Corlanor® (ivabradine) Clinical Fact Sheet

Heart Failure

- According to 2009–2012 National Health and Nutrition Examination Survey data, ~ 5.7 million people in the United States have heart failure (HF), with the lifetime risk of developing HF for both men and women at age 40 of 1 in 5.[1]
- HF is the leading cause of rehospitalization in patients on Medicare, and approximately half of hospitalized patients with HF are readmitted within 6 months of discharge.[2,3]
- Two categories of HF exist: (1) preserved ejection fraction (HF*p*EF) and (2) reduced ejection fraction (HF*r*EF).[4]

Ivabradine FDA-Approved Indication[5]

- *Corlanor® is indicated to reduce the risk of hospitalization for worsening heart failure in adult 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.*

In HF, the body compensates to increase: Ventricular blood volume → Cardiac filling pressure → Heart rate → Cardiac muscle mass

Enlarged Chambers

- The chambers of the heart stretch and contract more strongly, increasing blood flow

Increased Muscle Mass

- The increase in muscle mass occurs when the contracting cells of the heart expand, allowing the heart to pump more strongly (at least initially)

Neuroendocrine Axis and Sympathetic Tone

- Perfusion, contractility, and heart rate all increase

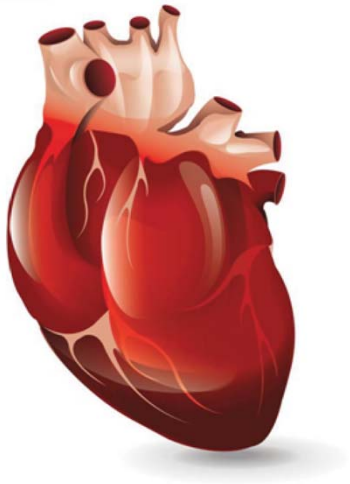
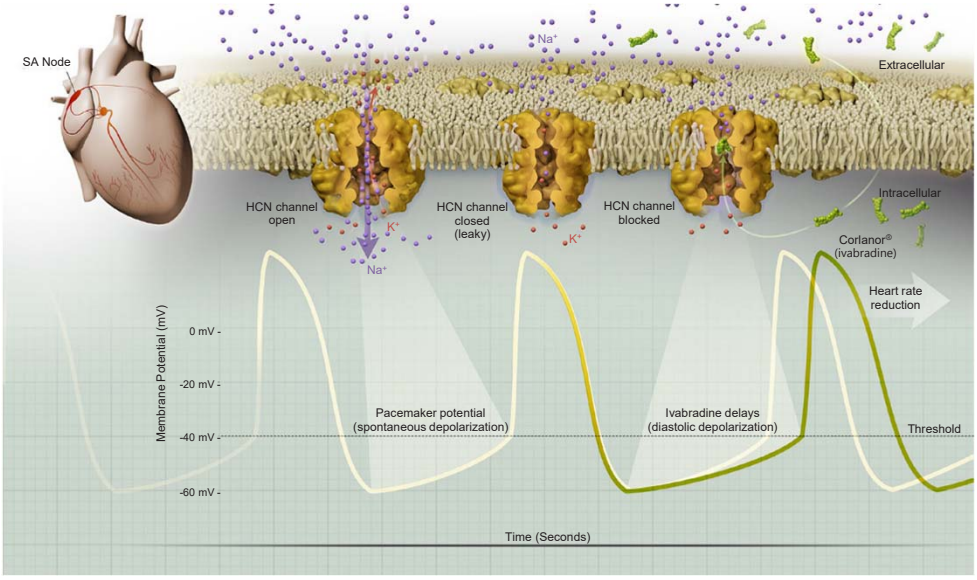


Figure 1: Etiology of HF. As HF progresses, the ejection fraction is reduced resulting in reduced cardiac output and increased end systolic and diastolic volume. With less fluid moving out of the heart, pulmonary congestion worsens.
Compensatory mechanisms are activated as a result of reductions in mean arterial pressure, which is closely regulated in an effort to maintain sufficient tissue perfusion. These mechanisms include the Frank-Starling mechanism to increase contraction as a result of chamber stretch, ventricular remodeling to increase muscle mass, and neurohormonal activation to increase contractility and heart rate. In the short term, these mechanisms provide significant benefit; however, in the long-term, these mechanisms result in a negative feedback loop worsening HF.[6]



Corlanor® Mechanism of Action[5]

- Corlanor® (ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I_f-current (I_f), resulting in heart rate reduction with no effects on ventricular repolarization and myocardial contractility (**Figure 2**).

Figure 2: Plot of the normal I_f–current (white line) which produces slow diastolic depolarization of the sinoatrial (SA) pacemaker potential. Ivabradine (green line) reduces the frequency of SA pacemaker potentials by blocking HCN channels.[7-9]
(Adapted from Postea O, et al. *Nature Reviews.* 2011;10:903-914 and DiFrancesco D, et al. *Drugs.* 2004;64:1757-1765).

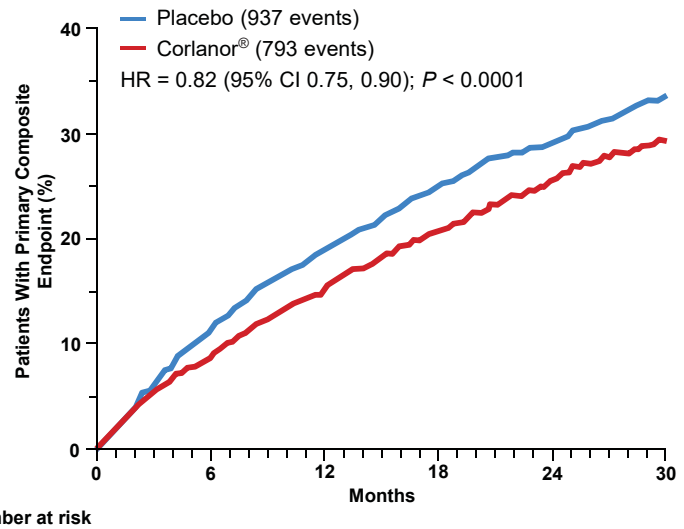
IMPORTANT SAFETY INFORMATION

Contraindications: Corlanor® is contraindicated in patients with acute decompensated heart failure, clinically significant hypotension, sick sinus syndrome, sinoatrial block, 3rd degree atrioventricular block (unless a functioning demand pacemaker is present), clinically significant bradycardia, severe hepatic impairment, pacemaker dependence (heart rate maintained exclusively by the pacemaker), and concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors.

Please see additional Important Safety Information on reverse side.

Efficacy – The SHIFT Study

- SHIFT was a large, multicenter, randomized, double-blind, placebo-controlled trial that enrolled 6,505 adult patients with stable chronic HF (for ≥ 4 weeks), New York Heart Association (NYHA) class II–IV, with a reduced left ventricular ejection fraction (LVEF ≤ 35%), and a resting heart rate ≥ 70 beats per minute (bpm). Patients received placebo or Corlanor® (initially 5 mg twice daily, then titrated to 7.5 or 2.5 mg twice daily, or stopped, depending on heart rate and tolerability), in addition to an optimized and stable clinical regimen, which included maximally tolerated doses of beta-blockers and, in most cases, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, spironolactone, and diuretics.[5,10]
- Corlanor® demonstrated an 18% relative risk reduction (RRR) over placebo for the primary endpoint of cardiovascular death or hospital admission for worsening HF (hazard ratio [HR] 0.82; 95% confidence interval [CI] 0.75, 0.90; *P* < 0.0001) (**Figure 3**).[10]



Number at risk

Placebo	3264	2868	2489	2061	1089	439
Corlanor®	3241	2928	2600	2173	1191	447

Figure 3: Kaplan-Meier cumulative event plot for composite of cardiovascular death or hospital admission for worsening HF (primary endpoint) following treatment with Corlanor® or placebo in the SHIFT study[10]

- The treatment effect reflected only a reduction in the risk of hospitalization for worsening HF; there was no statistically significant benefit on the mortality component of the primary endpoint.[5]
- Corlanor® showed a reduction in the relative risk of hospitalization for worsening HF (HR 0.74; 95% CI 0.66, 0.83; RRR 26%).[5]

2017 ACC/AHA/HFSA Recommendation for Corlanor® (Class IIa; LOE B-R)[11]

- Corlanor® can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II–III) stable chronic HF*r*EF (LVEF ≤ 35%) who are receiving guideline-directed treatments, including a beta-blocker at maximum tolerated dose, and who are in sinus rhythm with a resting heart rate ≥ 70 bpm.

IMPORTANT SAFETY INFORMATION (continued)

Fetal Toxicity: Corlanor® may cause fetal toxicity when administered to a pregnant woman based on embryo-fetal toxicity and cardiac teratogenic effects observed in animal studies. Advise females of reproductive potential to use effective contraception when taking Corlanor®.

Atrial Fibrillation: Corlanor® increases the risk of atrial fibrillation. The rate of atrial fibrillation in patients treated with Corlanor® compared to placebo was 5% vs. 3.9% per patient-year, respectively. Regularly monitor cardiac rhythm. Discontinue Corlanor® if atrial fibrillation develops.

Bradycardia and Conduction Disturbances: Bradycardia, sinus arrest and heart block have occurred with Corlanor®. The rate of bradycardia in patients treated with Corlanor® compared to placebo was 6% (2.7% symptomatic; 3.4% asymptomatic) vs. 1.3% per patient-year, respectively. Risk factors for bradycardia include sinus node dysfunction, conduction defects, ventricular dyssynchrony, and use of other negative chronotropes. Bradycardia may increase the risk of QT prolongation which may lead to severe ventricular arrhythmias, including torsades de pointes, especially in patients with risk factors such as use of QTc prolonging drugs.

Concurrent use of verapamil or diltiazem also increases Corlanor® exposure, contributes to heart rate lowering, and should be avoided. Avoid use of Corlanor® in patients with 2nd degree atrioventricular block unless a functioning demand pacemaker is present.

Adverse Reactions: The most common adverse drug reactions reported at least 1% more frequently with Corlanor® than placebo and that occurred in more than 1% of patients treated with Corlanor® were bradycardia (10% vs. 2.2%), hypertension or increased blood pressure (8.9% vs. 7.8%), atrial fibrillation (8.3% vs. 6.6%), and luminous phenomena (phosphenes) or visual brightness (2.8% vs. 0.5%).

In postmarketing experience, torsades de pointes has been observed.

Please see accompanying Full Prescribing Information and Medication Guide

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; HFSA, Heart Failure Society of America; LOE, level of evidence.

REFERENCES

1. Mozaffarian D, et al. *Circulation*. 2015;131:e29-e322. 2. Jencks SF, et al. *N Engl J Med.* 2009;360:1418-1428. 3. Krumholtz HM, et al. *Circ Cardiovasc Qual Outcomes.* 2009;2:407-413. 4. Yancy CW, et al. *Circulation*. 2013;128:e240-e327. 5. Corlanor® (ivabradine) prescribing information, Amgen. 6. Kemp CD, et al. *Cardiovasc Pathol*. 2012;21:365-371. 7. Postea O, et al. *Nature Reviews.* 2011;10:903-914. 8. Grant AO. *Circ Arrhythm Electrophysiol*. 2009;2:185-194. 9. DiFrancesco D, et al. *Drugs.* 2004;64:1757-1765. 10. Swedberg K, et al. *Lancet.* 2010;376:875-885. 11. Yancy CW, et al. *J Card Fail.* 2017;23:628-651.