Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCCAR045.0625	**CARDIOVASCULAR AGENT** **LODOCO®** (colchicine 0.5 mg tablet)
Effective Date: 8/1/2025	**Review/Revised Date**: 04/25 (MTW)
Original Effective Date: 06/24	**P&T Committee Meeting Date**: 04/24, 06/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

ASCOPE:
Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions 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

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 when all applicable indication-specific criteria below are met. The Early and Periodic Screening, Diagnostic and Treatment (EPSDT) benefit provides comprehensive and preventive health care services for children and adolescents up to their 21st birthday who are enrolled in Medicaid. Management of unfunded conditions falls under this benefit when they impact the ability to grow, develop or participate in school and the applicable indication-specific criteria below are met.

REQUIRED MEDICAL INFORMATION:
For initial authorization and reauthorization, patient must meet all the following criteria:
1. Diagnosis of clinical Atherosclerotic Cardiovascular Disease (ASCVD) (defined as one of the following: acute coronary syndromes, history of myocardial infarction, stable/unstable angina, coronary or other arterial revascularization, stroke or transient ischemic attack, peripheral artery disease presumed to be of atherosclerotic origin) or patient has multiple risk factors for cardiovascular disease (see Appendix 1)
2. For Commercial only:

a. Documentation that patient is receiving maximally tolerated statin therapy or, if statin intolerant, other lipid-lowering therapy unless contraindicated or not tolerated
b. Documentation of blood pressure less than 130/80 or that patient is optimized on standard of care medications for high blood pressure unless contraindicated or not tolerated
c. Documentation that patient is on aspirin therapy for secondary ASCVD prevention unless contraindicated or not tolerated

EXCLUSION CRITERIA:
1. Concurrent use of strong CYP3A4 or P-glycoprotein inhibitors
2. Renal failure (CrCl less than 15 mL/min)
3. Severe hepatic impairment
4. Pre-existing blood dyscrasias

AGE RESTRICTIONS: N/A

PRESCRIBER RESTRICTIONS:
For Commercial only: Must be prescribed by, or in consultation with, a cardiologist

COVERAGE DURATION:
Initial authorization and reauthorization will be approved for one year.

QUANTITY LIMIT:
30 tablets per 30 days

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:

Colchicine is a drug previously approved to treat gout flares and Familial Mediterranean Fever (FMF). Its mechanism of action is not fully understood however it is a known inhibitor of β-tubulin polymerization due to disruption in cytoskeletal functions which leads to the inhibition of neutrophils. This results in an anti-inflammatory effect which is thought to be involved in its efficacy in treating both of the previous indications as well as the new indication as Lodoco®, to reduce the risk of cardiovascular events.

FDA APPROVED INDICATIONS:
To reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease

POSITION STATEMENT:

- The use of colchicine in medicine goes back thousands of years, however it wasn't until the FDA approval of Colcrys® in 2009 that colchicine became fully regulated. Colcrys® is now available in the United States in both brand and generic 0.6 mg tablets. It is FDA approved for gout flares and Familial Mediterranean fever (FMF) and has compendial support for several additional indications including Behcet syndrome, pericarditis, and sweet syndrome.
- The LoDoCo (Low-Dose Colchicine) trial published in 2013 sought to identify whether colchicine, in its lowest dose form available (0.5 mg outside of the United States), would be beneficial in ASCVD (Atherosclerotic Cardiovascular Disease) risk reduction when added to standard therapy. Eligible patients had angiographically proven coronary disease, ages 35-85 years, clinically stable for at least six months, and no major competing comorbidities or contraindication to colchicine therapy. 532 patients were randomized to either colchicine 0.5 mg tablet or no colchicine. Baseline medications were comparable apart from there being significantly more patients on calcium channel blockers and fewer patients on beta-blockers in the colchicine group. The primary outcome was a composite of ACS (Acute Coronary Syndrome), fatal or nonfatal out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke. The primary outcome occurred in 5.3% of patients in the colchicine group and 16% in the no colchicine group over 3-4 years ($p<0.001$) and was primarily driven by ACS events (4.3% in colchicine group versus 13.4% in placebo group, $p<0.001$).
- The LoDoCo-MI (Low-Dose Colchicine – Myocardial Infarction) study published in 2019 sought to test the hypothesis that the use of low dose colchicine started shortly after an acute MI would result in lower levels of CRP (C-reactive protein), a biomarker of inflammation. Secondary objectives included the impact of low dose colchicine on levels of IL-6 (Interleukin-6), a regulator of CRP production and inflammation, and the safety and tolerability of the drug. 237 patients were randomized to receive colchicine 0.5 mg or placebo once daily. Results indicated

no significant difference in the levels of CRP or IL-6 in the colchicine group at 30 days. There was also no significant difference in safety or tolerability.

- The COLCOT (Colchicine Cardiovascular Outcomes Trial) was designed to address the limitations of the LoDoCo trial by enrolling more patients and including a placebo control group. The primary outcome was to determine the effect of colchicine on cardiovascular (CV) outcomes and address the long-term safety profile of colchicine in patients with a recent MI. 4745 patients were randomized to receive colchicine 0.5 mg or placebo once daily. The primary outcome (composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization) occurred in 5.5% of patients in the colchicine group versus 7.1% of patients in the placebo group (p=0.02). There was no significant difference found between the groups regarding the secondary efficacy outcome (composite of death from CV causes, cardiac arrest, MI, or stroke). The study concluded that colchicine was associated with a decrease in strokes and urgent hospitalizations for angina leading to coronary revascularization.
- FDA-approval of Lodoco can be primarily attributed to the results of the LoDoCo2 trial, published in 2020. Patients from Australia and the Netherlands were included in this trial if they were ages 35-82, had evidence of coronary angiography or computed tomography angiography or a coronary-artery calcium score of at least 400 Agatston units on a coronary-artery calcium scan, and clinically stable for at least six months. Patients were excluded if they had moderate to severe renal impairment, severe heart failure, severe valvular heart disease, or known side effects from colchicine. 5478 patients were randomized to receive colchicine 0.5 mg or placebo once daily. The primary composite outcome of CV death, spontaneous MI, ischemic stroke, or ischemia-driven coronary revascularization occurred in 6.8% of the colchicine group and 9.6% of the placebo group (p<0.001). The Netherlands required safety event reporting around myalgia and dysesthesia for their citizens which consisted of approximately 65% of randomized patients (3618 patients). There was a significant difference found for myalgia (with a higher incidence in the colchicine group) but no significant difference in the rate of dysesthesia. A total of 15.4% of patients initially enrolled in the trial did not undergo randomization with the primary reason of gastrointestinal side effects.
- ASCVD encompasses conditions resulting from the build-up of plaque in the coronary arteries. These conditions include coronary heart disease, peripheral artery disease, cerebrovascular disease, and aortic atherosclerotic disease. The American College of Cardiology and American Heart Associated published primary prevention guidelines in 2019 which included the following non-pharmacological recommendations for ASCVD prevention: healthy lifestyle, healthy diet, regular exercise, and smoking cessation. Evidence-based

pharmacological therapy recommended by the guidelines include medications for diabetes, cholesterol, and blood pressure.

Appendix 1: Risk Factors for Cardiovascular Disease

- Overweight/obesity or metabolic syndrome
- Hypertension
- Dyslipidemia or familial hypercholesterolemia
- Hyperglycemia
- Family history of premature ASCVD (males, age < 55 years; females, age <65 years)
- Diabetes
- Chronic kidney disease
- Cigarette smoking/ tobacco use
- Dietary factors (diets with high glycemic index, low consumption of fruits and vegetables, high consumption of trans fatty acids, low consumption of fiber)
- Chronic inflammatory conditions (e.g. psoriasis, RA, lupus, HIV/AIDS)
- Pregnancy-related complications (e.g., intrauterine growth retardation, hypertensive disorders of pregnancy, gestational diabetes)

REFERENCE/RESOURCES:

1. Lodoco prescribing information. Parsippany, NJ: AGEPHA Pharma USA, LLC; 2024 August.
2. Lodoco In: Lexi-Drugs Online [Internet database]. Hudson, OH: Lexi-Comp, Inc. Updated periodically. Accessed March 5, 2024
3. Dasgeb b, Kornreich D, McGuinn K, Okon L, et al. Colchicine: an ancient drug with novel applications. *Br J Dermatol* 2018;178(2):350-356.
4. Giouroukakis M, Dryer M. Unapproved Drugs – The Drug Information Pharmacists' Perspective. *J Pharm Pract* 2013;26(2):112-119.
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8. Hennessy T, Soh L, Bowman M, et al. The Low Dose Colchicine after Myocardial Infartion (LoDoCo-MI) study: A pilot randomized placebo controlled trial of colchicine following acute myocardial infarction. *Amer Heart J* 2019;215:62-69.

9. Tardif JC, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med* 2019;381(26):2497-2505.
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11. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140:e596-e646. DOI: 10.1161/CIR. .0000000000000678.
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