contraindicated. · For all volume overload, in NYHA class II-IV patients: it is recommended to add a diuretic, unless contraindicated, to improve symptoms. The loop diuretics are currently the preferred diuretics. · The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality in persistently symptomatic African Americans with NYHA class III-IV HFrEF receiving optimal therapy with ACEI and beta-blockers, unless contraindicated. · The combination of hydralazine and isosorbide dinitrate can be useful in patients with current or prior symptomatic HFrEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension or renal insufficiency, unless contraindicated. · In patients with NYHA class II-IV and who have LVEF ≤ 35% with an estimated creatinine clearance > 30 mL/min and potassium level < 5.0 mEq/dL: it is recommended to add an aldosterone antagonist. · Aldosterone receptor antagonists are also recommended to reduce morbidity and mortality following an acute MI in patients with a LVEF ≤ 40% who develop symptoms of HF or who have a history of diabetes mellitus, unless contraindicated. · Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF. · Digoxin can also be considered as an addition to the initial regimen in patients with severe symptoms who have not yet responded symptomatically to initial regimen. · Patients with chronic HF with permanent/persistent/paroxysmal AF and an additional risk factor for cardioembolic stroke (history of hypertension, diabetes mellitus, previous stroke or transient ischemic attack or ≥ 75 years of age) should receive chronic anticoagulant therapy. · The selection of an anticoagulant agent for permanent/persistent/paroxysmal AF should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions, and other clinical characteristics, including time in the international normalized ratio therapeutic range if the patient has been taking warfarin. · Chronic anticoagulation is reasonable for patients with chronic HF who have permanent/persistent/paroxysmal AF but are without additional risk factors for cardioembolic stroke. · Omega-3 polyunsaturated fatty acid (PUFA) supplementation is reasonable to use as adjunctive therapy in patients with NYHA class II-IV symptoms and HFrEF or HFpEF, unless contraindicated, to reduce mortality and cardiovascular hospitalizations. · Drugs known to adversely affect the clinical status of patients with current or prior symptoms of HFrEF are potentially harmful and should be avoided or withdrawn whenever possible (e.g., most antiarrhythmic drugs, most calcium channel-blocking drugs [except amlodipine], NSAIDS, or thiazolidinediones).

Clinical Guideline	Recommendations
	Pharmacologic treatment for Stage C HFpEF: · Systolic and diastolic blood pressure should be controlled in patients in accordance with published clinical practice guidelines to prevent morbidity. · Coronary revascularization is reasonable in patients with CAD in whom symptoms (angina) or demonstrable MI is judged to be having an adverse effect on symptomatic HFpEF despite GDMT · Management of AF according to published clinical practice guidelines in patients with HFpEF is reasonable to improve symptomatic HF. · The use of beta-blockers, ACEI and ARBs in patients with hypertension is reasonable to control blood pressure in patients with HFpEF. · The use of ARBs might be considered to decrease hospitalizations for patients with HFpEF.

ACEI=angiotensin-converting enzyme inhibitor, ACS=acute coronary syndrome, AF=atrial fibrillation, ARB=angiotensin-receptor blocker, CAD=coronary artery disease, EF=ejection fraction, GDMT=guideline-directed medical therapy, HF=heart failure, HFrEF=heart failure with reduced ejection fraction, HFpEF=heart failure with preserved ejection fraction, LV=left ventricular, LVEF=left ventricular ejection fraction, MI= myocardial infarction, NSAIDS=non-steroidal antiinflammatory drugs, NYHA=New York Heart Association

Conclusions

Corlanor® (ivabradine) in a novel agent indicated to reduce the risk of hospitalization for worsening HF in a small subset of HF patients. This medication is the first new agent for the management of chronic HF in nearly a decade. Current treatment guidelines in the U.S. have not yet been updated to include recommendations for ivabradine. However, they do recommend a combination of standard pharmacologic therapies for patients with symptomatic heart failure with reduced LVEF (unless contraindicated) to reduce the risk of hospitalization and death. This includes the use of an ACEI or ARB together with a β-blocker for all patients with stable heart failure with reduced LVEF (unless contraindicated) to reduce the risk of hospitalization and death. In addition, diuretics, aldosterone antagonists, hydralazine and isosorbide dinitrate can be added depending on the symptoms and heart failure severity.[8] Despite current therapies, many people continue to suffer hospitalizations due to worsening HF.

Phase III trial data from SHIFT has shown beneficial results for ivabradine in reducing the risk of hospitalization or cardiovascular death for worsening HF; however, there was no favorable effect on all-cause or cardiovascular mortality.[9]

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