Policy and Procedure

PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR035.0625	CARDIOVASCULAR AGENTS CORLANOR® (ivabradine tablets/solution)
Effective Date: 8/1/2025	**Review/Revised Date**: 08/16, 7/17, 05/18, 08/18, 03/19, 10/19, 07/20, 05/21, 07/22, 05/23, 04/24, 05/25 (ZJN)
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Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as “Company” and collectively as “Companies”).

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit and inappropriate sinus tachycardia, subject to criteria below.

REQUIRED MEDICAL INFORMATION:
For chronic heart failure in adults, all the following must be met:

1. Symptoms consistent with New York Heart Association (NYHA) Class II, III, or IV
2. Left ventricular ejection fraction (LVEF) of 35% or less
3. Documentation that patient is currently in normal sinus rhythm with resting heart rate of at least 70 beats per minute (bpm)
4. On maximally tolerated guideline-directed therapy including all the following, unless contraindicated or intolerant:
    a. Beta-blocker (specifically carvedilol, metoprolol succinate, or bisoprolol)
    b. SGLT-2 inhibitor (specifically empagliflozin or dapagliflozin)
    c. One of the following:
        i. Angiotensin receptor-neprilysin inhibitor (ARNI) such as sacubitril/valsartan (Entresto®)
        ii. Angiotensin-converting enzyme (ACE) inhibitor such as lisinopril
        iii. Angiotensin II receptor blocker (ARB) such as losartan
    d. Mineralocorticoid receptor antagonist as clinically appropriate (specifically spironolactone or eplerenone)
    e. Diuretic therapy for symptomatic patients with persistent volume overload

5. Documentation that the patient has been hospitalized for worsening heart failure in the previous 12 months

For inappropriate sinus tachycardia (IST):
1. Documentation of sinus rhythm and resting heart rate (HR) greater than 100 bpm (with a mean HR greater than 90 bpm over 24 hours)
2. Documentation that other causes of sinus tachycardia have been ruled out (such as thyroid disease, drug-induced, postural orthostatic tachycardia syndrome)
3. Documentation that inappropriate sinus tachycardia is causing significant functional impairment or distress, such as presyncope, headache, dyspnea, weakness

For heart failure, due to dilated cardiomyopathy (DCM), in pediatric patients, all the following criteria must be met:
1. Documentation that patient has stable (for at least four weeks) and symptomatic heart failure (NYHA Class II to IV)
2. Left ventricular ejection fraction (LVEF) of 45% or less
3. Documentation that patient is currently in normal sinus rhythm with a resting heart rate (HR) as follows:
    a. 6–12 months: HR at least 105 bpm
    b. 1–3 years: HR at least 95 bpm
    c. 3–5 years: HR at least 75 bpm
    d. 5–18 years: HR at least 70 bpm

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
Prescribed by, or in consultation with, a cardiologist or electrophysiologist

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

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Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale,

formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case

INTRODUCTION:

Corlanor® (ivabradine) is an I_f channel inhibitor with unique electrophysiological effects and is a potential therapeutic option for heart failure with reduced ejection fraction (HFrEF). Ivabradine selectively inhibits the inward funny channel (I_f) in the sinoatrial node which leads to prolongation of the slow depolarization phase and thus reducing the HR without compromising blood pressure. Ventricular repolarization and myocardial contractility are not affected, which is believed to be beneficial for heart failure patients.

FDA APPROVED INDICATIONS:

To reduce the risk of hospitalization due to heart failure in patients with stable HFrEF (LVEF ≤ 35%) in sinus rhythm with resting heart rate ≥ 70 bpm and on either maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.

The treatment of stable symptomatic heart failure due to dilated cardiomyopathy (DCM) in pediatric patients aged six months and older, who are in sinus rhythm with an elevated heart rate

POSITION STATEMENT:

Ivabradine was studied in three randomized, placebo-controlled trials. The Food and Drug Administration (FDA) approved ivabradine based on the inclusion criteria and results from the SHIFT trial that randomized 6,558 patients with stable HFrEF to receive ivabradine or matching placebo. Patients with stable symptomatic chronic HF with LVEF of ≤35%, in sinus rhythm with resting HR ≥70 bpm were enrolled if they had a worsening HF event within the previous 12 months. The primary endpoint was a composite of cardiovascular death or hospital admission for worsening HF. Ivabradine exhibited a statistically significant reduction in the number of events in the primary endpoint [24% vs 29%; HR 0.82 (0.75–0.90); p<0.0001]. Significant secondary endpoints that also showed clinical benefit with ivabradine, including reduced HF mortality [3% vs 5%; HR 0.74 (0.58–0.94); p=0.014] and reduced hospitalization [16% vs 21%; HR 0.74 (0.66–0.83); p<0.0001].[3,4]

The 2022 updated guidelines by the American College of Cardiology (ACC), American Heart Association (AHA), and Heart Failure Society of America (HFSA) recommends ivabradine in patients with stable HFrEF (NYHA II-III) in sinus rhythm and resting HR ≥ 70 bpm who are receiving background guideline-directed therapy that includes maximally tolerated dose of a beta-blocker to reduce the risk of hospitalization.[5] Guideline-directed medical therapy for HFrEF includes a beta-blocker, a SGLT-2 inhibitor, an angiotensin receptor-neprilysin inhibitor (ARNI), angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), an aldosterone antagonist and diuretics as needed.[5] The SGLT2 inhibitors dapagliflozin, and empagliflozin as well as the dual SGLT1 and SGLT2 inhibitor sotagliflozin have FDA approval for treatment of heart failure and are noted by the 2022 AHA/ACC/HFSA guidelines as agents that have demonstrated clinical benefit in heart failure.

In EDIFY, a randomized, double-blind, placebo-controlled clinical trial investigated potential benefits of ivabradine in the treatment of heart failure with preserved ejection fraction (HFpEF) in 179 patients with NYHA class II-III with LVEF ≥50% and heart rate ≥70 bpm. After eight months, ivabradine did not improve any of the three co-primary endpoints: echocardiographic ratio of early diastolic mitral inflow velocity divided by mitral annular early diastolic velocity (cardiac filling pressures), 6-min walk distance, and plasma N-terminal pro-B type natriuretic peptide. These findings do not support the use of ivabradine in HFpEF.[6]

Initially, investigators evaluated ivabradine as an anti-angina drug based on its negative chronotropic properties without affecting blood pressure. In BEAUTIFUL and SIGNIFY trials, the ivabradine treatment groups did not reach statistical significance in any of the primary or secondary endpoints associated with cardiovascular mortality and morbidity. In the SIGNIFY trial, patients with stable coronary artery disease (CAD) without HF (LVEF>40%) who received ivabradine were associated with an increased risk of cardiovascular events, although this did not reach statistical significance.[7,8]

Inappropriate sinus tachycardia (IST) is sinus tachycardia that is not explained by physiological demands at rest, with minimal exertion or during exercise recovery. It is a chronic condition associated with distressing symptoms such as palpitations, weakness, fatigue, lightheadedness and presyncope which can significantly affect quality of life. With IST, resting heart rate is commonly over 100 bpm (with a mean 24-hour heart rate over 90 bpm). Long-term outcomes with inappropriate sinus tachycardia are unclear and no known mortality has been associated with IST.

The etiology of IST is not well understood. It is typically a diagnosis of exclusion by eliminating other conditions that could lead to sinus tachycardia, such as postural

orthostatic tachycardia syndrome (POTS). A thorough medical history review and physical examination is crucial, including focus on the potential causes of sinus tachycardia, such as thyroid disease and drugs. Corlanor® (ivabradine) is not FDA approved for the treatment of IST and data to support its use for this indication is limited.[3,9] Ivabradine is recommended as reasonable ongoing medication management for IST by the joint American College of Cardiology, American Heart Association and Heart Rhythm Society guidelines for adults with supraventricular tachycardia. This recommendation is given a class IIa (moderate strength) recommendation based upon level B – randomized evidence. Beta blockers are given a weak recommendation for ongoing use in IST.[12]

Pediatric patients with dilated cardiomyopathy (DCM) were evaluated in a randomized double-blind, placebo-controlled, phase II/III study in 47 centers across 16 countries. Patients greater than six months of age were eligible for enrollment if they had a history of NYHA class II to IV symptomatic HF, a LVEF ≤45%, and were on stable treatment for chronic HF (94% of patients were on an ACE inhibitor, 76% on a beta-blocker). Patients had to be in sinus rhythm with resting heart rates in the normal range for age: ≥105 bpm for patients aged six to 12 months, ≥95 bpm for patients aged one to three years, ≥75 bpm for patients aged three to five years, and ≥70 bpm for patients aged five to 18 years. Patients (N=116) were randomized to receive ivabradine or placebo. The primary endpoint was the percentage of patients that achieved at least a 20% reduction in heart rate without inducing bradycardia and was found to be higher in patients in the ivabradine group [70% vs 12%; (OR: 17.24; 95% CI: 5.91 to 50.30; $p < 0.0001$)]. A key secondary endpoint of the percentage of patients that saw an improvement in NYHA functional class or Ross class from baseline was found to be non-significant (32% of patients taking ivabradine versus 17% of patients taking placebo by 6 months; ($p = 0.132$). Similar results were observed by 12 months (38% vs. 25%; $p = 0.239$).[10]

Ivabradine is approved by the European Medical Association (EMA) for use in patients with chronic stable angina; however, the Food & Drug Administration (FDA) did not grant this indication for Corlanor®. In their summary review, the FDA reviewers noted that clinical trials for the benefit of ivabradine in heart failure are “complex, inconsistent, and difficult to interpret.” They noted that in the SIGNIFY trial, a subgroup analysis “suggests a detrimental impact in patients with symptomatic angina.” The EMA subsequently has added restrictions to this indication based on these results. Therefore, this indication is not considered medically necessary.

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