CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215727Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	215727
Link to EDR	\\CDSESUB1\evsprod\NDA215727\0006
Submission Date	9/20/22
Submission Type	Priority
Brand Name	Lodoco
Generic Name	colchicine
Dosage Form and Strength	Tablet 0.5 mg
Route of Administration	Oral
Proposed Indication	To reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, (b) (4) (b) (4) and cardiovascular death among patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease
Applicant	Agepha Pharma Middle East Trading LLC
Associated IND	119015
OCP Review Team	Mohamad Kronfol Ph.D., Snehal Samant Ph.D.

Table of Contents

1. EXECUTIVE SUMMARY

The Applicant submitted NDA 215727 via the 505(b)(2) pathway on September 20, 2022, for once daily colchicine tablets 0.5 mg (Lodoco) to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, (b) (4), and cardiovascular death among patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease.

Colchicine 0.6 mg is marketed in the US under the trade name Colcrys (NDA 022351/022352/022353) and multiple ANDAs and is indicated for (1) prophylaxis and treatment of gout flares in adults, and (2) Familial Mediterranean Fever (FMF) in adults and children 4 years or older. The Applicant of NDA 215727 is not seeking the indications of Colcrys 0.6 mg. The Applicant of NDA 215727 is seeking a new indication for Lodoco.

This application is primarily relying on the literature reference report for LoDoCo2 study which is a randomized, placebo-controlled, double-blind, safety and efficacy study in patients with chronic coronary disease. Colgout (0.5 mg colchicine tablets) is one of the three products (Colgout, Teva, and Tiofarma formulations) used in the safety and efficacy study LoDoCo2 submitted in this application. The Applicant submitted the results of two PK bridging bioequivalence (BE) studies: (1) 294-20: A fasted state, cross-over study comparing PK of Lodoco (Applicant's colchicine 0.5 mg tablets) and Colgout tablets and (2) 295-20: A fed state, cross-over study comparing PK of Lodoco and Colgout tablets. The Applicant submitted qualitative formulation composition information and multimedia comparative in vitro dissolution data to compare the three immediate release (IR) formulations used in LoDoCo2. In addition, the Applicant submitted multimedia comparative in vitro dissolution data between Lodoco and Colcrys. All dissolution profile comparisons across all pH studied demonstrate rapid and similar dissolution (See Biopharmaceutics review for details).

The Applicant relies on Colcrys for clinical pharmacology information and non-clinical safety information. The application relies on Colcrys for clinical pharmacology information where colchicine is the victim drug in a drug-drug interaction. This is supported by an adequate scientific bridge between the Lodoco and Colcrys based on the following rationale. Colchicine has PK linearity between the dose range of 0.5 mg to 1.5 mg. The proposed dose of Lodoco (0.5 mg orally once daily) falls within the linear PK range for colchicine, supporting reliance on the clinical pharmacology drug-drug interaction studies with Colcrys where colchicine is a victim drug. Both Lodoco and Colcrys are immediate release (IR) tablets with rapid dissolution. Therefore, there is a low risk for any clinically significant difference in the bioavailability between the two. For Applicant's reliance on non-clinical safety information from Colcrys an adequate scientific bridge is established between Lodoco and Colcrys based on the following rationale. Colcrys is approved for use at daily doses up to 1.8 mg and 2.4 mg for treatment of gout flares and Familial Mediterranean Fever (FMF) respectively. Given the absolute bioavailability of Colcrys is about 45%, the area under the plasma concentration time curve (AUC) for 1.8 mg or 2.4 mg Colcrys is expected to be higher compared to that for Lodoco at the proposed 0.5 mg dose daily dose even if a worst-case scenario of 100% absolute bioavailability is assumed for Lodoco. The rapid dissolution profiles and the lower proposed strength of Lodoco (0.5 mg) compared to Colcrys reduces the risk of a higher peak plasma concentration (C_{max}) for Lodoco compared to Colcrys. From a clinical pharmacology perspective, the applicant has established an adequate scientific bridge to Colcrys.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (DCEP) has reviewed NDA 215727 and finds it adequate to support approval of Lodoco for the proposed indication.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Findings from the bioequivalence studies

Study 294-20 and 295-20 show that the 90% confidence intervals (CI) of colchicine geometric mean ratio of PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of Lodoco (Test) and Colgout (Reference) are within the 80-125% BE acceptance criteria under fasting and fed conditions (Table 1).

Table 1. Summary of statistical comparison of primary PK parameters between Test & Reference data for colchicine

PK parameter	Fasted BE Results[1] Ratio (Test/Reference) (90% CI)	Fed BE Results[2] Ratio (Test/Reference) (90% CI)
C_{max} (pg/mL)	97.48 (86.11 - 110.36)	94.69 (89.48-100.21)
AUC_{0-t} (pg.hr/mL)	97.73 (90.57 - 105.46)	102.48 (98.73-106.37)
$AUC_{0-\infty}$ (pg.hr/mL)	98.31 (91.55 - 105.56)	101.24 (98.12-104.47)

Source: [1]Table 2.0.4 on page 11 of 117 of the clinical study report of study 294-20 and [2]Table 2.0.4 on page 12 of 101 of the clinical study report of 295-20.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dose of colchicine tablets is 0.5 mg once daily. Colchicine tablets can be administered orally without regard to meals. The dose is consistent with that investigated in the literature reference report of LoDoCo2 study for safety and effectiveness and is acceptable.

2.2.2 Therapeutic individualization

2.2.2.1 Intrinsic factors

Renal impairment

The Applicant is not proposing dose adjustment for any renal impairment groups. The Applicant is proposing to contraindicate the use of Lodoco in patients (b) (4)

(b) (4) while allowing its use with close monitoring for adverse effects of colchicine in the remainder renal impairment groups.

To support this labeling recommendation, the Applicant cited a literature reference Wason et al 2014 (PMID: 25385362). The authors of Wason et al 2014 conclude that colchicine exposure was similar for subjects with normal renal function, mild impairment, or ESRD prior to and during hemodialysis, but was up to two-fold higher in subjects with moderate or severe renal impairment. In addition, another study in patients with renal insufficiency is reported in the literature by Ben-Chetrit et al 1994 (PMID: 8035398). Ben-Chetrit et al 1994 assessed the PK of colchicine in patients with and without renal insufficiency and concludes that a 4-fold decrease in clearance of colchicine was noted in patients with renal insufficiency compared to those with normal renal function, where the plasma half-life of colchicine was 4 times shorter. The clinical pharmacology team considered dose adjustment, however the potential for dose adjustment is limited by the availability of only one tablet strength (0.5 mg) and the absence of efficacy data from any alternative dosing interval. Finally, another literature reference submitted by the Applicant, Sadiq 2020, provide further support and states that in patients with renal impairment, elevated plasma concentrations of colchicine were observed and may lead to the development of adverse events like myeloneuropathy characterized by proximal weakness and elevated serum creatinine and possibly rhabdomyolysis. In totality, the clinical pharmacology team found the Applicant's proposal to contraindicate the use of Lodoco in patients (b) (4), and to add monitoring recommendations for all patients with renal impairment acceptable.

Hepatic impairment

The Applicant is not proposing dose adjustment for any hepatic impairment groups. The Applicant is proposing to contraindicate the use of Lodoco in patients with severe hepatic impairment while allowing its use with close monitoring for adverse effects of colchicine in the remainder hepatic impairment groups. To support this labeling recommendation, the Applicant cited literature references including Rudi et al 1994 and Leighton et al 1991. Rudi et al 1994 states that in 8 patients with chronic liver disease without ascites receiving 1 mg colchicine, the mean peak concentration was 3.6 ± 1.04 ng/mL and a mean AUC_{inf} of 24. 9 ± 8.47 ng * h/mL. Leighton et al 1991 enrolled 9 patients with liver disease and known alcoholic cirrhosis (Child-Pugh class A (n=5) and class B (n=4)) but did not enroll any patients with Child-Pugh class C. Leighton et al 1991 reports that the mean clearance in normal control subjects was of 10.65 ± 1.82 mL/min.kg, whereas cirrhotic patients had a mean clearance of 4.22 ± 0.45 mL/min.kg. The half-life was 57.4 ± 14.2 min in control subjects and 114.4 ± 19.7 min in cirrhotic patients. Volume of distribution was not different in the two groups. The authors of Leighton et al 1991 state that it is unknown whether this change would be clinically significant. The Applicant states that no PK data is reported for patients with severe hepatic impairment (Child-Pugh C). Therefore, for this NDA 215727, the clinical pharmacology team found the Applicant's proposed labeling text to contraindicate the use of Lodoco in patients with severe hepatic impairment, and to add monitoring recommendations for all patients with hepatic impairment acceptable.

2.2.2.2 Extrinsic factors

Drug- drug interaction

Colchicine is known to be metabolized by CYP3A4 and is a substrate of the P-gp transporter. To support labeling recommendation (in labeling sections 7 and 12 (see section 3.2 for the DDI tables)) regarding drug-drug interactions (DDI) between colchicine and CYP3A4 and P-gp inhibitors, the Applicant cited literature references including Terkeltaub 2011 and Sadiq 2020 as well as the approved product Colcrys. In these references, colchicine was investigated as a victim drug in most DDI evaluations with doses slightly higher than that proposed in this application. Colchicine has PK linearity between the dose range of 0.5 mg to 1.5 mg. The proposed dose of Lodoco of 0.5 mg orally once daily falls within the linear PK range for colchicine, supporting reliance on the clinical pharmacology DDI studies where colchicine is a victim drug.

The Applicant proposed that the use of strong CYP3A4 inhibitors and P-gp inhibitors is contraindicated in patients receiving Lodoco 0.5 mg. See Table 3 in section 3.2 for magnitude of effect for strong CYP3A4 and P-gp inhibitors on colchicine exposure. The clinical pharmacology team considered dose adjustment, however the potential for dose adjustment is limited by the availability of only one tablet strength (0.5 mg) and the absence of efficacy data from any alternative dosing interval. Similarly, concomitant administration of strong CYP3A4 inhibitors and P-gp inhibitors in patients with any renal and/or hepatic impairment is also contraindicated due to high possible exposure changes (see 2.2.2.1 above for effects of intrinsic factors).

The concomitant use of moderate CYP3A4 inhibitors and Lodoco is allowed with monitoring for signs and symptoms of toxicity of colchicine. However, concomitant administration of moderate CYP3A4 inhibitors and Lodoco is not recommended in patients with any degree of renal impairment and/or hepatic impairment due to possible elevated exposure changes.

The Applicant proposes to allow concomitant use of HMG-CoA reductase inhibitors (statins) and colchicine with labeling recommendation to weigh the potential benefit and risk of this concomitant use and to carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during initial therapy. This recommendation is communicated in Colcrys labeling for the following statins, atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin.

Statins are highly likely to be administered as part of the pharmacotherapy of people with cardiovascular disease. Of note, the literature references submitted by the Applicant supporting primary results of safety and efficacy of LoDoCo and LoDoCo 2 studies had high statin use reaching up to 95% in the colchicine group (see Nidorf et al 2013 and Nidorf et al 2020). The authors state that "*the results provide no evidence for a clinically important interaction between low-dose colchicine and high-dose statins*" (Nidorf 2020- page 8) without elaboration on the products nor actual doses of statins allowed to be used by the enrolled participants nor the percentages of each. The authors of Nidorf 2013 state the use of high dose statins was allowed in the study while Nidorf 2020 allowed use of low-moderate and high dose statins. Nidorf 2020 state that myalgia, which was assessed only in the Netherlands cohort, was common in both study groups, although it was

reported "*more frequently in the colchicine group"*. Further, one of the exclusion criteria in Nidorf 2020 (LoDoco2) study was "*Peripheral neuritis, myositis or marked myo-sensitivity to statins*" indicating that the apparent myalgia may possibly be emergent post enrollment. Although the authors provide subgroup analysis of the primary end point table for statin use showing that both high dose and low-moderate dose statins have a similar benefit with close Hazard Ratios (95%CI) of 0.68 (0.53-0.86) and 0.7 (0.52-0.95), the impact of low-moderate dose statins on risk of myalgia could not be ruled out due to lack of safety comparison between the statin dose groups or with patients not receiving statins in the study. Myotoxicity including rhabdomyolysis may occur with use of colchicine alone, especially in combination with other drugs known to cause this effect. Therefore, the clinical pharmacology team agrees with the Applicant's proposal to alert the prescriber in labeling about the potential of interaction between any dose statins and colchicine.

Finally, the clinical pharmacology team identified a relatively new case report of new DDI related information by Sabanis et al 2021 (PMID: 34028728) of myotoxicity when a specific statin, rosuvastatin 40 mg per day, was concomitantly administered with colchicine 0.5 mg twice daily. Therefore, due to the increased safety risk with this interaction and possible complication of rhabdomyolysis, and in order to communicate this risk with prescribers, the clinical pharmacology team added rosuvastatin to the list of HMG-CoA reductase inhibitors proposed in labeling sections 5, 7, and 17.

All other proposed labeling text pertaining to clinical pharmacology, with otherwise minor editorial changes is agreeable. Pending the agreement with the Applicant on those changes, the clinical pharmacology team finds the labeling text with edits acceptable.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

The proposed labeling language pertaining to clinical pharmacology in sections 5, 7, 8, 12 and 17 appears reasonable with minor modifications.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

The Applicant is developing colchicine tablets to reduce the risk of MI, stroke, coronary revascularization, (b) (4), and cardiovascular death among patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease. The Applicant submitted NDA 215727 via the 505(b)(2) pathway on September 20, 2022, for approval to market its formulation of colchicine tablets 0.5 mg.

Colchicine 0.6 mg is marketed in the US under the trade name Colcrys (NDA 022351/022352/022353) and multiple ANDAs and is indicated for (1) prophylaxis and treatment

of gout flares in adults, and (2) Familial Mediterranean fever (FMF) in adults and children 4 years or older. The Applicant of NDA 215727 is not seeking the indications of Colcrys 0.6 mg. The Applicant of NDA 215727 is seeking a new indication for colchicine 0.5 mg and is relying on literature reference reports of safety and effectiveness from LoDoCo studies, literature reference reports for clinical pharmacology information, and two PK bridging BE studies to support this NDA.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Mechanism of action

The exact mechanism of action of colchicine in the prevention of major cardiovascular events is not completely 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. Evidence suggests that colchicine may also interfere with the intracellular assembly of the inflammasome complex present in neutrophils and monocytes that mediates activation of interleukin-1β.

Pharmacodynamics

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

Pharmacokinetics

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

Table 2. Summary of colchicine 0.5 mg tablet PK parameters in healthy adults under fasting and fed conditions

BE studies	C_{max} pg/ml	T_{max}* hours	$t_{½}$ hours	AUC_{0-t} pg·h/ml
Single dose of 0.5 mg (fasting)	2056.11± 1001.879	1.00(0.50-2.33)	31.91	18582.28± 7032.605
Single dose of 0.5 mg (fed)	1756.67± 439.232	1.75(0.67- 3.50)	30.95	16407.66 ± 4406.878

*Median (Range)

Absorption

Oral colchicine undergoes entero-hepatic recirculation. In healthy adults, colchicine is absorbed when given orally, reaching a mean C_{max} 2056.11 pg/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 colchicine 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. colchicine may be administered with or without food. The mean peak plasma concentration of colchicine under fed conditions was found to be 1756.67 pg/mL in approximately 1.75 hours.

Distribution

Colchicine binding to serum protein is low, 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.

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 colchiceine). *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 minimal (less than 5% of parent drug).

Excretion/ Elimination

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. Colchicine is a substrate of P-gp.

Extracorporeal elimination: Colchicine is not removed by hemodialysis.

Specific populations

Geriatric patients

The PK studies of colchicine tablets 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 PK parameter values (mean ± SD) were observed for Colchicine in the young and elderly subjects, respectively: AUC (ng*hr/mL) 22.39 ± 6.95 and 25.01 ± 6.92; C_{max} (ng/mL) 2.61 ± 0.71 and 2.56 ± 0.97; T_{max} (hr.) 1.38 ± 0.42 and 1.25 ± 0.43; apparent elimination half-life (hr.) 24.92 ± 5.34 and 30.06 ± 10.78. No statistical difference in the PK parameters were found in between and the groups and concluded that no dosing adjustments were required in elderly patients.

Another study illustrated that after I.V. 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, decrease in distribution and total body clearance in the elderly is observed. Use colchicine tablets with caution in geriatric patients, because of the increased incidence of decreased renal function in this population, and the higher incidence of other co-morbid conditions requiring use of other medications.

Pediatric patients

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

Patients with renal impairment

The exposure of Colchicine was similar for normal renal function, mild impairment, or ESRD prior to and during hemodialysis (24.7–31.7 ng.h/mL) but was up to twofold higher in subjects with moderate or severe renal impairment (48.9 and 48.0 ng.h/mL, respectively). A very small amount of the colchicine dose (mean of 5.2 %) was recovered in dialysate.

Patients with hepatic impairment

From the published literature, in some subjects with mild to moderate cirrhosis, healthy subjects had a mean clearance of 10.65 +/-1.82 mL/min.kg, whereas cirrhotic patients had a mean clearance of 4.22 +/- 0.45 mL/min.kg. The half-life was 57.4 +/- 14.2 min in control subjects vs. 114.4 +/- 19.7 min in cirrhotic patients. Volume of distribution was not different in the two groups (0.718 +/- 0.1 L/kg in control subjects; 0.716 +/- 0.158 L/kg in cirrhotic patients. The study concluded that cirrhosis impairs colchicine clearance. No PK data are available for patients with severe hepatic impairment.

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 colchicine tablets on C_{max} and AUC are summarized in **Table 3**. For information regarding clinical recommendations, see **Table 4**.

Table 3. Effect of other drugs on colchicine PK

Co-administered drug	**Dose of Co-administered drug**	**Dose of Colchicine**	**Mean PK parameters (%CV) substrate drug**				**% Change in Colchicine Concentrations from Baseline (Range: Min - Max)**	
			C_{max} (ng/ml)	AUC_{0-t} (ng/hour/ml)	$T_{1/2}$ (hours)	Cl/F (L/hour)	C_{max}	AUC_{0-t}
Cyclosporine	100 mg OD	0.6 mg, single dose	2.72	12.55	6.77	48.24	270 (62 to 606.9)	259 (75.8 to 511.9)
Clarithromycin	250 mg BID	0.6 mg, single dose	2.84	12.37	8.89	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	2.78	11.99	6.28	49.3	101.7 (19.6 to 219)	212.2 (76.7 to 419.6)
Ritonavir	100 mg BID	0.6 mg, single dose	1.87	8.41	5.15	67.93	184.4 (79.2 to 447.4)	296 (53.8 to 924.4)
Verapamil	240 mg OD	0.6 mg, single dose	2.97	13.09	4.3	43.93	40.1(-47.1 to 149.5)	103.3(-9.8 to 217.2)
Diltiazem	240 mg OD	0.6 mg, single dose	2.17	10.04	5.51	58.88	44.2 (-46 to 318.3)	93.4(-30.2 to 338.6)
Azithromycin	500 mg OD	0.6 mg, single dose	2.74	11.98	6.07	50.24	21.6 (-41.7 to 222)	57.1 (-24.3 to 241.1)
Atorvastatin	40 mg OD	0.6 mg, single dose	2.49	10.71	4.27	58.59	130.60 (111.14-153.46)	127.33 (109.05–148.69)

Grapefruit juice	240 mL twice daily, 4 days	0.6 mg, single dose	-	-	-	-	-2.55 (-53.4 to 55.0)	-2.36 (-4.6 to 62.2)

Table 4. Drug-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; fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other strong CYP3A4 inhibitors.	Concomitant use of colchicine tablets with strong CYP3A4 inhibitors is contraindicated.
Moderate CYP3A4 Inhibitors amprenavir aprepitant diltiazem erythromycin fluconazole, fosamprenavir (prodrug of amprenavir) verapamil	Significant increase in colchicine plasma concentration is anticipated. Neuromuscular toxicity has been reported with diltiazem and verapamil interactions.	Weigh the potential benefits and risks and carefully monitor patients for any signs or symptoms of toxicity.
Grapefruit juice	Study data of potential interaction between grapefruit juice and colchicine suggests that grapefruit juice may augment colchicine oral bioavailability.	Advise patients to avoid grapefruit or grapefruit juice when taking LODOCO.
P- glycoprotein Inhibitors† cyclosporine ranolazine	Significant increase in colchicine plasma levels; fatal colchicine toxicity has been reported with cyclosporine, a P-gp inhibitor. Similarly, significant increase in colchicine plasma levels is anticipated with other P-gp inhibitors.	Concomitant use of colchicine tablets with strong P-gp inhibitors is contraindicated.
HMG-Co A Reductase Inhibitors atorvastatin fluvastatin lovastatin pravastatin simvastatin rosuvastatin	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)	Weigh the potential benefits and risks and carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during initial therapy; monitoring CPK (Creatine phosphokinase) will not necessarily prevent the occurrence of severe myopathy.
Other Lipid Lowering drugs fibrates gemfibrozil		
Digitalis Glycosides digoxin	P-gp substrate; rhabdomyolysis has been reported	
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. Colchicine can interact with oral contraceptives like norethindrone/ethinyl estradiol and can	Females using oral contraceptives should be prescribed LODOCO with caution and observe for adverse events.

	cause adverse events like diarrhea, nausea, upper abdominal pain, cold sweat

† Patients with renal or hepatic impairment should not be given colchicine tablets in conjunction with strong CYP3A4 or P-gp inhibitors.

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

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The primary evidence for efficacy and safety of colchicine in patients with cardiovascular disease is derived from published literature study LoDoCo2 where colchicine demonstrated efficacy over placebo for the primary composite endpoint of cardiovascular death, spontaneous myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. Please see Clinical review for final conclusion on efficacy and safety. The Applicant conducted two BE studies to support NDA 215727:(1) study 294-20, and (2) study 295-20. Both studies are pivotal bridging BE studies of the Applicant's formulation of colchicine tablet (Lodoco) to Colgout that supports the Applicant's reliance on the literature reference report of findings of safety and effectiveness in patients with cardiovascular disease in the LoDoCo studies.

3.3.1.1 Clinical Pharmacology studies conducted by the Applicant

Study 294-20 was an open label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, oral BE study of the Applicant's colchicine 0.5 mg tablets, Lodoco (Test) and Colgout 0.5 mg tablets (Reference) in healthy, adult, human subjects under fasting conditions. Study 295-20 was an open label, balanced, randomized, two-treatment, two-sequence, two-period, cross-over, single-dose, oral BE study of the Applicant's colchicine 0.5 mg tablets, Lodoco (Test) and Colgout 0.5 mg tablets (Reference) in healthy, adult, human subjects under fed conditions.

The main difference between the two BE studies is that study 294-20 was conducted under fasting conditions while study 295-20 was conducted under fed conditions. Fifty-five healthy volunteers completed both Lodoco and the Colgout tablet treatment periods in each of the studies. The batch of the Applicant's colchicine that was used in both BE studies was the commercial batch (Batch No EE60367). A 14 day washout period separated the two single-dose oral administrations.

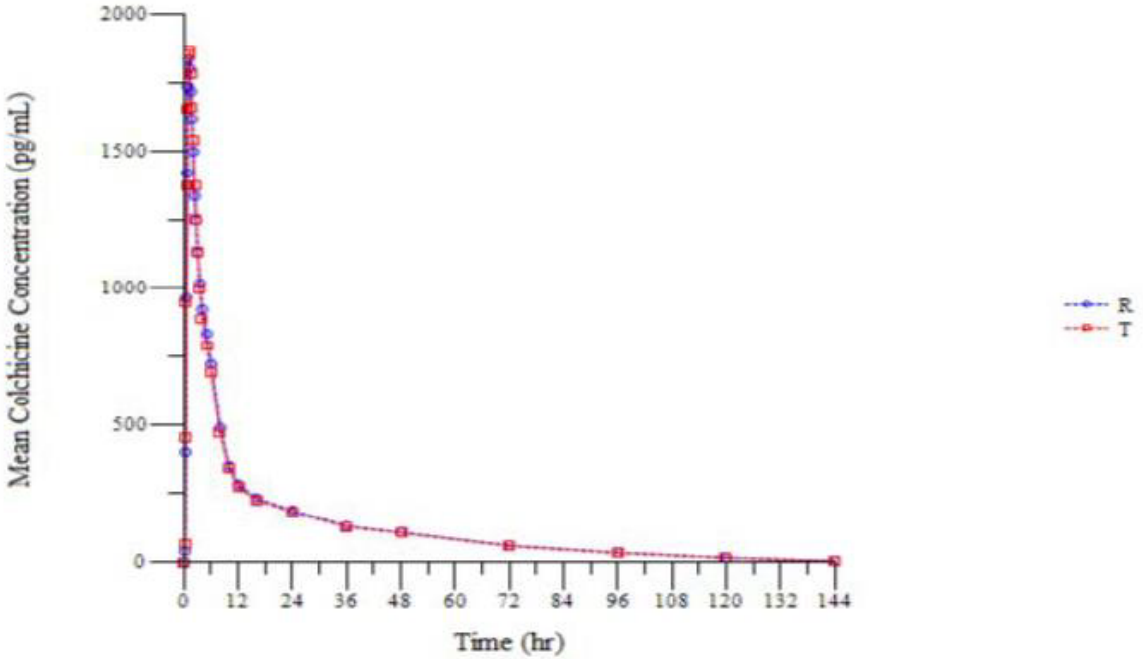
In both 294-20 and 295-20 studies, plasma was collected at pre-dose, 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 2.33, 2.67, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours post-dose to determine colchicine concertation via validated liquid chromatography coupled to tandem mass spectrometry assay (LC-MS/MS). Lodoco is bioequivalent to Colgout 0.5 mg tablet under fasting and fed conditions with the 90 % confidence interval (CI) of the ratios of geometric means of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ within the 80-125 % BE acceptance criteria (**Table 2**). Plasma colchicine concertation-time profile following administration of a single 0.5 mg dose of the Reference (Colgout) and the Test (Lodoco) under fasting and fed conditions are presented in **Figures 1** and **2** respectively. Descriptive statistics of the PK parameters from study 294-20 and 295-20 are presented in **Tables 5** and **6** respectively.

Table 5. Descriptive statistics of PK data from test and reference products in study 294-20

PK parameter	Arithmetic Mean ± SD	
	Test Product colchicine (T)	Reference Product Colgout (R)
C_{max} (pg/ml)	2056.11± 1001.879	2092.92± 995.696
AUC_{0-t} (pg·h/ml)	18582.28± 7032.605	19047.99± 6861.070
$AUC_{0-\infty}$ (pg.h/mL)	19822.41± 7096.379	20225.41± 6981.442
T_{max}* (h)	1.00(0.5-2.33)	1.00(0.5-2.33)
$t_{½}$ (h)	31.911±4.4660	30.978±4.6604

*median ± range. Source: Table 2.0.3 on page 11 of 117 of the clinical study report of 294-20.

Figure 1. Plasma colchicine concertation-time profile following administration of a single 0.5 mg dose of the reference (R- Colgout) and the test (T- Lodoco) product under fasting conditions



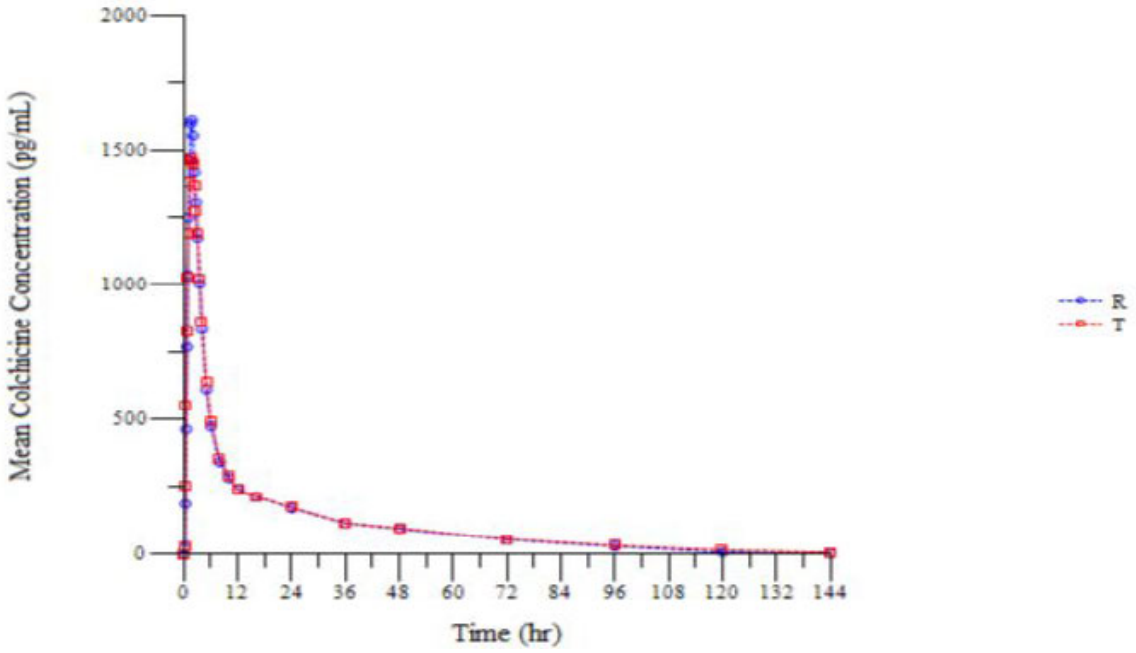
Source: page 114 of 117 of the clinical study report 294-20.

Table 6. Descriptive statistics of PK data from test and reference products in study 295-20

PK parameter	Arithmetic Mean ± SD	
	Test Product colchicine (T)	Reference Product Colgout (R)
C_{max} (pg/ml)	1756.67± 439.232	1847.83 ± 438.157
AUC_{0-t} (pg·h/ml)	16407.66 ± 4406.878	15986.78 ± 3958.331
$AUC_{0-\infty}$ (pg.h/mL)	17395.10 ± 4224.841	17205.56±4018.935
T_{max}* (h)	1.75(0.67- 3.50)	1.75(0.50-4.00)
$t_{½}$ (h)	30.953 ± 4.8049	29.773±3.7321

*median ± range. Source: Table 2.0.3 on page 12 of 101 of the clinical study report of 295-20.

Figure 2. Plasma colchicine concertation-time profile following administration of a single 0.5 mg dose of the reference (R- Colgout) and the test (T-Lodoco) product under fed conditions



Source: page 98 of 101 of the clinical study report 295-20

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the recommended dose of colchicine tablets is 0.5 mg once daily. Colchicine tablets can be administered orally without regard to meals. The dose is consistent with that investigated in the literature reference report of LoDoCo2 study for safety and effectiveness in cardiovascular disease and is acceptable. See Clinical review for final conclusions on safety and efficacy.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

The analytical method for detection of colchicine in human plasma was validated within acceptable limits. **Table 7** presents the summary of bioanalytical method validation of colchicine in human plasma samples.

Table 7. Summary of method validation report of colchicine in human plasma

Report Title	High Performance Liquid Chromatography – Mass Spectrometric Method Validation Report of Colchicine in K_2EDTA Human Plasma
Method Validation Report No. and Version	MV-482-00, Version: 00
Method Validation No.	MV-482-00
Method Validation Protocol/Plan No. (if any)	Nil
Validation Start Date	14/08/20
Validation End Date	01/09/20
Method Description	
Method SOP No.	(b) (4) BM-679-00
Analytical Technique	LC–MS/MS
Detection	Electrospray Ionization in Multiple Reaction Monitoring Mode
MRM Transitions (Q1/Q3 m/z values)	Q1 Mass / Q3 Mass Colchicine: 400.000 / 358.200 Colchicine D6: 406.100 / 362.200
Analytical Column	Kinetex XB-C18,150X4.6mm,100Å, 5µm
Mobile Phase	Acetonitrile: 2mM ammonium Acetate buffer 40: 60 v/v
Analyte	Colchicine
Internal Standard	Colchicine D6
Biological Matrix	Human Plasma
Anticoagulant	K_2EDTA
Source of Biological Matrix	(b) (4)
Sample Storage Temperature	-70 ± 15°C & -20 ± 5°C
Sample Extraction Method	Solid Phase Extraction
Sample Processing Volume	400 µL
Run Time	5.5 min.
Quantification	Peak Area Ratios
Regression, Weighting Factor	Linear Regression, $1/X^2$
Calibration Range	20.0 to 5008.2 pg/mL
LLOQ	20.0 pg/mL
ULOQ	5008.2 pg/mL
QC Sample Concentrations	20.1, 59.9, 1533.2 & 3832.9 pg/mL for LLOQQC, LQC, MQC & HQC respectively

Assay Performance	
Calibration Curve	Colchicine: No. of Standards: 8 Precision (%CV) 0.7 to 4.3% Accuracy (% Nominal) 97.0 to 103.8% Correlation Coefficient: 0.9986 to 0.9997
Precision (%CV)	Within Batch for Colchicine: LLOQQC: 2.4 to 16.2% LQC, MQC & HQC: 1.2 to 5.1% DIQC: 1.0 to 3.1% Between Batch for Colchicine: LLOQQC: 10.0% LQC, MQC & HQC: 2.4 to 4.4% DIQC: 3.0%
Accuracy (%Nominal)	Within Batch for Colchicine: LLOQQC: 97.4 to 104.4% LQC, MQC & HQC: 97.7 to 105.1% DIQC: 102.5 to 107.7% Between Batch for Colchicine: LLOQQC: 102.0% LQC, MQC & HQC: 98.7 to 102.0% DIQC: 104.3%
Sensitivity	Colchicine: Precision (%CV) 10.0% Accuracy (% Nominal) 102.0%
Signal to Noise Ratio	Colchicine: Mean S/N Ratio: 23:1
Recovery	Colchicine: Mean % Recovery 94.03% % CV for % Recovery 0.4% Colchicine D6 (ISTD): % Recovery: 93.8%
Ruggedness	Precision (%CV) for Colchicine: LLOQQC 5.6% LQC, MQC & HQC 0.9 to 2.7% Accuracy (%Nominal) for Colchicine: LLOQQC 92.0% LQC, MQC & HQC 96.5 to 97.3%

Re-injection Reproducibility	Colchicine: Precision (%CV) LQC & HQC: 1.9 to 4.9% Accuracy (%Nominal) LQC & HQC: 98.4 to 102.7% % Reproducibility At LQC: 104.3% At HQC: 102.3%
Extended Precision & Accuracy Run	On overall 100.0% of the QC samples has met the acceptance criteria including 50% at each level. Colchicine: Precision (%CV) — Accuracy (%Nominal) LQC, MQC & HQC — LQC, MQC & HQC 1.0 to 2.2% — 95.8 to 101.3%
Selectivity	
Matrix	14 out of 14 plasma lots met the acceptance criteria
Autosampler Carryover Test	Colchicine: Extracted samples: < 0.2% Colchicine D6: Extracted samples: < 0.0%
Matrix Effect	Colchicine at LQC Level: Precision (%CV) — ISTD NMF 2.7% — 0.92 to 1.02 Colchicine at HQC Level: Precision (%CV) — ISTD NMF 1.5% — 0.95 to 0.99
Concomitant Medication	No interferences were observed in presence of Paracetamol, Ibuprofen, Aceclofenac, Ranitidine, Ondansetron, Caffeine and Nicotine. Colchicine at LQC Level: Precision (%CV) — Accuracy for Mean (% Nominal) 5.0% — 100.6%
Stability	
Short-Term Stock Solution Stability of Analyte (After 25.13 hrs at ambient temperature, 25 ± 5°C)	Colchicine: Precision (%CV) 0.8 to 0.9% %Stability: 99.6%
Short-Term Stock Solution Stability of ISTD (After 25.33 hrs at ambient temperature, 25 ± 5°C)	Colchicine D6: Precision (%CV) 0.2 to 1.6% %Stability: 99.8%

Stock Dilution Stability of Analyte (After 21.55 hrs (low level) & 21.53 hrs (high level) at ambient temperature, 25 ± 5°C)	Colchicine: Precision (%CV): Low level: 0.8 to 2.8% High level: 0.8 to 1.8% % Stability: Low level: 101.4% High level: 100.0%
Stock Dilution Stability of ISTD (After 21.53 hrs at ambient temperature, 25 ± 5°C)	Colchicine D6 (high level): Precision (%CV) 0.7 to 1.5% %Stability: 101.3%
Long-Term Stock Solution Stability of Analyte (After 14.80 days at 1-10°C, in refrigerator)	Colchicine: Precision (%CV) 0.4 to 0.5% %Stability: 100.5%
Long-Term Stock Solution Stability of ISTD (After 14.80 days at 1-10°C, in refrigerator)	Colchicine D6: Precision (%CV) 1.0 to 1.1% %Stability: 99.5%
Bench Top Stability in Matrix (After 18.87 hrs at ambient temperature, 25 ± 5°C)	Colchicine: Precision (%CV) 1.3 to 3.2% %Nominal: LQC level: 100.0% HQC level: 98.5%
Freeze-Thaw Stability in Matrix (After 8 cycles, at -70 ± 15°C)	Colchicine: Precision (%CV) 0.6 to 2.8% %Nominal: LQC level: 99.9% HQC level: 98.2%
In-injector Stability (After 67.50 hrs at 10°C, in autosampler)	Colchicine: Precision (%CV) 1.3 to 2.9% %Nominal: LQC level: 101.5% HQC level: 97.5%
Dry Extract Stability (After 67.27 hrs at 1-10°C, in refrigerator)	Colchicine: Precision (%CV) 1.2 to 4.6% %Nominal: LQC level: 101.9% HQC level: 98.0%

Long-term Stability in Matrix (After 13.73 days at -70 ± 15°C)	Colchicine: Precision (%CV) 0.7 to 3.3% %Nominal: LQC level: 96.0% HQC level: 97.2%
Long-term Stability in Matrix (After 13.74 days at -20 ± 5°C)	Colchicine: Precision (%CV) 1.1 to 2.6% %Nominal: LQC level: 97.4% HQC level: 96.9%
Stability in Whole Human Blood (After 2.58 hrs at ambient temperature, 25 ± 5°C)	Colchicine: Precision (%CV) 0.9 to 5.0% %Stability: LQC level: 97.3% HQC level: 100.3%
Stability in Whole Human Blood (After 2.80 hrs at below 10°C in wet-ice water bath)	Colchicine: Precision (%CV) 0.9 to 3.2% %Stability: LQC level: 101.3% HQC level: 100.7%

Source: page 16 bioanalytical method validation: report MV-482-00

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MOHAMAD M KRONFOL
03/03/2023 11:34:54 AM

SNEHAL N SAMANT
03/03/2023 11:41:07 AM