Canadian Journal of Health Technologies

CADTH

March 2022 Volume 2 Issue 3

CADTH Reimbursement Recommendation

Colchicine (Myinfla)

Indication: For the reduction of atherothrombotic events in adult patients with existing coronary artery disease, in addition to standard therapies, including low-density lipoprotein cholesterol lowering and antithrombotic drug treatment

Sponsor: Pendopharm, a division of Pharmascience Inc.

Final recommendation: Do not reimburse

CADTH

ISSN: 2563-6596

Redactions: Confidential information in this document may be redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Myinfla?

CADTH recommends that Myinfla should not be reimbursed by public drug plans for the reduction of atherothrombotic events in adults with coronary artery disease.

Why Did CADTH Make This Recommendation?

- Evidence from 4 clinical trials in patients with coronary artery disease showed that adding Myinfla to standard preventive treatments lowered patients' chances of having major cardiovascular events.
- There was not enough evidence to show that Myinfla reduced mortality, heart attack and/or stroke, or improved health-related quality of life.

Additional Information

What Is Coronary Artery Disease?

Coronary artery disease is a common type of heart disease that may lead to heart attack, stroke, or early death. An estimated 2.4 million Canadian adults have been diagnosed with coronary heart disease, including 578,000 adults who have experienced a heart attack.

Unmet Needs in Coronary Artery Disease

Although there are several medications and other treatments available to manage coronary artery disease, many patients continue to experience death, heart attack, stroke, and hospitalization because of coronary artery disease. Therefore, additional treatment options are needed.

How Much Does Myinfla Cost?

Treatment with Myinfla is expected to cost approximately $182 per patient per year.

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that colchicine not be reimbursed for the reduction of atherothrombotic events in adult patients with existing coronary artery disease.

Rationale for the Recommendation

Four randomized controlled trials that enrolled adults with an acute myocardial infarction (COLCOT), stable coronary artery disease (LoDoCo2, LoDoCo), or acute coronary syndrome (COPS) showed statistically significant differences in the time to first occurrence of an adjudicated major cardiovascular event (a composite end point) favouring colchicine as add-on to standard secondary prevention therapy relative to placebo. Of the major cardiovascular events included in the composite end points, myocardial infarction, and revascularization procedures were the most frequently reported, with resuscitated cardiac arrest, stroke, and cardiovascular death reported less frequently. None of the included studies were designed to provide evidence of the effects of colchicine on cardiovascular mortality, all-cause mortality, or the reduction of the risk of subsequent myocardial infarction or stroke. In addition, results of the secondary outcomes and individual components of the composite end point were not consistently supportive of the statistically significant result of the primary composite end point. This evidence, along with other limitations associated with the internal and external validity of the included studies, constitute a high degree of uncertainty regarding the added clinical value of colchicine 0.5 mg in addressing important clinical outcomes, specifically related to mortality, subsequent myocardial infarction, and/or stroke, and health-related quality of life.

Discussion Point

- CDEC discussed that the short duration of the studies and the life-long application of the treatment raise concerns regarding adherence, adverse events, and long-term efficacy. In patients with coronary artery disease, comparative evidence on safety was limited by the incomplete collection and reporting of adverse events, the enrolment of an enriched patient population in the LoDoCo2 study, the sample size, and duration of the trials.

Background

Colchicine has a Health Canada indication for the reduction of atherothrombotic events in adult patients with existing coronary artery disease, in addition to standard therapies, including low-density lipoprotein cholesterol (LDL-C) lowering and antithrombotic drug treatment. Colchicine is an anti-inflammatory drug. It is available as 0.5 mg extended release tablet and the Health Canada–approved dose is 0.5 mg once daily.

Sources of Information Used by the Committee

To make their recommendation, CDEC considered the following information:

- A systematic review that included 4 randomized controlled clinical trials in patients with coronary artery disease.
- Input from public drug plans that participate in the CADTH review process.
- Input from 2 clinical specialists with expertise diagnosing and treating patients with coronary artery disease.
- A review of the pharmacoeconomic model and report submitted by the sponsor.
- No patient group input was received for this review.

Stakeholder Perspectives

Clinician Input

Input From Clinical Experts Consulted by CADTH

Despite widespread implementation of guideline recommended therapies, many patients with coronary artery disease and acute coronary syndrome (ACS) continue to experience subsequent cardiovascular events (death, myocardial infarction [MI], stroke, and hospitalization for revascularization procedures). According to the clinical experts consulted for this review, colchicine would be used long-term for the secondary prevention of ischemic cardiac events and is best suited for those with coronary artery disease who have experienced an MI. Colchicine would be used as add-on therapy and would not replace any of the standard guideline recommended secondary prevention drugs. Colchicine should be avoided in patients who are using certain drugs metabolized via the cytochrome P450 enzyme (CYP) 3A4 or P-glycoprotein pathways due to the increased risk of colchicine toxicity, or in patients with other contraindications to therapy. The development of adverse effects may lead to discontinuation of colchicine, according to the experts consulted, and the use of colchicine for secondary prevention may not be an option for patients who have experienced intolerable adverse effects with colchicine in the past.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for colchicine:

- Considerations for initiation of therapy.
- Considerations for discontinuation of therapy.
- Considerations for prescribing of therapy.
- Generalizability of trial populations to the broader populations in the jurisdictions.
- Care provision issues.

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

The drug programs requested input on the patients most likely to be prescribed colchicine, the longer-term safety and tolerance of colchicine, and the potential for off-label use of colchicine 0.6 mg dosage form as secondary prevention therapy. In response, the clinical experts expect that colchicine will be used primarily in patients with a history of MI, including some patients who were excluded from the clinical trials (e.g., low ejection fraction, prior bypass surgery). A large number of patients are potentially eligible for treatment with colchicine, as the drug could be initiated irrespective of how much time has elapsed since a prior myocardial ischemic event. Colchicine is associated with gastrointestinal adverse effects, and a portion of patients will discontinue therapy due to intolerance. Based on previous experience with colchicine, the frequency of discontinuation due to adverse effects is expected to be similar to other secondary prevention drugs.

The clinical expert stated that colchicine may be beneficial as primary prevention therapy however, direct evidence is lacking as no clinical trials have been conducted in this population. Primary prevention is outside the Health Canada indication for colchicine. The experts state that some clinicians have prescribed colchicine 0.6 mg tablets for secondary prevention therapy, and it is possible that off-label use may continue after the 0.5 mg dosage formulation is available in Canada. There is some uncertainty in regards to long-term safety of colchicine in patients with coronary artery disease and additional data are required.

Clinical Evidence

Description of Studies

Four randomized controlled trials (RCTs) met the inclusion criteria for the systematic review, including 3 double-blind placebo-controlled studies (COLCOT, COPS, LoDoCo2) and 1 open-label, observer-blinded trial (LoDoCo). The trials enrolled adults with an acute MI (COLCOT), ACS (COPS), or stable coronary artery disease (LoDoCo2, LoDoCo), and had a sample size that ranged from 532 to 5,522 patients. Patients received colchicine 0.5 mg daily versus placebo or no treatment as add-on therapy to standard secondary prevention therapies. In the LoDoCo2 study, all patients received open-label colchicine during a 1-month run-in period and those who were tolerant and adherent to therapy were randomized. The primary outcome in all trials was the time to first occurrence of a composite outcome that included several major cardiovascular events. The median follow-up duration ranged from 1 to 3 years.

The mean age of patients enrolled ranged from 59.7 years (standard deviation [SD] 10.2) to 67 years (SD 9.2), and 78% to 89% of patients per treatment group were male. Approximately half of the patients enrolled had a history of hypertension (50% to 52%), 18% to 33% had diabetes, and 4% to 37% were smokers. In the LoDoCo2 and LoDoCo studies, 84% and 24% of patients, respectively, had a history of ACS. In the COLCOT study, patients were enrolled a mean of 13.5 days following their MI, and in the COPS study, patients were enrolled during their hospital admission for ACS.

Efficacy Results

The COLCOT study reported a similar number of deaths in the colchicine (43 patients, 1.8%) and placebo groups (44 patients, 1.8%) over a median follow-up period of 22.6 months (hazard ratio [HR] 0.98; 95% CI, 0.64 to 1.49, P = 0.93) (total N = 4,745). For the primary composite outcome, 131 patients (5.5%) in the colchicine group and 170 patients (7.1%) in the placebo group experienced an adjudicated event of cardiovascular death, resuscitated cardiac arrest, acute MI, stroke, or urgent revascularization. The unadjusted HR for the time to first occurrence of the primary composite end point was 0.77, 95% CI, 0.61 to 0.96 (P = 0.02) for colchicine versus placebo.

In the 1-year COPS study, 8 patients who received colchicine died (2.0%), compared with 1 patient in the placebo group (0.3%) (HR 8.20, 95% CI, 1.03 to 65.61, P = 0.047, not adjusted for type I error rate). In this trial, 24 patients in the colchicine group (6.1%) and 38 patients (9.5%) in the placebo group experienced a primary adjudicated end point of either death, ACS, ischemia-driven urgent revascularization, or non-cardioembolic ischemic stroke by 12 months (P = 0.09 log-rank test). The estimated HR for the time to first adjudicated primary end point was 0.65, 95% CI, 0.38 to 1.09 (total N = 795).

The LoDoCo2 study reported 73 deaths (2.6%) in the colchicine group and 60 (2.2%) deaths in the placebo group after a median follow-up of 28.6 months (HR 1.21 95% CI, 0.86 to 1.71) (total N = 5,522). The primary composite outcome was time to first occurrence of an adjudicated cardiovascular death, non-procedural MI, ischemic stroke, or ischemia-driven revascularization. In the colchicine group, 187 patients (6.8%) experienced an adjudicated primary end point compared with 264 patients (9.6%) in the placebo group, with a cause-specific HR of 0.69 95% CI, 0.57 to 0.83, P < 0.001.

A total of 4 patients died (1.4%) in the colchicine group and 10 patients (4.0%) died in the control group of the LoDoCo study, which had a median follow-up duration of 36 months (total N = 532). Fifteen patients (5.3%) in the colchicine group and 40 patients (16.0%) in the control group experienced an adjudicated primary end point event of ACS, fatal or non-fatal out of hospital cardiac arrest or non-cardioembolic stroke (unadjusted HR 0.33 95% CI, 0.18 to 0.59, P < 0.001).

In the LoDoCo2 and LoDoCo studies, the treatment effects for the primary composite end point were similar in the subgroup of patients with a history of ACS, as in the overall population.

Across all 4 trials, the time to event analyses of the individual components of the primary composite end point showed point estimates for the HR that favoured colchicine versus control, however the 95% CI did not exclude the null for all outcomes. Of the major cardiovascular events included in the composite end points, MI, and revascularization procedures were the most frequently reported, with resuscitated cardiac arrest, stroke, and death reported less frequently. Only the LoDoCo2 study used a hierarchical testing procedure to control the type I error rate for secondary outcomes, which included the time to ischemia-driven revascularization (HR 0.75 95% CI 0.60 to 0.94; P = 0.01), MI (HR 0.70 95% CI, 0.53 to 0.93, P = 0.01), ischemic stroke (HR 0.66 95% CI 0.35 to 1.25, P = 0.20) and cardiovascular death (0.80 95% CI, 0.44 to 1.44; P value not reported as statistical testing was stopped). Of note, the experts consulted for this review indicated that not all end points in the composite were of equal importance. A significant reduction in revascularization, while important from a health care resource perspective, may be considered of lesser relevance to patients than

death, or potentially disabling stroke or MI. These differences in clinical importance of the end points should be considered when interpreting the results of the composite outcomes.

Harms Results

The collection and reporting of harms data were incomplete for all studies. No studies collected data on the overall frequency of adverse events and only the COLCOT study reported the number of patients with 1 or more serious adverse events (16% in the colchicine group and 17% in the placebo group).

The overall frequency of gastrointestinal adverse effects was 17% per treatment group in the COLCOT study, and 21% to 23% in the COPS study. Gastrointestinal adverse effects were the reason for treatment discontinuation for 4% of colchicine-treated patients in the COLCOT study, 9% in the COPS study, and 14% in the LoDoCo study. During the run-in period of the LoDoCo2 study 9% of patients withdrew due to intolerance, and during the double-blind phase another 3% of patients per group stopped treatment.

Generally, the frequency of neoplasms and serious infections appeared to be numerically similar between groups in the COLCOT and LoDoCo2 studies. Myalgia was reported in 21.2% of patients in the colchicine group compared with 18.5% of patients in the placebo group, based on data from a subgroup of the LoDoCo2 study.

Critical Appraisal

No major sources of bias were identified for the pivotal COLCOT and LoDoCo2 studies. Potential limitations include unclear allocation concealment in the LoDoCo2 study, and lack of control of multiplicity in the COLCOT study.

Several limitations were identified for the 2 other trials. This included the sample size (532 and 795) and lack of statistical power (COPS), as well as poor reporting of methods to maintain blinding of all participants in the double-blind COPS study or outcome assessors in the open-label, assessor blinded LoDoCo study. In the COPS study, follow-up was incomplete for many patients (number not reported) at the time of the pre-planned primary analysis. The randomization process was potentially biased in the LoDoCo study, and some imbalances in patient characteristics were noted at baseline; thus, it is unclear if all prognostic and effect modifiers were balanced between groups. Due to the open-label design, the LoDoCo study may also be subject to performance bias, outcome ascertainment bias, and reporting bias.

Of note, the trials were designed and powered to detect differences in the primary composite outcome, not the individual outcomes of the composite, or for mortality. None of the trials collected data on health-related quality of life, and limited hospitalization data were reported in the COPS study.

The safety data available were limited by the sample size and study duration of the key trials, which may have been insufficient to detect infrequent adverse events or those that require a longer time to develop. Moreover, the collection and reporting of adverse event data was incomplete. Although colchicine has been available in Canada for decades, some uncertainty remains regarding its comparative longer-term safety in patients with coronary artery disease.

With regard to external validity, the LoDoCo2 study enrolled an enriched population that was tolerant and adherent to colchicine, and thus, may overestimate the treatment effects in an unselected patient population. The pivotal trials excluded patients with more severe heart

failure, valvular heart disease or prior coronary bypass graft, as well as those with renal or hepatic impairment. As a result, the findings may not be generalizable to these patients. Although the patients enrolled may not reflect the gender, racial or ethnic diversity of the Canadian population, the experts had no major concerns with the generalizability of the study populations.

Economic Evidence

Table 1: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Markov Model
Target population	Patients with existing coronary artery disease (CAD)
Submitted price	Colchicine, 0.5 mg, tablet: $0.50
Treatment cost	Colchicine: annual per patient cost: $182.50. SOC was not defined by the sponsor and no costs for SOC were included in the analysis.
Treatment	Colchicine plus standard of care (SOC)[a]
Comparator	SOC[a]
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	Lifetime (44 years)
Key data sources	LoDoCo2 trial, COLCOT trial
Key limitations	• The sponsor's model lacks face validity in that, after a first non-fatal cardiovascular event (MI, stroke, coronary revascularization), patients were not at risk of subsequent non-fatal events. Clinical experts consulted by CADTH indicated that multiple CV events are common in this population. Patients were assumed to continue to receive colchicine for the entire model time horizon, which does not account for treatment discontinuation observed in clinical trials. • Costs related to SOC were not included in the model. Because the sponsor's model predicts a survival benefit with colchicine + SOC, the exclusion of SOC costs underestimates the total drug costs associated with the use of colchicine. • The long-term effectiveness of colchicine + SOC compared to SOC is highly uncertain for several reasons. The sponsor assumed that the relative treatment effects observed during the clinical trials would remain constant over the entire treatment duration, which is unlikely. The sponsor predicts a survival benefit with the use of colchicine which has not been observed in clinical trials, and the clinical experts consulted by CADTH indicated that the proportion of patients assumed to remain free of CV events is likely overestimated.

Component	Description
	• The effectiveness of colchicine in reducing CV events was based on a composite outcome from the LoDoCo2 trial, which included CV death, non-fatal MI, non-fatal stroke, and ischemia-driven coronary revascularizations. (The composite outcome for COLCOT in a post-MI population additionally included resuscitated cardiac arrest.) The events included within the composite outcome are of varying degrees of severity and importance to patients. The sponsor assumed that the distribution of individual CV events within the composite outcome would be equivalent between the colchicine + SOC and SOC groups, which is inconsistent with clinical trial data. • Regional differences in treatment efficacy were observed in the LoDoCo2 trial, and the generalizability of LoDoCo2 trial data to Canadian patients with stable CAD is uncertain owing to a lack of Canadian study centres. • The cost of colchicine was underestimated. The sponsor assumed 65% adherence for colchicine based on claims data for statins. Reduced adherence was assumed to affect drug costs but not effectiveness, which inappropriately reduces the cost of colchicine in the model. • The impact of colchicine on quality of life is uncertain. Quality of life was not assessed in the LoDoCo2 or COLCOT trials, and health state utility values were obtained from the literature from multiple sources. The baseline utility value adopted for patients with CAD and MI lacks face validity in that it was higher than that adopted for post non-fatal MI in patients with CAD.
CADTH reanalysis results	• To account for key limitations, several changes were made to the CADTH base case. CADTH analyses assume that the Health Canada indication is represented by two subgroups: patients with stable CAD and patients with a recent MI (CAD+MI). Owing to a lack of data on the full Health Canada indication, the cost-effectiveness of colchicine in patients with unstable angina or severe heart failure is unknown. • For the stable CAD subgroup, CADTH reanalyses included adopting a 20-year time horizon, adopting treatment-specific distributions of CV events, and assuming full treatment adherence. For the CAD+MI subgroup, CADTH made additional changes including adding an annual cost of SOC and adopting alternative health state utility values. CADTH was unable to address the lack of consideration for multiple CV events, the varying severity of CV events within the composite outcome, the generalizability of LoDoCo2 trial data to Canadian patients, and uncertainty regarding the impact of colchicine on health-related quality of life. • In the stable CAD subgroup, colchicine + SOC was associated with an ICER of $100 per QALY when compared to SOC alone (incremental costs: $14; incremental QALYs: 0.14). The probability of colchicine + SOC being cost-effective at a $50,000 per QALY threshold was 63%. Based on the mean ICER, no price reduction would be required to achieve an ICER below $50,000 per QALY for patients with stable CAD; however, given the wide uncertainty around the probabilistic ICER, a price reduction may still be necessary. • In the CAD+MI subgroup, colchicine was associated with an ICER of $64,922 per QALY when compared to SOC alone (incremental costs: $1,389; incremental QALYs: 0.02). The probability of colchicine + SOC being cost-effective at a $50,000 per QALY threshold was 47%. In this subgroup, a 15% price reduction would be required to achieve an ICER below $50,000 per QALY; however, given the wide uncertainty around the probabilistic ICER, further price reductions may still be necessary. • For both patients with stable CAD and those with CAD+MI, the majority of the predicted clinical benefits are accrued beyond the clinical trial duration (88% to 97%). Owing to this, an assumed constant clinical benefit for colchicine in the composite outcome, and considerable uncertainty in model parameters (e.g., individual event rates within the composite outcome), there is a high degree of uncertainty in the model results.

CAD = coronary artery disease; CV = cardiovascular; ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; SOC = standard of care; LY = life year; QALY = quality-adjusted life-year.

[a]The composition of SOC was not defined by the sponsor.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the number of individuals eligible for public drug plan coverage is underestimated; the cost of colchicine is underestimated; there is a high degree of uncertainty in assumptions around the market share and uptake rate of colchicine; and the cost of prolonged survival on colchicine is not captured in the estimated budget impact. The CADTH reanalysis included using the proportion of patients eligible for coverage to calculate market size and assuming full colchicine adherence.

Although the sponsor suggested colchicine would be associated with a budget impact of $24,421,794 over the 3-year time horizon, based on CADTH reanalyses, the estimated budget impact to the public drug plans of reimbursing colchicine for the full Health Canada–indicated population (patients with CAD) is $7,650,184 in year 1, $15,021,976 in year 2, and $30,254,348 in year 3, for a 3-year total of $52,926,508. The estimated budget impact is sensitive to the proportion of patients eligible for public drug plan coverage and treatment adherence.

CDEC Information

Members of the Committee

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Initial Meeting Date: October 28, 2021

Regrets: 1 CDEC member did not attend

Conflicts of interest: None

Reconsideration Meeting Date: February 23, 2022

Regrets: None

Conflicts of interest: None