

LODOCO

(colchicine) tablets



1st Anti-inflammatory for CVD

**31% Additional risk reduction
as compared to placebo***

One tablet daily



*The absolute risk was found to be 6.8% in colchicine group and 9.6% in the placebo group, with an absolute risk reduction of 2.8%.

LODOCO FDA APPROVAL

0.5 mg colchicine tablets

LODOCO can reduce cardiac event risk in adult patients with established atherosclerotic cardiovascular disease by 31% when compared to placebo on top of standard of care including high intensity statins.

INDICATIONS AND USAGE

LODOCO is an alkaloid indicated:

- 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 (1).

DOSAGE AND ADMINISTRATION

The recommended dosage is 0.5 mg orally once daily (2.1).

LODOCO FDA APPROVED LABEL



1ST ANTI-INFLAMMATORY DRUG FOR CARDIOVASCULAR DISEASE

LODOCO is the first anti-inflammatory drug approved by the FDA specifically to reduce risks of heart attack, stroke, coronary revascularization and cardiovascular death

LODOCO's anti-inflammatory effects are consistent with clinical data demonstrating that colchicine reduces high sensitivity C-reactive protein (hs-CRP).

LODOCO targets residual inflammation as an underlying cause of ASCVD and can be used alone or in combination with cholesterol-lowering medications.

LODOCO is a highly effective and safe treatment that significantly reduces cardiovascular inflammation, leading to a reduction in major adverse cardiovascular events (MACE). When used alongside adjunctive lipid-lowering therapies such as statins, LODOCO further enhances cardiovascular benefits, particularly in patients with chronic stable atherosclerotic disease, improving outcomes beyond what statins alone can achieve.

ADDING LODOCO BOOSTS CAD THERAPY OUTCOMES

Adding low-dose colchicine to standard lipid- and blood pressure-lowering therapy delivers greater benefits than intensified LDL-c or SBP reduction alone.

Analysis of 36,642 CAD patients showed colchicine **reduced MACE+** (revascularization, MI, stroke, or cardiovascular death) **by 8.6% over 10 years**, compared to 5.2% for LDL-c and 2.9% for SBP reduction, **adding 3.4 MACE+ free years**. These findings highlight the powerful role of inflammation control in secondary prevention

Medication Intervention Summary

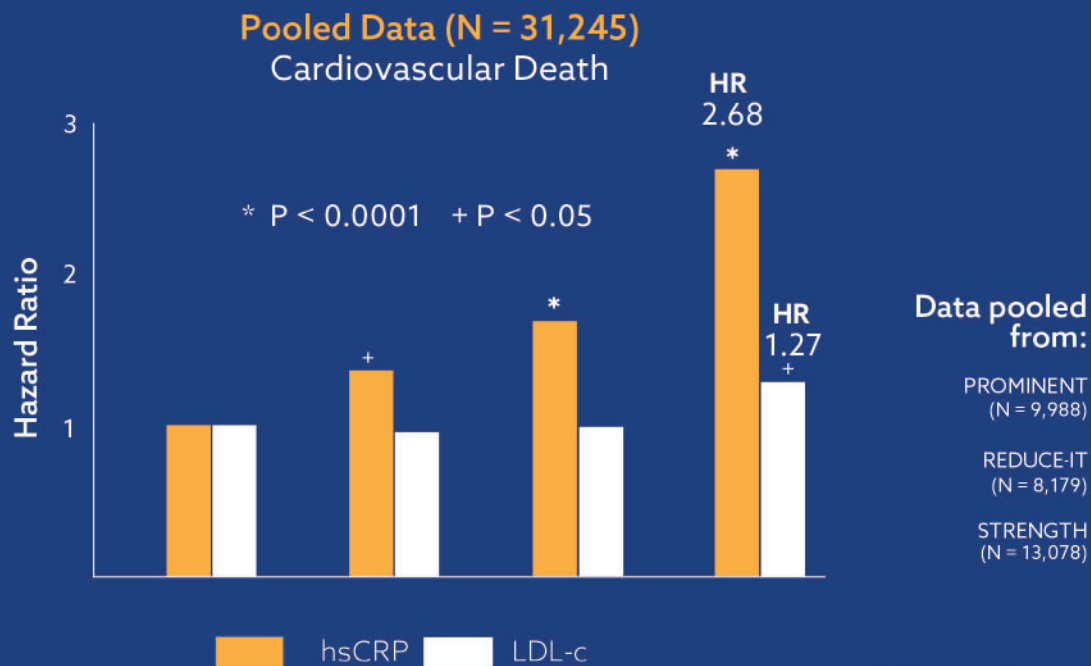
10-year Absolute Risk Reduction (%, IQR)	
Low Dose Colchicine 0.5	8.6% (7.6 – 9.8%)
LDL Lowering	5.2% (2.5 – 8.7%)
BP Reduction	2.9% (0.0 – 9.5%)
All 3 Interventions	15.9% (12.2 – 21.1%)
Life-years Gained (median, IQR)	
Low Dose Colchicine 0.5	3.4 years (2.6 – 4.2 years)
LDL Lowering	1.8 years (0.8 – 3.3 years)
BP Reduction	0.9 years (0.0 – 3.4 years)
All 3 Interventions	6.6 years (4.6 – 9.5 years)

Benefit of low-dose colchicine, intensive LDL-c reduction, and SBP reduction on MACE+.

(Burger, Pascal M., et al., 2023)

RESIDUAL INFLAMMATORY RISK: A PREDICTOR OF CV DEATH

hsCRP vs LDL-c



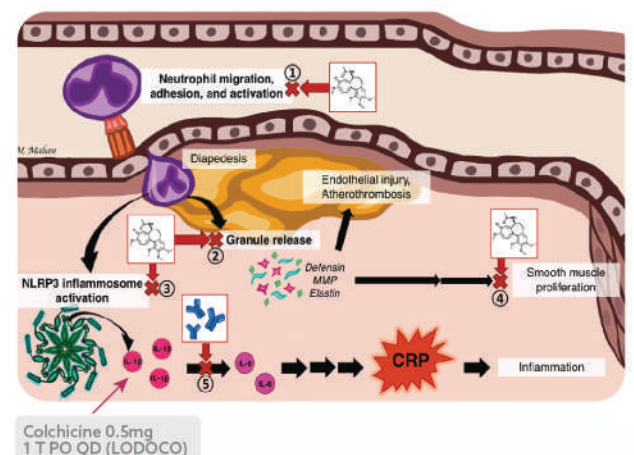
(Ridker, Paul M., et al., 2023)

Among patients receiving contemporary statins, inflammation assessed by high-sensitivity CRP, was a stronger predictor for risk of future cardiovascular events and death than cholesterol, assessed by LDL-c.

These data have implications for the selection of adjunctive treatments beyond statin therapy and suggest that combined use of aggressive lipid-lowering and inflammation inhibiting therapies might be needed to further reduce atherosclerotic risk.

ANTI-INFLAMMATORY MECHANISM OF ACTION

- Colchicine blocks the NLRP3 inflammasome, which is responsible for activating the immune response and triggering inflammation
- This inhibition decreases the production of inflammatory molecules like IL-1 β and IL-6, which are critical drivers of systemic inflammation
- As inflammation is suppressed, levels of high-sensitivity C-reactive protein (hs-CRP), a key marker of cardiovascular inflammation, are reduced
- The reduced inflammation helps stabilize plaques in the arteries, preventing them from rupturing
- With stabilized plaques and lower inflammation, the risk of heart attacks and strokes is significantly reduced



RESIDUAL INFLAMMATORY RISK

Despite receiving standard care therapies, including high-intensity statins and blood pressure medication, many patients remain at high-risk of cardiovascular events due to residual inflammatory risk

43% – 47%

Of patients on aggressive statin therapy have residual inflammatory risk

Residual inflammatory risk is not sufficiently addressed by current therapies

(Ridker, 2017)



INFLAMMATION DOUBLES HEART ATTACK RISK

Twice as many patients have a risk of a heart attack or stroke from untreated inflammation, than those that have remaining risk from untreated cholesterol, as seen in recent lipid-lower trials

2x

(Ridker, 2017)

RECENT STUDIES ON INFLAMMATION AND CARDIOVASCULAR RISK

In the VIRGO registry, **60%** of young acute MI patients had elevated hs-CRP (≥ 2 mg/L).

Similarly, the PROVE-IT and IMPROVE-IT trials found that **43%** and **47%** of patients on intensive lipid-lowering therapy, respectively, had residual inflammation, which correlated with increased cardiovascular risk despite controlled LDL-C.

(Alfaddagh et al., 2020)



3 in 5 young patients with acute MI had elevated hs-CRP



An analysis has shown a **67%** reduction in cardiovascular death in patients treated with colchicine after a recent myocardial infarction.

Early initiation of colchicine (**within 3 days**) was associated with significant reductions in all-cause and cardiac deaths.

(Chang et al., 2024)



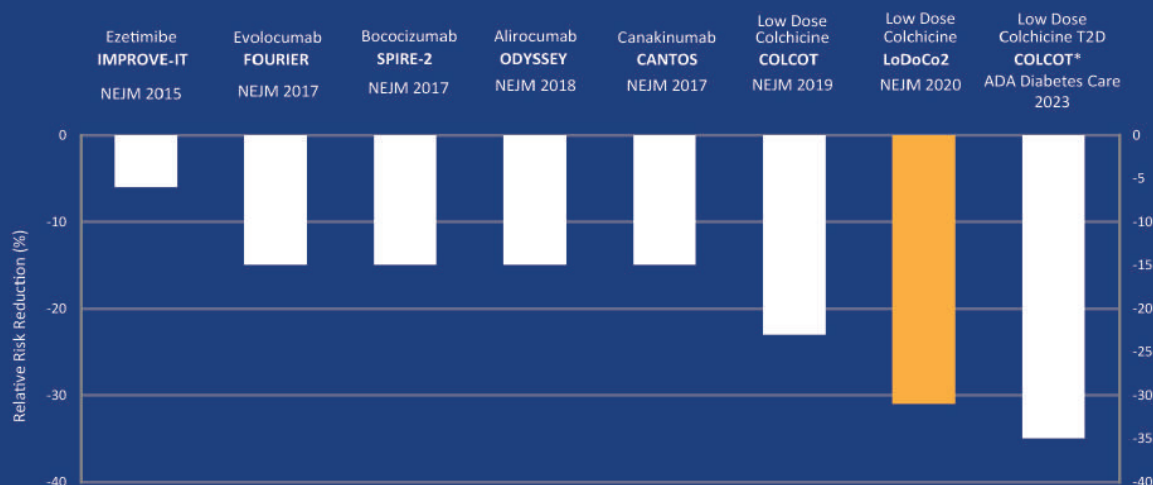
Early initiation in particular was associated with **67%** reduction in cardiovascular deaths



0.5 MG COLCHICINE CUTS ASCVD RISK

Low Dose Colchicine Demonstrates a Higher Relative CV Risk Reduction

Than Ezetimibe and PCSK9 Inhibition with Concomitant Aggressive Use of Statin Therapy



LoDoCo2 TRIAL

Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. N Engl J Med. 2020;383:1838–1847

- Randomized, placebo controlled, double-blind trial
- 5,522 chronic coronary diseases patients on guideline directed medical care including aggressive statin therapy
- 96.6% were already treated with a lipid lowering agent
- Mean age = 66 +/- 8.6 years
- Serious adverse events were low in both groups

STUDY DESIGN



PRIMARY ENDPOINT: Cardiovascular death, Myocardial infarction, Ischemic stroke, or ischemia-driven coronary revascularization

COLCHICINE REDUCES CARDIOVASCULAR EVENTS

In the LoDoCo2 trial, 187 patients (6.8%) in the colchicine group and 264 patients (9.6%) in the placebo group experienced an endpoint event, with incidence rates of 2.5 and 3.6 events per 100 person-years, respectively. Landmark analyses confirmed that colchicine consistently reduced event risk compared to placebo at all yearly checkpoints.

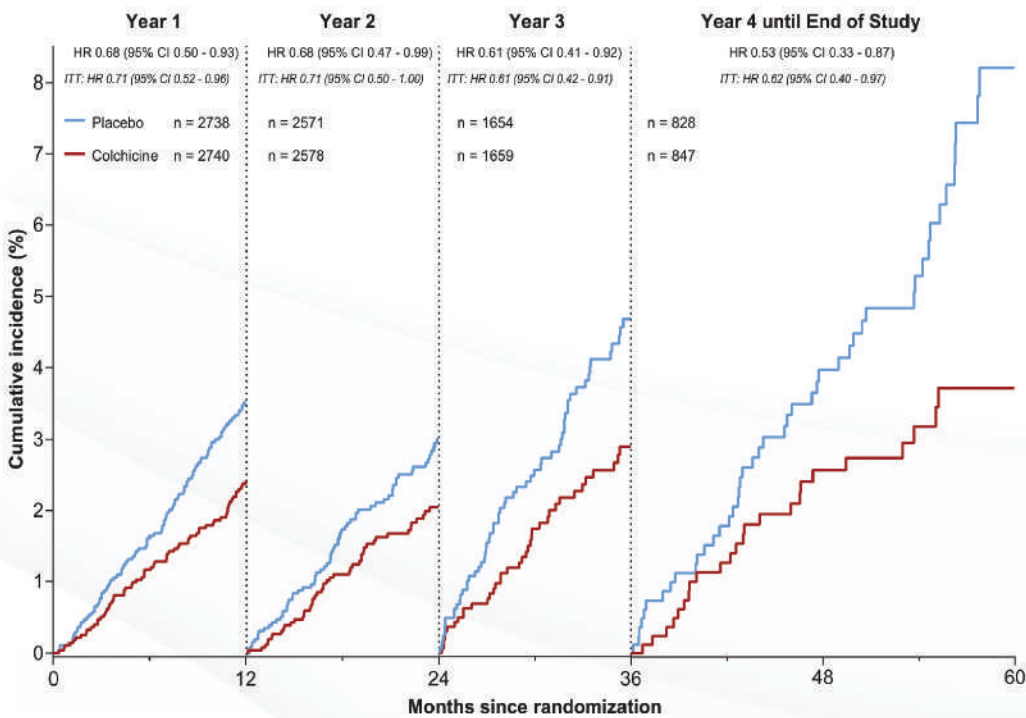
Adverse Events Summary

	Colchicine (N = 2762)	Placebo (N = 2760)
Diagnosis of new cancer (n, %)	120 (4.3)	122 (4.4)
Hospitalization for infection (n, %)	137 (5.0)	144 (5.2)
Hospitalization for pneumonia (n, %)	46 (1.7)	55 (2.0)
Hospitalization for gastrointestinal reason (n, %)	53 (1.9)	50 (1.8)
Neutropenia (n, %)	4 (0.1)	3 (0.1)
Myotoxicity (n, %)	3 (0.1)	3 (0.1)
Gout* (n, %)	38 (1.4)	95 (3.4)

ADVERSE EVENTS

Gout was less common in the colchicine group, and side effects like neutropenia and myotoxic effects were rare across both trial groups, with similar rates of cancer diagnosis, infections, and hospitalizations observed in both groups.

31%
**ADDITIONAL RISK
REDUCTION AS
COMPARED TO
PLACEBO**



PROTECT PATIENTS FROM OVERDOSE RISKS

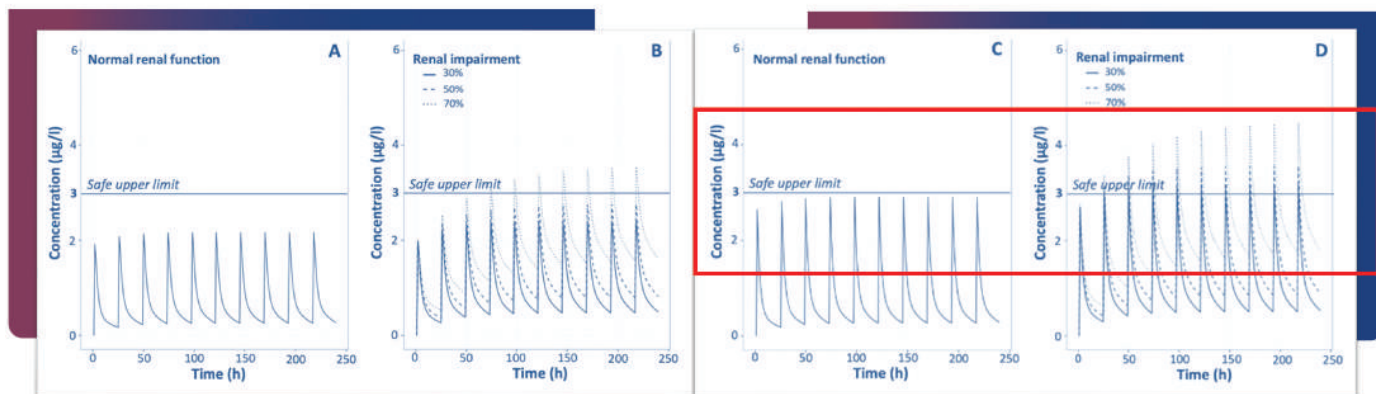
With colchicine, precision is key: even small dose changes can mean big impacts. As a narrow therapeutic index drug, even slight overdosage risks serious, life-threatening effects. Trust the guidelines, and dose with care.

	0.5 mg LODOCO	0.6 mg COLCHICINE 0.6
INDICATION	To reduce CV events	To treat acute gout and Familial Mediterranean fever (FMF)
DOSAGE	Low: 0.5 mg tablets, one tablet daily	High: 0.6 mg tablets, 3 tablets daily (20% higher API per tablet)
DURATION	Long-term use at low doses	Short-term use at high doses
PATIENT PROFILE	Prevent major adverse cardiovascular events with an acceptable safety window	Alleviate and reverse acute inflammatory response tolerate higher risk for a short period of time

LOWER API, LOWER RISK

Colchicine serum levels in patients with normal and impaired renal function

With a 20% higher API per tablet, there is a greater risk of increased serum concentrations with Colchicine 0.6mg vs LODOCO 0.5mg Daily



0.5 mg colchicine / day

0.6 mg colchicine / day

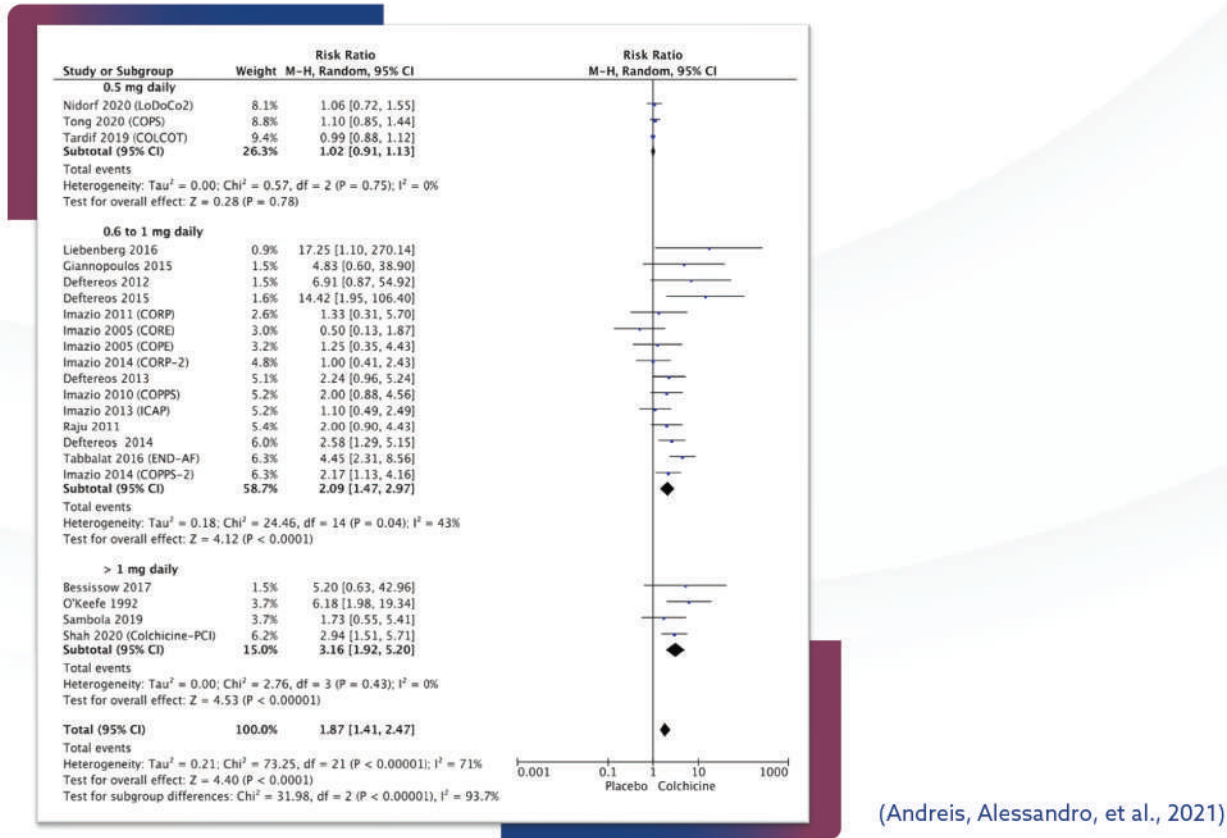
(Robinson, Philip C., et al., 2022)

LONG TERM SAFETY OF LOW-DOSE COLCHICINE

When appropriately prescribed to patients without significant renal or hepatic impairment, low-dose colchicine:

HAS NO ADVERSE EFFECT ON:	TEMPORARY HOLD WITH CONCOMITANT USE	AVOID OR CEASE
Renal Liver Cognitive Function Bleeding Wound Healing Fertility Pregnancy Cancer Serious Infection Specific Mortality Serious drug-drug interaction Myelosuppression Myotoxicity Neonatal Health	Clarithromycin Ketoconazole Fluconazole Cyclosporine Ritonavir	eGFR < 45 mL/min Cytopenia Advanced Liver Disfunction CK or ALT > 3xULN
✓	⚠	✗

LOWER DOSE, FEWER SIDE EFFECTS



A lower daily dose of colchicine (0.5 mg) is associated with significantly fewer gastrointestinal side effects compared to higher doses.

Large meta-analyses show that 0.5 mg daily does not increase the risk of gastrointestinal events (RR 1.02, 95% CI 0.91–1.13, $p = 0.78$, $I^2 = 0\%$), while doses of 0.6–1 mg daily double the risk (RR 2.09, 95% CI 1.47–2.97, $p < 0.0001$, $I^2 = 43\%$) and doses over 1 mg triple it (RR 3.16, 95% CI 1.92–5.20, $p < 0.0001$, $I^2 = 0\%$). These findings align with Nidorf et al.'s study, which reported no increase in gastrointestinal-related hospitalizations for patients on low-dose colchicine compared to placebo.

Low daily doses offer a safer profile and align with the FDA approval and CVD treatment guidelines.

Ridker, Paul M., et al. "Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials." *The Lancet* 401.10384 (2023): 1293-1301.

Pan, Zimo, et al. "Effect of colchicine on inflammatory markers in patients with coronary artery disease: a meta-analysis of clinical trials." *European Journal of Pharmacology* 927 (2022): 175068.

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Deftereos, Spyridon G., et al. "Colchicine in cardiovascular disease: in-depth review." *Circulation* 145.1 (2022): 61-78.

Chen T, Liu G, Yu B. Colchicine for Coronary Artery Disease: A Review. *Front Cardiovasc Med*. 2022 Jun 16;9:892588. doi: 10.3389/fcvm.2022.892588. PMID: 35783861; PMCID: PMC9246049.

Burger, Pascal M., et al. "Individual lifetime benefit from low-dose colchicine in patients with chronic coronary artery disease." *European journal of preventive cardiology* 30.18 (2023): 1-9.

Ridker PM. How Common Is Residual Inflammatory Risk? *Circ Res*. 2017 Feb 17;120(4):617-619. doi: 10.1161/CIRCRESAHA.116.310527. PMID: 28209792.

Robinson, Philip C., et al. "Consensus statement regarding the efficacy and safety of long-term low-dose colchicine in gout and cardiovascular disease." *The American journal of medicine* 135.1 (2022): 32-38.

Karatza, Eleni, George Ismailos, and Vangelis Karalis. "Colchicine for the treatment of COVID-19 patients: efficacy, safety, and model informed dosage regimens." *Xenobiotica* 51.6 (2021): 643-656.

Nidorf, Stefan Mark, Eldad Ben-Chetrit, and Paul M. Ridker. "Low-dose colchicine for atherosclerosis: long-term safety." *European Heart Journal* (2024): ehae208.

Andreis, Alessandro, et al. "Adverse events of colchicine for cardiovascular diseases: a comprehensive meta-analysis of 14 188 patients from 21 randomized controlled trials." *Journal of Cardiovascular Medicine* 22.8 (2021): 637-644.

Alfaddagh A, Martin SS, Leucker TM, Michos ED, Blaha MJ, Lowenstein CJ, Jones SR, Toth PP. Inflammation and cardiovascular disease: From mechanisms to therapeutics. *Am J Prev Cardiol*. 2020 Nov 21;4:100130. doi: 10.1016/j.ajpc.2020.100130. PMID: 34327481; PMCID: PMC8315628.

Chang, Yu-Ching, et al. "Colchicine to prevent cardiovascular death after an acute myocardial infarction." *Journal of the Formosan Medical Association* (2024).

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use LODOCO safely and effectively. See full prescribing information for LODOCO.

LODOCO (colchicine) tablets, for oral use Initial U.S. Approval: 1961

-----INDICATIONS AND USAGE-----

LODOCO is an alkaloid indicated:

- 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 (1).

-----DOSAGE AND ADMINISTRATION-----

The recommended dosage is 0.5 mg orally once daily (2.1).

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 0.5 mg (3).

-----CONTRAINDICATIONS-----

- Concurrent use of strong CYP3A4 inhibitors or P-gp inhibitors with LODOCO is contraindicated, including in patients with hepatic or renal impairment (4).
- LODOCO is contraindicated in patients with pre-existing blood dyscrasias, renal failure, and severe hepatic impairment (4).

-----WARNINGS AND PRECAUTIONS-----

- *Blood dyscrasias*: myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia have been reported (5.1).
- *Neuromuscular toxicity*: Myotoxicity including rhabdomyolysis may occur, especially

in combination with other drugs known to cause this effect. Consider temporary interruption or discontinuation of LODOCO (5.2).

-----ADVERSE REACTIONS-----

The common side-effects reported in published clinical studies and literature with the use of colchicine are gastrointestinal symptoms (diarrhea; vomiting; abdominal cramping) and myalgia (6).

To report SUSPECTED ADVERSE REACTIONS, contact AGEPHA Pharma FZ LLC at 1 (800) 963-0353 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

Coadministration of P-gp and/or CYP3A4 inhibitors (e.g., cyclosporine or clarithromycin) have been demonstrated to alter the concentration of colchicine. The potential for drug-drug interactions must be considered prior to and during therapy. See FPI for a complete list of reported and potential interactions (7).

-----USE IN SPECIFIC POPULATIONS-----

- Females and Males of Reproductive Potential: Advise males that LODOCO may rarely and transiently impair fertility (8.3).
- Patients with renal or hepatic impairment should be monitored closely for adverse effects of colchicine (8.6, 8.7).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2023

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

LODOCO is indicated 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage is 0.5 mg orally once daily.

If a dose of LODOCO is missed, the missed dose should be taken as soon as possible, and the patient should then return to the normal dosing schedule. If a dose is skipped, the patient should not double the next dose.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 0.5 mg - White to slightly yellow, round, biconvex tablets, debossed with 'L1' on one side and plain on the other side.

4 CONTRAINDICATIONS

- Concurrent use of strong CYP3A4 inhibitors or P-glycoprotein inhibitors with LODOCO is contraindicated, because life-threatening and fatal colchicine toxicity has been reported in these patients with colchicine taken in therapeutic doses [see *Drug Interactions* (7)].
- LODOCO use is contraindicated in patients with renal failure (Creatinine clearance less than 15 mL/minute) and severe hepatic impairment.
- LODOCO is contraindicated in patients with pre-existing blood dyscrasias and in patients hypersensitive to this drug or any inactive ingredient of LODOCO [see *Description* (11)].

5 WARNINGS AND PRECAUTIONS

5.1 Blood Dyscrasias

LODOCO can cause myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia, which can be life-threatening or fatal [see *Adverse Reactions* (6)]. Gastrointestinal symptoms often are the first sign of colchicine toxicity, so new symptoms should prompt an evaluation for toxicity. Concomitant use of drugs that reduce the metabolism of colchicine or the presence of hepatic or renal impairment increases the risk of developing blood dyscrasias.

Use of LODOCO in patients with pre-existing blood dyscrasias, renal failure (Creatinine clearance less than 15 mL/minute), or severe hepatic dysfunction, and concomitant use of strong CYP3A4 inhibitors or P-glycoprotein inhibitors is contraindicated [see *Contraindications* (4)]. Concomitant use of moderate CYP3A4 inhibitors with LODOCO should be avoided in patients with risk factors for increased systemic exposure of colchicine. Monitor patients with any degree of renal impairment and hepatic impairment for colchicine toxicity [see *Use in Specific Populations* (8.6, 8.7)].

5.2 Neuromuscular Toxicity

LODOCO can cause neuromuscular toxicity and rhabdomyolysis. Concomitant use of drugs that reduce the metabolism of colchicine or the presence of hepatic or renal impairment increases the risk of developing neuromuscular toxicity. Gastrointestinal symptoms often are the first sign of colchicine toxicity, so new symptoms should prompt evaluation for toxicity. Use of LODOCO in patients with renal failure (Creatinine clearance less than 15 mL/minute), or severe hepatic dysfunction, and concomitant use of strong CYP3A4 inhibitors or P-glycoprotein inhibitors is contraindicated [see *Contraindications* (4)]. Concomitant use of moderate CYP3A4 inhibitors with LODOCO should be avoided in patients with risk factors for increased systemic exposure of colchicine [see *Use in Specific Populations* (8.6, 8.7) and *Drug Interactions* (7)].

If a patient develops signs of neuromuscular toxicity, discontinue LODOCO, investigate other causes, and treat appropriately. Concomitant use of LODOCO and HMG CoA reductase inhibitors, gemfibrozil, and fenofibric acid or cyclosporine may potentiate the development of myopathy [see *Drug Interactions* (7)]. Monitor patients with any degree of renal and hepatic impairment for adverse effects of LODOCO.

6. ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying and controlled conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

In the LoDoCo2 trial, myalgia was reported for 21.2% of individuals randomized to colchicine and 18.5% of individuals randomized to matching placebo (hazard ratio 1.15, 95%CI 1.01-1.31).

6.2 Postmarketing Experience

The following adverse reactions have been identified with colchicine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or establish a causal relationship to drug exposure.

These most often occur with excessive accumulation or overdosage [see *Overdosage* (10)].

Neuromuscular: myotoxicity, weakness, numbness, paresthesia, rhabdomyolysis.

Gastrointestinal: diarrhea, vomiting, abdominal cramping, abdominal pain.

Renal: acute renal impairment

Dermatology: rashes and alopecia

Hematological: thrombocytopenia, leukopenia, pancytopenia

7 DRUG INTERACTIONS

Colchicine is a substrate for the efflux transporter P-glycoprotein (P-gp). CYP3A4 is the primary enzyme involved in the metabolism of colchicine. If LODOCO is administered with drugs that inhibit P-gp, most of which also inhibit CYP3A4, increased concentrations of colchicine are likely (Table 1).

Table 1: Drug Interactions

Drug class	Outcome/effect	Clinical comment
Strong CYP3A4 Inhibitors † atazanavir clarithromycin darunavir/ritonavir indinavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir ritonavir saquinavir telithromycin tipranavir/ritonavir	Significant increases in colchicine plasma levels [see <i>Clinical Pharmacology</i> (12.3)]	Concomitant use of LODOCO with strong CYP3A4 inhibitors is contraindicated [see <i>Contraindications</i> (4)].
Moderate CYP3A4 Inhibitors amprenavir aprepitant diltiazem erythromycin fluconazole fosamprenavir (prodrug of amprenavir) verapamil	Significant increase in colchicine plasma concentration is anticipated.	Monitor patients receiving moderate CYP3A4 inhibitors for signs of colchicine toxicity. Avoid use in patients with existing renal or hepatic impairment [see <i>Warnings and Precautions</i> (5)].
Grapefruit grapefruit juice	Grapefruit juice increases exposure to colchicine.	Advise patients to avoid grapefruit or grapefruit juice when taking LODOCO.
P-glycoprotein Inhibitors † cyclosporine ranolazine	Significant increase in colchicine plasma levels is anticipated with P-gp inhibitors.	Concomitant use of LODOCO with strong P-gp inhibitors is contraindicated [see <i>Contraindications</i> (4)].
HMG-Co A Reductase Inhibitors Other Lipid Lowering drugs fibrates gemfibrozil	Pharmacokinetic and/or pharmacodynamic interaction: the addition of one drug to a stable long term regimen of the other has resulted in myopathy and rhabdomyolysis (including fatality)	Monitor patients for signs or symptoms of muscle pain toxicity.
Digitalis Glycosides digoxin	P-gp substrate; rhabdomyolysis has been reported	
Oral contraceptives Ethinyl estradiol and norethindrone (Ortho-Novum 1/35)	In healthy female volunteers given coadministered with 0.6 mg colchicine twice daily, hormone concentrations are not affected [see <i>Clinical Pharmacology</i> (12.3)]. Colchicine can interact with oral contraceptives like norethindrone/ethinyl estradiol and can cause adverse events like diarrhea, nausea, upper abdominal pain, cold sweat etc.	Females using oral contraceptives should be prescribed LODOCO with caution and observed for adverse events.

† Patients with renal or hepatic impairment should not be given LODOCO in conjunction with strong CYP3A4 or P-gp inhibitors [see *Contraindications* (4)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk summary

Available human data from published literature on colchicine use in pregnancy over several decades have not identified any drug associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes (see *Data*). Colchicine crosses the human placenta. Although animal reproduction and developmental studies were not conducted with LODOCO (colchicine), published animal reproduction and development studies indicate that colchicine causes embryofetal toxicity and altered postnatal development at exposures within or above the clinical therapeutic range.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Human Data

Available data from published observational studies, case series, and case reports over several decades do not suggest an increased risk for major birth defects or miscarriage in pregnant women with rheumatic diseases (such as rheumatoid arthritis, Behcet's disease, or Familial Mediterranean fever (FMF)) treated with colchicine at therapeutic doses during pregnancy.

Limitations of these data include the lack of randomization and inability to control for confounders such as underlying maternal disease and maternal use of concomitant medications.

8.2 Lactation

Risk summary

Colchicine is present in human milk (see *Data*). Adverse events in breastfed infants have not been reported in the published literature after administration of colchicine to lactating women. There are no data on the effects of colchicine on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for LODOCO and any potential adverse effects on the breastfed infant from LODOCO or from the underlying maternal condition.

Data

Limited published data from case reports and a small lactation study demonstrate colchicine is present in breastmilk. A systematic review of literature reported no adverse effects in 149 breastfed children and advised to reconsider breastfeeding if the infant has diarrhea. In a prospective observational cohort study, no gastrointestinal or other symptoms were reported in 38 colchicine-exposed breastfed infants.

8.3 Females and Males of Reproductive Potential

Infertility

Case reports and epidemiology studies in human male subjects on colchicine therapy indicated that infertility from colchicine is rare and may be reversible.

8.4 Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

8.5 Geriatric Use

The total number of subjects included in the LoDoCo2 study who were 65 and over and 75 and over were 3098 (56.1%). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

8.6 Renal Impairment

Colchicine is known to be excreted renally. In renally impaired patients, the total clearance of colchicine is significantly reduced. In patients, with renal impairment, elevated plasma concentrations of colchicine were observed, and may lead to the development of colchicine toxicity and adverse reactions like myeloneuropathy characterized by proximal weakness and elevated serum creatinine, and possibly rhabdomyolysis [see *Warnings and Precautions* (5)].

LODOCO is contraindicated in patients with renal failure (Creatinine clearance less than 15 mL/minute). Patients with renal impairment should be monitored closely for adverse effects of colchicine [see *Contraindications* (4)].

Avoid use in patients with moderate renal impairment receiving moderate CYP3A4 inhibitors [see *Contraindications* (4), *Warnings and Precautions* (5) and *Clinical Pharmacology* (12.3)]

8.7 Hepatic Impairment

Colchicine is primarily metabolized in liver. The clearance of colchicine may be significantly reduced, and plasma half-life prolonged in patients with chronic hepatic impairment, compared to healthy subjects [see *Clinical Pharmacology* (12.3)]. In patients with hepatic impairment, monitor closely for adverse reactions with LODOCO. LODOCO use in severe hepatic impairment is contraindicated. Avoid use in patients with any degree of hepatic impairment and receiving strong P-gp inhibitors or strong or moderate CYP3A4 inhibitors [see *Contraindications* (4) and *Clinical Pharmacology* (12.3)].

10 OVERDOSAGE

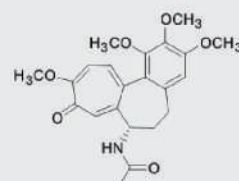
Acute overdose exceeding 0.5 mg/kg (35 mg for a 70 kg average adult) is usually fatal. Fatalities have been reported with as little as 7 mg.

Symptoms: Colchicine poisoning presents in three sequential and usually overlapping phases. The first stage of acute colchicine toxicity typically occurs within 24 hours of ingestion and includes gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea, and significant fluid loss, leading to volume depletion. Peripheral leukocytosis may also be seen. The second stage develops 24 to 72 hours after ingestion and is characterized by multi-organ failure. Death is usually a result of respiratory depression and cardiovascular collapse. Recovery may be accompanied by rebound leukocytosis about one week after the initial ingestion.

Treatment: No specific antidote is known. Elimination of toxins by gastric lavage followed by activated charcoal should be attempted within 1-2 hours of ingestion. Colchicine is not effectively removed by hemodialysis.

11 DESCRIPTION

LODOCO contains colchicine, which is an alkaloid chemically described as (S)-N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[a]heptalen-7-yl)acetamide with a molecular formula of C₂₂H₂₅NO₆ and a molecular weight of 399.4 g/mol. The structural formula of colchicine is given below.



Colchicine occurs as white to pale yellow powder, very soluble in water.

LODOCO (colchicine) tablets are supplied for oral administration as white to slightly yellow, round, biconvex tablets debossed with 'L1' on one side and plain on the other side containing 0.5 mg of colchicine USP as the active ingredient and the following inactive ingredients: gelatin, lactose monohydrate, magnesium stearate, potato starch, and talc.

12 CLINICAL PHARMACOLOGY

The mechanism of action of colchicine in the prevention of major cardiovascular events is not understood. However, it is known that colchicine disrupts cytoskeletal functions through inhibition of β -tubulin polymerization into microtubules and consequently prevents the activation, degranulation, and migration of neutrophils. Colchicine may also interfere with the intracellular assembly of the inflammasome complex in neutrophils and monocytes that mediates activation of interleukin-1 β . These anti-inflammatory effects are consistent with clinical data demonstrating that colchicine reduces high sensitivity C-reactive protein (hs-CRP).

12.2 Pharmacodynamics

The pharmacodynamics of colchicine in the intended indication is not completely understood.

12.3 Pharmacokinetics

In healthy adults, colchicine exhibits linear pharmacokinetics within a dose range of 0.5 to 1.5 mg. Mean pharmacokinetic parameter values of LODOCO in healthy adults are shown in table 2.

Table 2: Summary of LODOCO Pharmacokinetic Parameters in Healthy Adults under Fasting and Fed Conditions

BE studies	C _{max} ng/ml	T _{max} * hours	t _{1/2} hours	AUC ₀₋₄ ng•h/ml
Single dose of 0.5 mg (fasting)	2.1 ± 1.0	1.0 (Range 0.5-2.3)	31.9	18.6 ± 7.0
Single dose of 0.5 mg (fed)	1.8 ± 0.4	1.7 (Range 0.7- 3.5)	31.0	16.4 ± 4.4

*Median and range are presented

Absorption

Oral colchicine intake undergoes an entero-hepatic recirculation. In healthy adults, LODOCO is absorbed when given orally, reaching a mean C_{max} 2.1 ng/ml in approximately 1 hour after a single dose administered under fasting conditions. The mean absolute bioavailability of colchicine is reported to be approximately 45%. Effect of food When LODOCO was administered with or following a high-fat, high-calorie meal in a bioavailability study, the results showed a lack of a significant food effect, see Table 2, above. LODOCO may be administered with or without food. The mean peak plasma concentration of LODOCO under fed conditions was found to be 1.8 ng/ml in approximately 1.75 hour.

Distribution

The mean apparent volume of distribution in healthy volunteers is approximately 1300 L. Colchicine binding to serum protein is 39 ± 5%, primarily to albumin regardless of concentration. After reabsorption, is rapidly removed from the plasma and distributed to various tissues. Colchicine is found in high concentrations in leucocytes, kidneys, the liver, and spleen. Colchicine crosses the placenta. Colchicine also distributes into breast milk. Colchicine can also cross the blood-brain barrier and accumulate within the brain, which contains large amount of tubulin [see Use in Specific Populations (8.1, 8.2)].

Elimination

Metabolism

Colchicine is demethylated to two primary metabolites, 2-O-demethylcolchicine and 3-O-demethylcolchicine (2- and 3-DMC, respectively) and one minor metabolite, 10-O-demethylcolchicine (also known as colchicine). In vitro studies using human liver microsomes have shown that CYP3A4 is involved in the metabolism of colchicine to 2- and 3-DMC. Plasma levels of these metabolites are (less than 5% of parent drug).

Excretion

In healthy volunteers (n=12), 40 to 65% of 1 mg orally administered colchicine was recovered unchanged in urine. Enterohepatic recirculation and biliary excretion are also postulated to play a role in colchicine elimination. Following single oral dose of 0.5 mg daily, the mean effective half-life in healthy volunteers is 19 hours. Colchicine is a substrate of P-gp. Colchicine is not removed by hemodialysis.

Specific Populations

Geriatric Patients

The pharmacokinetic studies of LODOCO were not conducted in elderly patients. In a study, conducted to compare the relative bioavailability in between 18 elderly subjects and 20 young subjects, the following pharmacokinetic parameter values (mean ± SD) were observed for colchicine in the young and elderly subjects, respectively: AUC (ng.hr/mL) 22.4 ± 7.0 and 25.0 ± 6.9; C_{max} (ng/mL) 2.6 ± 0.7 and 2.6 ± 1.0; T_{max} (h) 1.4 ± 0.4 and 1.3 ± 0.4; apparent elimination half-life (h) 24.9 ± 5.3 and 30.1 ± 10.8. No statistical difference in the pharmacokinetic parameters were found between the groups and it was concluded that no dosing adjustments were required in elderly patients. Another study illustrated that after IV administration of 0.5 mg colchicine to six healthy male adults and 1mg colchicine to four elderly group the absorption is similar in healthy volunteers and elderly subjects. However, a 31 percent decrease in volume of distribution at steady state (2.9 vs 4.2 L/kg) and 48 percent decrease in total body clearance (5.5 vs 10.5 L/h) was seen in elderly patients when compared to healthy volunteers.

Pediatric Patients

The sponsor did not conduct any pharmacokinetic studies in pediatric patients. No literature was found in the database on pharmacokinetics of colchicine in pediatric patients with the intended indication.

Patients with Renal Impairment

The exposure of colchicine was similar for normal renal function and mild impairment (24.7–27.2 ng.h/mL) but doubled in subjects with moderate or severe renal impairment (48.9 and 48.0 ng.h/mL, respectively). The same study showed an unexpected result that subjects with ESRD, prior to and during hemodialysis, only have a modest increase in exposure to colchicine (30.6 – 31.7 ng.h/mL) compared to healthy control. The reason for this is not clear. A small amount of the colchicine dose (mean of 5.2 %) was recovered in dialysate [see Use in Specific Population (8.6)]. In another study, subjects with end-stage renal disease requiring dialysis had 75% lower colchicine clearance (0.17 vs 0.73 L/hr/kg) and prolonged plasma elimination half-life (18.8 vs 4.4 hours) as compared to subjects with normal renal function.

Patients with Hepatic Impairment

From the published literature, in some subjects with mild to moderate cirrhosis, healthy subjects had a mean clearance of 10.7 ml/min.kg, whereas cirrhotic patients had a mean clearance of 4.2 ml/min.kg. The mean half-life was about 57 minutes in control subjects vs. about 114 minutes in cirrhotic patients. Volume of distribution was not different in the two groups (0.7 ± 0.1 L/kg in control subjects; 0.7 ± 0.2 L/kg in cirrhotic patients). The study concluded that cirrhosis impairs colchicine clearance. No pharmacokinetic data are available for patients with severe hepatic impairment [see Use in Specific Population (8.7)].

Drug Interaction Studies

In vitro drug interactions:

In vitro studies in human liver microsomes have shown that colchicine is not an inhibitor or inducer of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 activity.

In vivo drug interactions:

The effects of co-administration of other drugs with LODOCO on C_{max}, AUC, and C_{min} are summarized in Table 3 (effect of other drugs on colchicine). For information regarding clinical recommendations, see Table 1 [see Drug Interactions (7)].

Table 3: Effect of other drugs on colchicine pharmacokinetics

Co-administered drug	Dose of Co-administered drug	Dose of Colchicine	Mean pharmacokinetic parameters (%CV) substrate drug				% Change in Colchicine Concentrations from Baseline (Range: Min - Max)	
			C _{max} (ng/ml)	AUC ₀₋₄ (ng/ hour/ ml)	T _{1/2} (hours)	Cl/F (L/ hour)	C _{max}	AUC ₀₋₄
Cyclosporine	100 mg OD	0.6 mg, single dose	2.7	12.6	6.8	48.2	270 (62 to 606.9)	259 (75.8 to 511.9)
Clarithromycin	250 mg BID	0.6 mg, single dose	2.8	12.4	8.9	46.8	227.2 (65.7 to 591.1)	281.5 (88.7 to 851.6)
Ketoconazole	200 mg BID	0.6 mg, single dose	2.8	12.0	6.3	49.3	101.7 (19.6 to 219)	212.2 (76.7 to 419.6)
Ritonavir	100 mg BID	0.6 mg, single dose	1.9	8.4	5.2	67.9	184.4 (79.2 to 447.4)	296 (53.8 to 924.4)
Verapamil	240 mg OD	0.6 mg, single dose	3.0	13.1	4.3	43.9	40.1 (-47.1 to 149.5)	103.3 (-9.8 to 217.2)
Diltiazem	240 mg OD	0.6 mg, single dose	2.2	10.0	5.5	58.9	44.2 (-46 to 318.3)	93.4 (-30.2 to 338.6)
Azithromycin	500 mg OD	0.6 mg, single dose	2.7	12.0	6.1	50.2	21.6 (-41.7 to 222)	57.1 (-24.3 to 241.1)
Atorvastatin	40 mg OD	0.6 mg, single dose	2.5	10.7	4.3	58.6	130.60 (111.1-153.5)	127.3 (109.1–148.7)
Grapefruit juice	240 mL twice daily, 4 days	0.6 mg, single dose	–	–	–	–	-2.6 (-53.4 to 55.0)	-2.4 (-4.6 to 62.2)

Estrogen-containing oral contraceptives: In healthy female volunteers given ethinyl estradiol and norethindrone (Ortho-Novum 1/35) co-administered with colchicine 0.6 mg b.i.d. ×14 days, hormone concentrations are not affected.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year studies were conducted in mice and rats to assess the carcinogenic potential of colchicine. No evidence of colchicine-related tumorigenicity was observed in mice or rats at colchicine oral doses up to 3 and 2 mg/kg/day, respectively, approximately 29 and 38 times, the recommended human dose of 0.5 mg on a mg/m2 basis.

Mutagenesis

Colchicine was negative for mutagenicity in the bacterial reverse mutation assay. In a chromosomal aberration assay in cultured human white blood cells, colchicine treatment resulted in the formation of micronuclei. Since published studies demonstrated that colchicine induces aneuploidy from the process of mitotic nondisjunction without structural DNA changes, colchicine is not considered clastogenic, although micronuclei are formed.

Impairment of Fertility

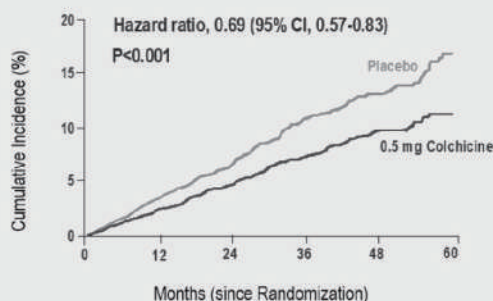
No studies of colchicine effects on fertility were conducted with LODOCO. However, published nonclinical studies demonstrated that colchicine-induced disruption of microtubule formation affects meiosis and mitosis. Reproductive studies also reported abnormal sperm morphology and reduced sperm counts in males, and interference with sperm penetration, second meiotic division and normal cleavage in females when exposed to colchicine. Colchicine administered to pregnant animals resulted in fetal death and teratogenicity. These effects were dose-dependent, with the timing of exposure critical for the effects on embryofetal development. The nonclinical doses evaluated were generally higher than an equivalent human therapeutic dose, but safety margins for reproductive and developmental toxicity could not be determined.

14 CLINICAL STUDIES

The evidence for the efficacy of colchicine in patients with cardiovascular events is derived from published literature (LoDoCo2) along with other supportive studies. The LoDoCo2 trial was an investigator-initiated, randomized, placebo controlled, double-blind, event-driven trial conducted to assess the efficacy of colchicine 0.5mg once daily orally in patients with stable coronary artery disease. The study included 5522 patients, in which 2762 were assigned to the colchicine group and 2760 to placebo. The baseline characteristics of the patients were balanced between the trial groups. Patients were treated for chronic coronary disease, with 99.7% taking an antiplatelet agent or an anticoagulant, 96.6% a lipid-lowering agent, 97.3% of which were statins, 62.1% a beta-blocker, and 71.7% an inhibitor of the renin-angiotensin system. LoDoCo2 assessed the efficacy of colchicine 0.5 mg once daily in patients with stable coronary artery disease. Patients between 35-85 years were eligible for participation in the LoDoCo2 trial if they had proven coronary artery disease, were clinically stable for at least 6 months, without comorbidities that would preclude follow-up, or contraindication to colchicine use. The mean ($\pm$ SD) age of the patients was 66 $\pm$ 8.6 years, and 846 (15.3%) were female. The median time on study medication was 28.6 months. The primary end point of LoDoCo2 trial was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization.

In the LoDoCo2 trial, 0.5 mg of colchicine once daily resulted in a 31% lower relative risk (RRR) of the primary composite endpoint events compared to placebo (HR, 0.69; 95% CI] 0.57 to 0.83; $p < 0.001$) and the number needed to treat (NNT) was 36.

Figure 1: Cumulative Incidence of Primary End point in LoDoCo2 trial



No. at Risk

Placebo	2760	2655	1703	821	590	161
0.5 mg Colchicine	2762	2685	1761	890	629	166

The results of the primary endpoint are summarized in Table 4.

Table 4: Summary of efficacy results of LoDoCo2 trial

End Point	LoDoCo2 Trial			
	Colchicine (N=2762) No. of patients (%)	Placebo (N=2760) No. of patients (%)	Hazard ratio (95% CI)	P value
Primary end point Cardiovascular death, myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization	187 (6.8)	264 (9.6)	0.69 (0.57-0.83)	<0.001
Ischemia-driven coronary revascularization	135 (4.9)	177 (6.4)	0.75 (0.60-0.94)	
Myocardial infarction	83 (3.0)	116 (4.2)	0.70 (0.53-0.93)	
Ischemic stroke	16 (0.6)	24 (0.9)	0.66 (0.35-1.25)	
Cardiovascular death	20 (0.7)	25 (0.9)	0.80 (0.44-1.44)	

Myocardial infarction refers to spontaneous (non-procedural) myocardial infarction.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

LODOCO (colchicine) tablets 0.5 mg are white to slightly yellow, round, and biconvex and debossed with 'L1' on one side and plain on the other side and they are available as a single Aluminum/PVC blister pack of 30 tablets, which is secondary packaged in a carton: NDC 82867-001-01

16.2 Storage

Store LODOCO at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F), [See USP Controlled Room Temperature]. Store LODOCO tablets in the original package in order to protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Dosing Instructions

- Advise patients to take LODOCO as prescribed, and patients should not alter or discontinue the medication without consulting their healthcare provider.
- Advise patients that if the dose of LODOCO is missed, they should take the missed dose as soon as possible and return to the normal dosing schedule.
- If a dose is skipped advise patient not to double the next dose.

Drug and food interactions

Patients should be advised that many drugs or other substances may interact with LODOCO and some interactions could be fatal. Therefore, patients should report to their healthcare provider all of the current medications they are taking and check with their healthcare provider before starting any new medications, particularly antibiotics. Patients should also be advised to report the use of nonprescription medication or herbal products. Advise patients that grapefruit and grapefruit juice may also interact and should not be consumed during LODOCO treatment.

Colchicine Toxicity

Advise patients that gastrointestinal symptoms are often the first sign of colchicine toxicity. Patients should be instructed to contact their healthcare provider if new symptoms develop.

Neuromuscular Toxicity

Inform patients that muscle pain or weakness, tingling or numbness in fingers or toes may occur with LODOCO alone or when it is used with certain other drugs. Concomitant use of LODOCO and HMG CoA reductase inhibitors, gemfibrozil, and fenofibric acid or cyclosporine may potentiate the development of myopathy (muscles weakness, fatigue). Patients developing any of these signs or symptoms must discontinue LODOCO and seek medical evaluation immediately. Concomitant use of interacting drugs, including statins, or renal or hepatic insufficiency increases the risk of developing toxicity.

Infertility

Advise males of reproductive potential that LODOCO may rarely and transiently impair fertility [see Use in Specific Populations (8.3)].

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AGEPHA Pharma USA, LLC
181 New Road, Suite 304
Parsippany, NJ 07054



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