FDA APPROVED INDICATIONS AND DOSAGE\(^1\)

| Corlanor\(^\circ\) (ivabradine) | To reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction \(\leq 35\%\), who are in sinus rhythm with resting heart rate \(\geq 70\) beats per minute and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use. | 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. In patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise, initiate dosing at 2.5 mg twice daily. |

CLINICAL RATIONALE

Guidelines

Ivabradine was approved after the current 2013 American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) Practice Guideline for the Management of Heart Failure was published. The guideline does not include ivabradine.

The ACCF/AHA guideline classifies heart failure by the following in relation to New York Heart Association (NYHA) Functional Classification:\(^2\)

<table>
<thead>
<tr>
<th>ACCF/AHA Stages of HF</th>
<th>ACCF/AHA Stage Description</th>
<th>NYHA Functional Classification</th>
<th>NYHA Functional Classification Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At high risk for HF but without structural heart disease or symptoms of HF</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but without signs or symptoms of HF</td>
<td>I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with prior or current symptoms of HF</td>
<td>I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF</td>
</tr>
<tr>
<td>ACCF/AHA Stages of HF</td>
<td>ACCF/AHA Stage Description</td>
<td>NYHA Functional Classification</td>
<td>NYHA Functional Classification Description</td>
</tr>
<tr>
<td>-----------------------</td>
<td>---------------------------</td>
<td>-------------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td>III</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF</td>
</tr>
<tr>
<td>IV</td>
<td></td>
<td>IV</td>
<td>Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions</td>
<td>IV</td>
<td>Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest</td>
</tr>
</tbody>
</table>

The ACCF/AHA guideline recommends the following algorithm for the treatment of heart failure with reduced ejection fraction (HFrEF) (≤40%) ACCF/AHA Class C and NYHA Class I-IV:

- All patients should receive an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in addition to a beta blocker
- For volume overloaded NYHA Class II-IV patients, a loop diuretic should be added
- For persistently symptomatic African American NYHA class III-IV patients, hydralazine and isosorbide dinitrate should be added
- For NYHA Class II-IV patients with estimated creatinine >30 mL/min and potassium <5.0 mEq/dL, an aldosterone antagonist should be added

The ACCF/AHA/HFSA (Heart Failure Society of America) state that ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF ≤35%) who are receiving guideline directed evaluation and management (GDEM), including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest

The ACCF/AHA/HRF (Heart Rhythm Society) guideline for the treatment of tachycardia lists ivabradine, with or without a beta blocker, as a reasonable treatment option for patients with symptomatic inappropriate sinus tachycardia (IST) also called chronic nonparoxysmal sinus tachycardia.

**Efficacy**

Ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel responsible for the cardiac If current. If current regulates heart rate. In clinical electrophysiology studies, the cardiac effects were most pronounced in the sinoatrial (SA) node, but prolongation of the AH interval has occurred on the surface ECG, as has PR interval prolongation. There was no effect on ventricular repolarization and no effects on myocardial contractility. Ivabradine can also inhibit the retinal current Ih which is involved in curtailing retinal responses to bright light stimuli. Under triggering circumstances (e.g. rapid changes in luminosity), partial inhibition of Ih by ivabradine may underlie the luminous phenomena experienced by patients. Luminous phenomena (phosphenes) are described as a transient enhanced brightness in limited area of the visual field.
The Systolic Heart failure treatment with the If inhibitor ivabradine Trial (SHIFT) was a randomized, double-blind trial comparing ivabradine and placebo in 6558 adult patients with stable NYHA class II to IV heart failure, left ventricular ejection fraction ≤ 35%, and resting heart rate ≥ 70 bpm. Patients had to have been clinically stable for at least 4 weeks on an optimized and stable clinical regimen, which included maximally tolerated doses of beta-blockers and, in most cases, ACE inhibitors or ARBs, spironolactone, and diuretics, with fluid retention and symptoms of congestion minimized. Patients had to have been hospitalized for heart failure within 12 months prior to study entry. All subjects were initiated on ivabradine 5 mg (or matching placebo) twice daily and the dose was increased to 7.5 mg twice daily or decreased to 2.5 mg twice daily to maintain the resting heart rate between 50 and 60 bpm, as tolerated. The primary endpoint was a composite of the first occurrence of either hospitalization for worsening heart failure or cardiovascular death. Most patients (89%) were taking beta-blockers, with 26% on guideline-defined target daily doses. The main reasons for not receiving the target beta-blocker doses at baseline were hypotension (45% of patients not at target), fatigue (32%), dyspnea (14%), dizziness (12%), history of cardiac decompensation (9%), and bradycardia (6%). For the 11% of patients not receiving any beta-blocker at baseline, the main reasons were chronic obstructive pulmonary disease, hypotension, and asthma. Most patients were also taking ACE inhibitors and/or angiotensin II antagonists (91%), diuretics (83%), and anti-aldosterone agents (60%). Few patients had an implantable cardioverter-defibrillator (ICD) (3.2%) or a cardiac resynchronization therapy (CRT) device (1.1%). Median follow-up was 22.9 months. At 1 month, 63%, 26%, and 8% of ivabradine-treated patients were taking 7.5, 5, and 2.5 mg BID, whereas 3% had withdrawn from the drug, primarily for bradycardia. SHIFT demonstrated that ivabradine reduced the risk of the combined endpoint of hospitalization for worsening heart failure or cardiovascular death based on a time-to-event analysis (hazard ratio: 0.82, 95% confidence interval [CI]: 0.75, 0.90, p < 0.0001). The treatment effect reflected only a reduction in the risk of hospitalization for worsening heart failure; there was no favorable effect on the mortality component of the primary endpoint. In the overall treatment population, ivabradine had no statistically significant benefit on cardiovascular death.

BEAUTIFUL was a randomized, double-blind, placebo-controlled trial in 10,917 adult patients with coronary artery disease, impaired left ventricular systolic function (ejection fraction < 40%) and resting heart rate ≥ 60 bpm. Patients had stable symptoms of heart failure and/or angina for at least 3 months, and were receiving conventional cardiovascular medications at stable doses for at least 1 month. Beta-blocker therapy was not required, nor was there a protocol mandate to achieve any specific dosing targets for patients who were taking beta-blockers. Patients were randomized 1:1 to ivabradine or placebo at an initial dose of 5 mg twice daily with the dose increased to 7.5 mg twice daily depending on resting heart rate and tolerability. The primary endpoint was the composite of time to first cardiovascular death, hospitalization for acute myocardial infarction, or hospitalization for new-onset or worsening heart failure. Most patients were NYHA class II (61.4%) or class III (23.2%) - none were class IV. Through a median follow-up of 19 months, ivabradine did not significantly affect the primary composite endpoint (HR 1.00, 95% CI = 0.91, 1.10).

SIGNIFY was a randomized, double-blind trial administering ivabradine or placebo to 19,102 adult patients with stable coronary artery disease but without clinically evident heart failure (NYHA class I). Beta blocker therapy was not required. Ivabradine was initiated at a dose of 7.5 mg twice daily and the dose could be increased to as high as 10 mg twice daily or down-titrated to 5.0 mg twice daily to achieve a target heart rate of 55 to 60 bpm. The primary endpoint was a composite of the first occurrence of either cardiovascular death or myocardial infarction. Through a median follow-up of 24.1 months, ivabradine did not significantly affect the primary composite endpoint (HR 1.08, 95% CI = 0.96, 1.20).
Safety

Ivabradine is contraindicated in patients with:
- Acute decompensated heart failure
- Blood pressure less than 90/50 mmHg
- Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present
- Resting heart rate less than 60 bpm prior to treatment
- Severe hepatic impairment
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker)
- Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors

Ivabradine increases the risk of atrial fibrillation. In SHIFT, 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 placebo. Regularly monitor cardiac rhythm. Discontinue ivabradine if atrial fibrillation develops.

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% 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.

REFERENCES
Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) Channel Blocker (Corlanor) Prior Authorization and Quantity Limit

OBJECTIVE
The intent of the Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) prior authorization (PA) and Quantity Limit (QL) program is to appropriately select patients for therapy according to product labeling and/or clinical guidelines and according to dosing recommended in product labeling. Corlanor will be approved for use in patients with stable, symptomatic chronic heart failure; who have a baseline or current left ventricular ejection fraction of ≤35%; who are in sinus rhythm with a resting heart rate of ≥70 beats per minute; who is on maximally tolerated dose of beta blocker or the patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to beta blockers. The program will also approve for patients with a diagnosis of inappropriate sinus tachycardia (IST), also called chronic nonparoxysmal sinus tachycardia, who are symptomatic. The program will approve for doses within the set limit. Doses above the set limit will be approved if the requested quantity is below the FDA limit and cannot be dose optimized or when the quantity is above the FDA limit and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis. Requests for an HCN agent will be reviewed when patient specific documentation is provided.

TARGET DRUG
Corlanor® (ivabradine)

<table>
<thead>
<tr>
<th>Brand (generic)</th>
<th>GPI</th>
<th>Multisource Code</th>
<th>Quantity Limit Per Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corlanor (ivabradine)</td>
<td>40700035100320 M, N, O, or Y</td>
<td>2 tablets</td>
<td></td>
</tr>
<tr>
<td>5 mg tablet</td>
<td>40700035100330 M, N, O, or Y</td>
<td>2 tablets</td>
<td></td>
</tr>
</tbody>
</table>

PRIOR AUTHORIZATION CRITERIA FOR APPROVAL
Corlanor will be approved when ALL of the following are met:

1. ONE of the following:
   a. ALL of the following:
      i. The patient has stable, symptomatic chronic heart failure (e.g. NYHA Class II, III, IV; ACCF/AHA Class C, D) AND
      ii. The patient has a baseline OR current left ventricular ejection fraction of ≤35% AND
      iii. Prior to initiating therapy with the requested agent, the patient is in sinus rhythm with a resting heart rate of ≥70 beats per minute AND
      iv. ONE of the following:
         1. The patient is on a maximally tolerated dose of beta blocker (e.g. atenolol, bisoprolol, carvedilol, metoprolol) OR
         2. The patient has a history of a documented intolerance, FDA labeled contraindication, or hypersensitivity to a beta blocker (e.g. atenolol, bisoprolol, carvedilol, metoprolol) OR
   b. BOTH of the following:
      i. The patient has a diagnosis of inappropriate sinus tachycardia (IST) or chronic nonparoxysmal sinus tachycardia AND
ii. The patient’s IST is symptomatic

**AND**

2. The patient does NOT have any FDA labeled contraindication(s) to the requested agent **AND**

3. **ONE** of the following:
   a. The quantity requested is less than or equal to the program quantity limit **OR**
   b. The quantity (dose) requested is above the program limit, less than or equal to the maximum dose recommended in FDA approved labeling and the prescribed dose cannot be achieved using a lesser quantity of a higher strength **OR**
   c. The quantity (dose) requested is greater than the maximum dose recommended in FDA approved labeling and the prescriber has submitted documentation in support of therapy with a higher dose for the intended diagnosis which has been reviewed and approved by the Clinical Review pharmacist

**Length of Approval:** 12 months
### FDA Labeled Contraindications

<table>
<thead>
<tr>
<th>Agent</th>
<th>Contraindications</th>
</tr>
</thead>
</table>
| Corlanor (ivabradine) |  - Acute decompensated heart failure  
- Blood pressure less than 90/50 mmHg  
- Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present  
- Resting heart rate less than 60 bpm prior to treatment  
- Severe hepatic impairment  
- Pacemaker dependence (heart rate maintained exclusively by the pacemaker)  
- Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors |