CADTH

CADTH REIMBURSEMENT REVIEW

Stakeholder Feedback on Draft Recommendation

COLCHICINE (Myinfla)

(Pendopharm, a division of Pharmascience Inc.)

Indication: Reduction of atherothrombotic events in adult patients with existing coronary artery disease, in addition to standard therapies, including LDL-C lowering and antithrombotic drug treatment.

December 2, 2021

CADTH

CADTH Reimbursement Review
Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0691-000
Brand name (generic)	Myinfla (colchicine 0.5 mg)
Indication(s)	Reduction of atherothrombotic events in adult patients with existing coronary artery disease, in addition to standard therapies, including LDL-C lowering and antithrombotic drug treatment.
Organization	Co-authors of "Colchicine for Prevention of Atherothrombotic Events in Patients with Coronary Artery Disease: Review and Practical Approach for Clinicians", published in the Canadian Journal of Cardiology and Principal Investigators of the COLCOT and LoDoCo2 Trials
Contact information[a]	[redacted]

Stakeholder agreement with the draft recommendation		
1. Does the stakeholder agree with the committee's recommendation.	Yes	☐
	No	☒

As lead clinical researchers in the pursuit of new therapies for secondary prevention of coronary disease who are familiar with the evidence of efficacy and safety of low-dose colchicine, we believe that the committee's recommendation not to reimburse colchicine 0.5 mg daily for this purpose has not fully taken into account the scope of the available evidence it was provided.

Despite existing guidelines-based secondary prevention strategies, residual risk of subsequent vascular events remains high, emphasizing the need to identify additional therapeutic targets in order to further improve patient outcomes.

We co-authored the article: "Colchicine for Prevention of Atherothrombotic Events in Patients with Coronary Artery Disease: Review and Practical Approach for Clinicians" published in 2021 by the Canadian Journal of Cardiology. This article is mainly based on our review and interpretation of the COLCOT, LoDoCo2, LoDoCo and COPS trials and meta-analyses of colchicine for the prevention of ischemic cardiovascular events in patients with coronary artery disease. The conclusion of our article is as follows:

"Although the anti-inflammatory agent colchicine has been known for centuries, data has recently positioned the novel use of this inexpensive and safe drug as part of the pharmacological armamentarium for the prevention of non-fatal atherothrombotic events in patients with CAD. Along with other guideline-recommended secondary prevention strategies and lifestyle modifications, colchicine at a dose of 0.5 mg once daily should be considered in patients with a recent MI or with established stable CAD to improve non-fatal cardiovascular outcomes."

As practicing cardiologists and healthcare professionals, we are concerned that CADTH's draft recommendation would limit access to a safer lower dose of colchicine already approved by Health Canada that significantly reduces residual risk of subsequent vascular events.

We are suggesting that CADTH reconsider its draft recommendation not to reimburse this low-dose preparation of colchicine based on the following points:

1. The results of the large trials (COLCOT and LoDoCo2) are robust and fully aligned. The reductions in the primary efficacy endpoint with colchicine compared to placebo were large (23% and 31% in COLCOT and LoDoCo2 respectively), statistically significant and have rarely been observed when tested in addition to excellent standard care. Furthermore, the reduction of 34% in COLCOT of the prespecified endpoint of the total burden of both first and recurrent primary endpoint events with colchicine compared to placebo has never been obtained with any other therapy administered in

addition to the intensive use of statins (99% and 94% of patients were taken a statin in COLCOT and LoDoCo2 respectively). Despite their smaller sizes, LoDoCo and COPS also support COLCOT and LoDoCo2.

2. Reductions in the risk of the individual non-fatal outcomes of myocardial infarction, stroke and unscheduled coronary revascularization as well as the composite endpoint of cardiovascular death, myocardial infarction and stroke with low-dose colchicine have been confirmed in published meta-analyses. These reductions in individual ischemic cardiovascular events are clinically meaningful, statistically significant and similar to those achieved with statin therapy and were achieved on top of standard therapy.
3. These meta-analyses and systematic reviews confirming the consistency of effects on individual non-fatal cardiovascular outcomes have provided Level A evidence to support the use of colchicine in recent updates of guidelines for secondary prevention of cardiovascular disease in Europe and Central America, as well as in our multi-author article in Canada.
4. The risk of harm of colchicine 0.5 mg as used in the clinical trials is very low: early intolerance is mild and self-limiting, and long-term use has proven its safety in COLCOT and LoDoCo2 that have included more than 10,000 patients followed for a mean of more than 2 years and extending out to 5 years.
5. If the decision to reimburse colchicine 0.5 mg daily for secondary prevention of coronary disease is rejected, it is likely that some physicians and patients will choose to use the 0.6 mg dose of colchicine for this purpose. Although this dose is likely to be effective, the 0.5 mg dose appears to be better tolerated and has a wider margin of safety, which is especially important in the treatment of elderly patients and those with some degree of renal impairment and who are at high risk from their disease. Furthermore, why should patients and physicians have to revert to using a dosage (0.6 mg) that was not tested in cardiovascular clinical trials and that has not been approved by Health Canada?
6. A convincing published cost-effectiveness analysis has shown that the use of colchicine to reduce the risk of ischemic cardiovascular events is economically dominant in multiple scenarios. There are very few cardiovascular medications that reach this status. Given this economic dominance, the cost of the new preparation of low-dose colchicine (0.50$ per day) is obviously smaller than the healthcare cost savings related to its use.

“CDEC noted that the patient population that would be eligible for colchicine 0.5 mg may have multiple medical comorbidities and already have high pill burden. Colchicine has an established risk profile and is associated with known tolerability issues.” (page 4)

1. We agree that patients eligible for colchicine 0.5 mg for secondary prevention of atherothrombotic events may have multiple comorbidities and may already have high pill burden, as was the case in the COLCOT and LoDoCo2 trials.
2. Despite co-morbidities and high pill burden, colchicine 0.5 mg ER tablet (MYINFLA) once daily was tolerated well and did not cause a significant increase in the incidence of diarrhea in COLCOT. LoDoCo2 reported early and late gastro-intestinal intolerance separately and showed that late gastro-intestinal intolerance was uncommon with low-dose colchicine and no more frequent than that seen in the placebo group.
3. Serious interactions with low-dose colchicine have not been recorded with any cardiovascular medications, including high-dose statins, in cardiovascular trials. In COLCOT, aspirin, a second anti-platelet agent and a statin were administered in 99, 98 and 99% of patients, respectively. Statins were used in 94% of patients in LoDoCo2.

4. Late intolerance to colchicine 0.5 mg daily is uncommon. In the LoDoCo2 trial, 3.4% of patients on colchicine and placebo stopped their study medication due to perceived side effects.

“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. The risk of adverse effects

may be underestimated as patients reporting adverse effects in the run-in phase of LoDoCo2 were excluded from further participation." (page 4)

1. The COLCOT and LoDoCo2 trials have included more than 10,000 patients followed for a mean of more than 2 years and extending up to 5 years, which do not qualify as short duration studies. The durations of the pivotal and supportive cardiovascular trials for colchicine 0.5 mg daily are generally consistent with those of the landmark statin trials, which also ranged from 2 to 5 years in duration.
2. Colchicine 0.5 mg ER tablet (MYINFLA) once daily was tolerated well and did not cause a significant increase in diarrhea in COLCOT, which did not include a run-in period. As stated above, LoDoCo2 reported early and late gastro-intestinal intolerance separately and showed that late gastro-intestinal intolerance was uncommon with low-dose colchicine and no more frequent than that seen in the placebo group.
3. In the cardiovascular trials to date, long-term colchicine has not increased the risk of fatal infection or the development of a new or fatal form of any cancer.

Clinical Evidence and Critical Appraisal (pages 5-7):

1. CADTH's conclusions fail to take into account the results of the meta-analyses of clinical trials, which show that colchicine reduces the risk of the individual non-fatal endpoints including myocardial infarction, stroke, and urgent coronary revascularization, as well as the composite endpoint of cardiovascular death, myocardial infarction and stroke compared to placebo.
2. We agree with the experts consulted for the CADTH review that not all endpoints in the composite endpoint may be of equal importance to individual patients. A significant reduction in coronary revascularizations is important from a healthcare resource perspective. The need for urgent coronary revascularization is a clear marker of disease progression that is invariably associated with hospitalization and may be associated with vascular injury, myocardial infarction, ischemic stroke, death, and the need for dual antiplatelet therapy which is associated with the risk of future hospitalization related to significant bleeding.
3. We agree that there is always a risk that collection of harms may be under-estimated in any clinical trial, especially when follow-up is incomplete. It is notable however that follow-up completenesss was excellent in the LoDoCo2 and COLCOT trials.
4. Reporting the total number of all harms in each treatment arm fails to provide insight into the risk of specific important harms. It is more appropriate that studies report the risk of serious harms including new or fatal cancer or serious or fatal infection, which were recorded in the colchicine studies and did not suggest a source for concern in the meta-analyses.
5. We agree that gastrointestinal intolerance is the most common side effect of colchicine, however it is not a marker of systemic toxicity nor a serious harm. It becomes evident within days of starting therapy, is typically mild, often transient, and invariably ceases once colchicine is stopped. The reported frequencies of gastrointestinal intolerance differ as COLCOT and COPS reported all gastro-intestinal event regardless of timing whereas LoDoCo2 reported early and late intestinal intolerance separately. The LoDoCo2 trial therefore informs patients and physicians about the likely experience in clinical practice. Late gastrointestinal intolerance was uncommon and no more frequent than that seen in the placebo group.
6. The primary efficacy endpoint in all colchicine trials was based upon composite outcomes, as is usual for trials of this nature. Meta-analyses of all colchicine studies in coronary artery disease were sufficiently powered to examine the effect on all individual non-fatal outcomes and confirmed large and statistically significant reductions in myocardial infarction, stroke and urgent coronary revascularization.
7. We acknowledge that to date the data is insufficiently powered to detect the possibility of harm related to very rare events, however it is reassuring that no signal of serious harm has yet been found in meta-analyses of colchicine use over several decades in a broad range of patients with and without cardiovascular disease.

2. Does the recommendation demonstrate that the committee has considered the stakeholder input that your organization provided to CADTH?	Yes	☐
	No	☐
N/A, no stakeholder input was previously provided to CADTH.		
Clarity of the draft recommendation		
3. Are the reasons for the recommendation clearly stated?	Yes	☐
	No	☒
The information that requires clarification is mentioned above.		
4. Have the implementation issues been clearly articulated and adequately addressed in the recommendation?	Yes	☐
	No	☐
If not, please provide details regarding the information that requires clarification.		
5. If applicable, are the reimbursement conditions clearly stated and the rationale for the conditions provided in the recommendation?	Yes	☐
	No	☐
N/A, no reimbursement conditions are associated with the recommendation.		

[a] CADTH may contact this person if comments require clarification.

Appendix 2. Conflict of Interest Declarations for Clinician Groups

- To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest.
- This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the feedback from patient groups and clinician groups.
- CADTH may contact your group with further questions, as needed.
- Please see the *Procedures for CADTH Drug Reimbursement Reviews* for further details.
- For conflict of interest declarations:
  - Please list any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.
  - Please note that declarations are required for each clinician that contributed to the input.
  - If your clinician group provided input at the outset of the review, only conflict of interest declarations that are new or require updating need to be reported in this form. For all others, please list the clinicians who provided input are unchanged
  - Please add more tables as needed (copy and paste).
  - All new and updated declarations must be included in a single document.

A. Assistance with Providing the Feedback		
1. Did you receive help from outside your clinician group to complete this submission?	No	☒
	Yes	☐
2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission?	No	☒
	Yes	☐
B. Previously Disclosed Conflict of Interest		
3. Were conflict of interest declarations provided in clinician group input that was submitted at the outset of the CADTH review and have those declarations remained unchanged? If no, please complete section C below.	No	☒
	Yes	☐
If yes, please list the clinicians who contributed input and whose declarations have not changed: • Clinician 1 • Clinician 2 • *Add additional (as required)*		

C. New or Updated Conflict of Interest Declarations

New or Updated Declaration for Clinician 1	
Name	Jean-Claude Tardif MD
Position	Director of the Research Center at the Montreal Heart Institute and Professor of medicine, Université de Montréal
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.
Conflict of Interest Declaration	

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.				
Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Pendopharm	☐	☒	☐	☐

New or Updated Declaration for Clinician 2	
Name	Guillaume Marquis-Gravel MD
Position	Assistant professor of medicine, Montreal Heart Institute and Université de Montréal
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Pendopharm	☒	☐	☐	☐

New or Updated Declaration for Clinician 3	
Name	Shaun Goodman MD
Position	Professor of medicine at St-Michael's Hospital, University of Toronto
Date	27-NOV -2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	**Check Appropriate Dollar Range**			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
Pendopharm	☐	☒	☐	☐

New or Updated Declaration for Clinician 4	
Name	Todd Anderson MD
Position	Professor of medicine, University of Calgary
Date	27-NOV-2021

☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Company	Check Appropriate Dollar Range			
	$0 to 5,000	**$5,001 to 10,000**	**$10,001 to 50,000**	**In Excess of $50,000**
N/A	☐	☐	☐	☐

New or Updated Declaration for Clinician 5	
Name	Alan Bell MD
Position	Professor of medicine, University of Toronto
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Pendopharm	☒	☐	☐	☐

New or Updated Declaration for Clinician 6	
Name	Jean C. Grégoire MD
Position	Associate professor of medicine, Montreal Heart Institute, Université de Montréal
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Pendopharm	☒	☐	☐	☐

New or Updated Declaration for Clinician 7

Name	Anil Gupta MD
Position	Cardiologist, Trillium Health Center, Mississauga
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Pendopharm	☒	☐	☐	☐

New or Updated Declaration for Clinician 8	
Name	Thao Huynh MD
Position	Associate professor of medicine, McGill University Health Center
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Pendopharm	☒	☐	☐	☐

New or Updated Declaration for Clinician 9	
Name	Simon Kouz MD
Position	Centre Hospitalier Régional de Lanaudière, Université Laval
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Pendopharm	☒	☐	☐	☒

New or Updated Declaration for Clinician 10	
Name	Philippe L. L'Allier MD
Position	Associate professor of medicine, Montreal Heart Institute and Université de Montréal
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Conflict of Interest Declaration

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Pendopharm	☒	☐	☐	☐

New or Updated Declaration for Clinician 11	
Name	John Mancini MD
Position	University of British Columbia
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Pendopharm	☒	☐	☐	☐

New or Updated Declaration for Clinician 12	
Name	Ruth McPherson MD
Position	Professor of medicine, University of Ottawa Heart Institute
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Pendopharm	☒	☐	☐	☐

New or Updated Declaration for Clinician 13	
Name	Graham Wong MD
Position	Associate professor of medicine, Vancouver General Hospital, University of British Columbia
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Pendopharm	☒	☐	☐	☐

New or Updated Declaration for Clinician 14	
Name	David Bewick MD
Position	Cardiologist,New Brunswick Heart Center, St John, New Brunswick
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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Pendopharm	☒	☐	☐	☐

New or Updated Declaration for Clinician 15	
Name	Mark Nidorf MD
Position	Cardiologist, Department of Medicine, Peninsula Health, Frankston, Victoria, Australia
Date	27-NOV-2021
☒	**I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

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N/A	☐	☐	☐	☐

CADTH

CADTH Reimbursement Review

Feedback on Draft Recommendation

Stakeholder information	
CADTH project number	SR0691
Name of the drug and Indication(s)	Colchicine (Myinfla) 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
Organization Providing Feedback	FWG

1. Recommendation revisions Please indicate if the stakeholder requires the expert review committee to reconsider or clarify its recommendation.		
Request for Reconsideration	**Major revisions:** A change in recommendation **category** or patient **population** is requested	☐
	Minor revisions: A change in reimbursement **conditions** is requested	☐
No Request for Reconsideration	**Editorial revisions:** Clarifications in recommendation **text** are requested	☐
	No requested revisions	X

2. Change in recommendation category or conditions Complete this section if major or minor revisions are requested
Please identify the specific text from the recommendation and provide a rationale for requesting a change in recommendation.

3. Clarity of the recommendation Complete this section if editorial revisions are requested for the following elements
a) Recommendation rationale
Please provide details regarding the information that requires clarification.
b) Reimbursement conditions and related reasons
Please provide details regarding the information that requires clarification.
c) Implementation guidance

CADTH

Please provide high-level details regarding the information that requires clarification. You can provide specific comments in the draft recommendation found in the next section. Additional implementation questions can be raised here.