Corlanor® (ivabradine) Clinical Fact Sheet

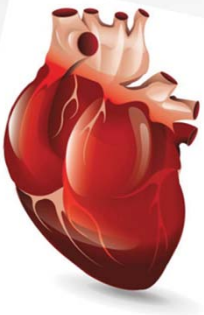
Corlanor® FDA-Approved Indications[1]

- 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.
- Corlanor® is indicated for the treatment of stable symptomatic heart failure due to dilated cardiomyopathy (DCM) in pediatric patients aged 6 months and older, who are in sinus rhythm with an elevated heart rate.

Heart Failure (HF)

- According to 2013–2016 NHANES data, approximately 6.2 million people ≥ 20 years old in the US have HF[2]
- The lifetime risk of developing HF is 20% to 45% for adults at 45 through 95 years of age[2]
- HF is the leading cause of rehospitalization in adult patients on Medicare; almost half of hospitalized patients with HF are readmitted within 6 months of discharge[3,4]
- In HF, the body's adaptations to maintain cardiac output often worsen HF in the long-term[5] (**Figure 1**)
- Two categories of HF exist: (1) preserved ejection fraction and (2) reduced ejection fraction[6]
- In the US, HF-related hospitalizations occur in 11,000 to 14,000 children annually[7]
- The most common causes of pediatric HF are congenital heart disease and cardiomyopathies, primarily DCM, which involves impairment in the ability of the myocardium to generate force due to altered structure[8]
- Pediatric DCM is rare and debilitating; annual incidence in the US is 0.57 cases per 100,000 person-years[9]
- Approximately 40% of children either undergo cardiac transplantation or die within 5 years of being diagnosed with DCM[9]

Figure 1: Etiology of HF[5]



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)

Neurendocrine Axis and Sympathetic Tone

- Perfusion, contractility, and heart rate all increase

In HF, the body compensates to increase:[5] Ventricular blood volume → Cardiac filling pressure → Heart rate → Cardiac muscle mass

As HF progresses, reduced ejection fraction results 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.[5]

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. These mechanisms provide significant short-term benefit; however, in the long-term, they result in a negative feedback loop that worsens HF.[5]

Corlanor® Mechanism of Action[1]

Corlanor® 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.

Efficacy of Corlanor® – The SHIFT Study in Adults

- **SHIFT** was a large, multicenter, randomized, double-blind, placebo-controlled trial that enrolled 6,505 adult patients with stable chronic HF (for ≥ 4 weeks), NYHA class II–IV, with a reduced LVEF (≤ 35%), and a resting heart rate ≥ 70 bpm. Patients received placebo or Corlanor® tablets (initially 5 mg BID, then titrated to 7.5 or 2.5 mg BID, or stopped, depending on heart rate and tolerability), in addition to an optimized clinical regimen, including maximally-tolerated doses of beta-blockers and, in most cases, ACE inhibitors or angiotensin II receptor blockers, spironolactone, and diuretics.[1,10]
- Corlanor® demonstrated an 18% relative risk reduction (RRR) compared to placebo for the primary combined endpoint of CV death or hospital admission for worsening HF (first events; hazard ratio [HR] 0.82; 95% confidence interval [CI] 0.75, 0.90; $P < 0.0001$)[1,10] (**Figure 2**).

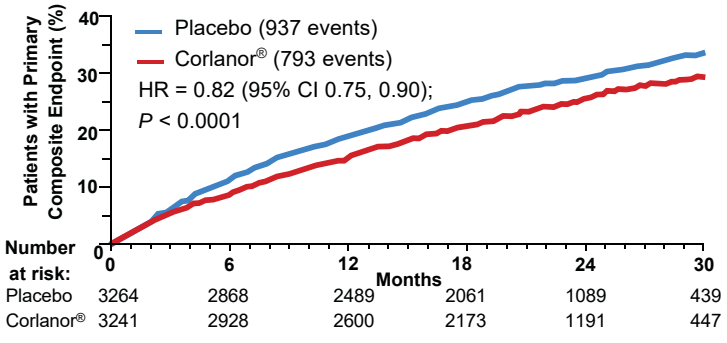


Figure 2: Kaplan-Meier cumulative event plot for primary endpoint following treatment with Corlanor® or placebo[10]

- 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.[1,10]
- Corlanor® showed a 26% reduction in the relative risk of hospitalization for worsening HF (HR 0.74; 95% CI 0.66, 0.83).[1,10]

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 of Corlanor® – The Pediatric Study

- This randomized, double-blind, placebo-controlled, phase 2/3 study evaluated the effect of Corlanor® vs. placebo on heart rate in 116 pediatric patients (ivabradine: n = 74; placebo: n = 42) aged 6 months to 18 years with DCM and symptomatic chronic HF.[11]
- Study treatment was administered as an oral liquid at a starting dose of 0.02 mg/kg BID for patients aged 6-12 months and 0.05 mg/kg BID for patients aged > 1 year to 18 years. Liquid Corlanor® was specially formulated for this study and was delivered as single-dose units of 10 mL containing 1, 5, or 13.3 mg of Corlanor®. Tablet form Corlanor® was given to patients weighing ≥ 40 kg with a starting dose of 2.5 mg BID.[11]
- The duration of the titration period was governed by the magnitude of heart rate reduction and could last up to 8 weeks or until the patient reached the primary endpoint (≥ 20% reduction in heart rate without bradycardia or symptoms of bradycardia).[11]
- Titration could involve a maximum of 4 steps. Patients who were initiated on 0.02 mg/kg BID could be uptitrated to 0.05, 0.10, 0.15 and 0.20 mg/kg BID, and those initiated on 0.05 mg/kg BID could be uptitrated to 0.10, 0.15, 0.20 and 0.30 mg/kg BID. Patients weighing ≥ 40 kg, who started on 2.5 mg BID (tablet form), could be uptitrated to 5,7.5, 10 and 15 mg BID. The titration period was followed by a 2 week maintenance period. This was followed by monitoring for a further 12 months on treatment, with monthly visits up to 3 months and then visits at 6, 9 and 12 months.[11]
- The target heart rate reduction was obtained at the end of the titration period in a significantly higher proportion of patients with Corlanor® vs. placebo (72% vs. 16%, respectively; OR = 15; 95% CI = [5 to 47]). The Prescribing Information reports on the per-protocol set titration (PPS Titration) analysis set.[1] (**Figure 3**).

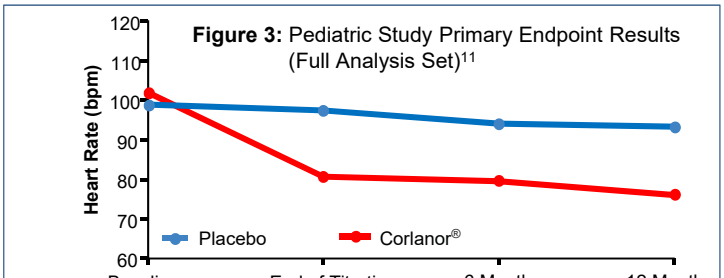


Figure 3: Pediatric Study Primary Endpoint Results (Full Analysis Set)[11]

- A statistically significant reduction in heart rate was observed with Corlanor® compared to placebo at the end of the titration period (-23 ± 11 bpm vs. -2 ± 12 bpm, respectively).[1]
- The mean (SD) change in LVEF at 12 months from baseline was 13.5% (13.1) and 6.9% (11.4) in the Corlanor® and placebo groups, respectively (mean difference = 5.57%; 95% CI = 0.75 to 10.40).[11]

Abbreviations: ACC, American College of Cardiology; ACE, angiotensin-converting enzyme; AE, adverse event; AHA, American Heart Association; BID, twice daily; bpm, beats per minute; CI, confidence interval; HF*r*EF, heart failure with reduced ejection fraction; HFSA, Heart Failure Society of America; LVEF, left ventricular ejection fraction; LOE: B-R, level of evidence: benefit in proportion to risk; NHANES, National Health and Nutrition Examination Survey; NYHA, New York Heart Association; OR, odds ratio; SD, standard deviation; **SHIFT**, **S**ystolic **H**eart failure treatment with the I_f inhibitor ivabradine **T**rial.

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:

Adult Heart Failure Patients
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.

Pediatric Heart Failure Patients
Bradycardia and first-degree heart block were observed in pediatric patients treated with Corlanor®. Asymptomatic and symptomatic bradycardia were observed in 6.8% and 4.1% of pediatric patients treated with Corlanor®, respectively. In the placebo treatment arm, 2.4% of pediatric patients had asymptomatic bradycardia, but none had symptomatic bradycardia. Bradycardia was managed through dose titration but did not result in study drug discontinuation.

Adverse Reactions:

Adult Heart Failure Patients
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.

Pediatric Heart Failure Patients
Bradycardia (symptomatic and asymptomatic) occurred at rates similar to those in adults. Phosphenes were observed in pediatric patients treated with Corlanor®.

Please see accompanying Full Prescribing Information and Medication Guide

REFERENCES: 1. Corlanor® (ivabradine) prescribing information, Amgen. 2. Virani SS, et al. *Circulation*. 2020;141:00–00. DOI: 10.1161/CIR.0000000000000757. 3. Jencks SF, et al. *N Engl J Med.* 2009;360:1418-1428. 4. Krumholz HM, et al. *Circ Cardiovasc Qual Outcomes*. 2009;2:407-413. 5. Kemp CD, et al. *Cardiovasc Pathol*. 2012;21:365-371. 6. Yancy CW, et al. *Circulation*. 2013;128:e240-e327. 7. Rossano JW, et al. *J Card Fail.* 2012;18:459-470. 8. Hsu DT, et al. *Circ Heart Fail*. 2009;2:63-70. 9. Lipshultz SE, et al. *Future Cardiol*. 2013;9:817-848. 10. Swedberg K, et al. *Lancet.* 2010;376:875-885. 11. Bonnet D, et al. *J Am Coll Cardiol*. 2017;70:1262-1272.