CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215727Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Executive Summary

PDUFA Date	20 JUNE 2023
From	Fred Senatore MD, PhD, FACC
Priority or Standard	Priority
NDA/BLA # and Supplement#	215727
Applicant	AGEPHA PHARMA Middle East Trading, LLC
Date of Submission	20 SEP 2022
PDUFA Goal Date	20 JUN 2023
Proprietary Name	LODOCO
Established or Proper Name	Colchicine
Dosage Form(s)	Oral
Applicant Proposed Indication(s)/Population(s)	To reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, (b) (4) nd cardiovascular death among patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease
Applicant Proposed Dosing Regimen(s)	0.5 mg, PO, once daily
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	(b) (4)
Recommended Dosing Regimen(s)	Same as Applicant's proposed dosing regimen:

This secondary review is based on the following reviews, consults, and meeting minutes:

Materials Reviewed		
Reviews		
#	Discipline (Date)	Reviewers
1	Clinical Pharmacology	Mohamad Kronfol, PhD; Snehal Samant, PhD.
2	Pharmacology / Toxicology	Phil Gatti, Ph.D.; Xuan Chi, PhD.
3	CMC	Drug Substance: Ben Zhang, PhD; Zhengfu Wang, PhD Drug Product / Labeling: Rao Kambhampati, PhD, Ted Carver, PhD Manufacturing: Nancy Waites, PhD; Alexander Gontcharov, PhD Biopharmaceutics: Nadia Ahmed, PhD; Haritha Mandula, PhD
4	Labelling: DMEPA-2	Jody Kundreskas, Pharm D.; Hina Mehta, Pharm D
5	Clinical	Rosalyn Adigun, MD, Pharm D

Conclusions on the Substantial Evidence of Effectiveness

Pursuant to §21 CFR 314.126, it is reasonable to conclude that substantial evidence was presented to warrant approval of colchicine (Applicant's product Lodoco™) (b) (4)

(b) (4)

Substantial evidence of effectiveness was based on the single pivotal LoDoCo2 trial[1] with confirmatory evidence from the antecedent LoDoCo trial[2]. Pursuant to §21 CFR 314.54, the Applicant's 505(b)(2) submission relied on the aforementioned publications but without patient-level datasets. The Applicant also relied on FDA's previous finding of safety for the listed drug COLCRYS (colchicine) tablets, 0.6 mg (NDA 022352; Takeda Pharmaceuticals America, Inc). A total of three, non-FDA approved, colchicine formulations were used in the LoDoCo-2 trial (Colgout, Tiofarma colchicine tablets, and Teva colchicine tablets). Colgout was scientifically bridged to COLCRYS and Lodoco (refer to Clinical Pharmacology and CMC review summaries below).

The randomized, double-blind, placebo-controlled LoDoCo-2 trial evaluating patients with stable coronary artery disease (*sample size of 5522 subjects; n= 2762 in the colchicine 0.5 mg daily dosing arm and n= 2760 in the placebo daily dosing arm with a median follow-up duration of 29 months in the colchicine arm and 28.1 months in the placebo arm*), showed a hazard ratio of 0.69 (95% CI 0.57-0.83; p<0.001) for the composite primary efficacy endpoint of CV death, spontaneous MI, ischemic stroke, and UTVR. The components of spontaneous MI and UTVR statistically significantly favored colchicine over placebo. The components of CV death and ischemic stroke trended in favor of colchicine but were not respectively statistically significant. Secondary endpoints were hierarchically ranked but were variable combinations of the components of the primary efficacy endpoint.

There were no data made available for review to evaluate the dependence of treatment effect on body weight. Such data may have addressed the question about whether it was important to match the proposed dose of the Applicant's formulation to the dose used in the LoDoCo trials. Given the proximity of the approved daily dose of the US-FDA approved colchicine product (0.6 mg) to the Applicant's proposed daily dose (0.5 mg) that was used in the LoDoCo trials for the major adverse cardiac event indication, significant pharmacokinetic overlap between the two doses is anticipated, suggesting that either dose would be equally safe and effective. Clinical Pharmacology evaluation (*see clinical pharmacology discipline review below in this docum*ent) specified a low risk for any clinically significant difference in the bioavailability between the Applicant's product and the US-FDA approved product.

The safety data presented in the LoDoCo-2 publication showed a similar distribution and similar number of adverse events between the colchicine arm and the placebo arm (*i.e., non-CV death,*

[1] https://www.nejm.org/doi/full/10.1056/nejmoa2021372
[2] https://pubmed.ncbi.nlm.nih.gov/23265346/

cancer, hospitalizations for infection/pneumonia/gastrointestinal disorders, neutropenia, myotoxic effects, myalgia, dysesthesia).

The benefit in reducing the incidence of CV death, spontaneous MI, ischemic stroke, and UTVR outweighed the risk observed in the intention-to-treat population, thus yielding a recommendation for approval. The recommended labeled indication is (b) (4) (b) (4) from the LoDoCo-2 trial.

Reviews from clinical pharmacology, pharmacology-toxicology, CMC, labeling, and clinical all endorsed approval of Lodoco. The CDTL evaluation of each discipline's review confirms the endorsement for approval.

Product Introduction

Colchicine was originally derived from the autumn blooming flowering plant colchicum autumale, a member of the plant family Colchicaceae. Colchicine blocks mitosis in metaphase. It binds to soluble tubulin to form tubulin-colchicine complexes in a poorly reversible manner, which then binds to the ends of microtubules to prevent the elongation of the microtubule polymer. At low concentrations, colchicine arrests microtubule growth and, at higher concentrations, colchicine promotes microtubule depolymerization. It causes severe toxicity to normal tissues at high dose, which limits its use in cancer therapies. Colchicine exerts an anti-inflammatory effect. Newly described mechanisms include various inhibitory effects on macrophages including: 1) inhibition of the nucleotide-binding domain-leucine rich-containing family-pyrin domain-containing-3 (NALP3) inflammasome; 2) inhibition of pore formation activated by purinergic receptors P2X7 and P2X2; and 3) stimulation of dendritic cell maturation and antigen presentation. Colchicine also has anti-fibrotic activities and various effects on endothelial function. The contribution of the inflammatory pathway towards the pathophysiology of cardiovascular disease has prompted the generation of a hypothesis regarding the utility of colchicine in reducing the risk of cardiovascular events.

Colchicine (brand name COLCRYS™) was approved in 1961 for gout flares and Familial Mediterranean Fever (FMF). Posology for gout flares is 1.2 mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 tablet) one hour later. For FMF, daily dosages are 1.2--2.4 mg for adults and children older than 12 years; 0.9--1.8 mg for children 6-12 years; and 0.3--1.8 mg for children 4-6 years.

Colchicine is contraindicated in patients with renal or hepatic impairment in conjunction with P-gp or strong CYP3A4 inhibitors because of life-threatening or fatal toxicity. Additional warning and precautions include fatality on overdose, blood dyscrasias, and neuromuscular toxicity including rhabdomyolysis. The most common adverse reactions in patients with gout flares are diarrhea (23%) and pharyngolaryngo pain (3%). In patients with FMF, the most common adverse events are abdominal pain, diarrhea, nausea, and vomiting (up to 20%). These events are reported as mild, transient, and reversable upon lowering the dose.

To satisfy the 505(b)(2) requirement, the Applicant relied on the FDA findings of clinical pharmacology, clinical safety, and nonclinical safety for the listed drug (LD), COLCRYS™ tablets, 0.6 mg (NDA 022352). The Applicant also bridged their product to Colgout (0.5 mg tablets), one of three colchicine formulations studied in the LoDoCo-2 trial: the other two formulations used in LoDoCo-2 were from Teva and Tiofarma. The Applicant performed two (fed state administration and fasted state administration) relative bioavailability studies (294-20 and 295-20) to compare the proposed product (Lodoco) to Colgout (see summary of the Clinical Pharmacology review in this memo).

The Applicant has not sought approved indications at the approved doses of 0.6 mg tablets, but rather only for the cardiovascular indication at the dose of 0.5 mg once daily based on the LoDoCo-2 trial.

Discipline Reviews

Clinical Pharmacology

The clinical pharmacology review was written by Mohamad Kronfol, PhD and Snehal Samant, PhD, and found the NDA 215727 package adequate to support approval of Lodoco for the indication derived from the efficacy endpoints of the LoDoCo-2 trial.

Regarding the bridge between Lodoco and COLCRYS™, colchicine was shown to retain pharmacokinetic (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) fell within the linear PK range for colchicine. Both Lodoco and COLCRYS™ are immediate release tablets with rapid dissolution. Therefore, there is a low risk for any clinically significant difference in the bioavailability between the two products.

Two bioavailability trials showed that Lodoco was bioequivalent to Colgout with 90% confidence intervals around the geometric mean ratio of the PK parameters within the 80-125% bioequivalence range. The Applicant provided multimedia comparative in-vitro dissolution data between Lodoco and Colgout. Also, the Applicant submitted qualitative formulation composition information and multimedia comparative in vitro dissolution data to compare the three immediate release (IR) formulations used in LoDoCo-2 (Colgout, Tiofarma colchicine tablets, and Teva colchicine tablets). All dissolution profile comparisons across all pH studied demonstrated rapid and similar dissolution and multimedia comparative dissolution between Lodoco and the three colchicine products used in the LoDoCo2 trial. These findings were considered acceptable.

Pharmacology/Toxicology

The pharmacology / toxicology review was written by Phil Gatti, PhD, and Xuan Chi, PhD. The reviewers concluded that labelling language in section 8.1 (pregnancy), 12.1 (mechanism of action), and 13.1 (carcinogenesis, mutagenesis, and fertility impairment) were acceptable.

In section 12.1, the reviewers specified that the Applicant's additional language: (b) (4)

(b) (4) is not in keeping with the COLCRYS label and suggest its removal.

In section 13.1, the reviewers added safety margins under carcinogenesis based on the human dose of 0.5 mg on a mg/m^2 basis.

CMC Review

The CMC review, divided into Drug Substance (authored by Ben Zhang, Zhengfu Wang), Drug Product / Labeling (authored by Rao Kambhampati, Ted Carver), Manufacturing (authored by Nancy Waites, Alexander Gontcharov) and Biopharmaceutics: (authored by Nadia Ahmed, Haritha Mandula) with Ted Carver as acting team lead, yielded a recommendation to approve the Applicant's product for the LoDoCo-2 trial derived indication.

Regarding drug substance, the proposed specification included in the NDA was found during the review to be adequate to support the quality of the drug substance. All CMC information was cross-referenced to DMF (b) (4) which has been reviewed and found adequate to support this NDA, including all recent amendments.

Regarding drug product, the acceptance criteria for impurities were found to be acceptable based on limits for degradants in the drug substance specification, levels measured in the reference drug products, and compendial impurity limits. The initial manufacturing process submitted in the original NDA did not include (b) (4) (b) (4). In response to information requests and teleconference held on February 10, 2023, the Applicant agreed to add (b) (4) to the drug product manufacturing process and submitted an amendment (b) (4) and batch data (b) (4) (b) (4) which was reviewed and found to be adequate after an extension of the review period. Based on 18 months long-term stability data for three drug product batches manufactured at commercial scale, the drug product was found to be stable for 18 months when stored at 25°C and protected from light by storing the blister pack in the carton.

Regarding manufacturing, the process for the manufacture of 0.5 mg tablets was based on the well-established process (b) (4) The process was found to be adequate to support the quality of the colchicine tablet drug product after clarifications and revisions to the process description, master and executed batch records, and in-process controls, including (b) (4). The facilities were each determined to be approvable based on previous history, with an overall recommendation to approve the NDA with respect to manufacturing and facilities.

Regarding biopharmaceutics, the dissolution method was found to be adequate based on the Applicant's responses to information requests, clarification regarding the proposed Biopharmaceutics Classification System (BCS), and revised dissolution acceptance criteria. The biopharmaceutics review concluded that comparative dissolution profiles for test and reference drug product demonstrated rapid dissolution for all drug products tested. The review recommended approval from the biopharmaceutics perspective.

Labeling

The Division of Medication Error Prevention and Analysis-2 (DMEPA2) memo was authored by Jody Kundreskas and Hina Mehta. The revised container label and carton labeling for Lodoco were reviewed and found to be acceptable.

Clinical Review

The clinical review was written by Rosalyn Adigun, M.D., Pharm.D. and recommended approval for the indications reflecting the primary endpoint of the LoDoCo-2 trial.

LoDoCo-2 was a randomized, placebo-controlled, double-blind trial comparing colchicine 0.5 mg once daily to placebo over standard of care. The intention-to-treat population were characterized as patients with stable coronary artery disease without an acute ischemic event for at least 6 months prior to enrollment. After a 1 month open-label run-in period where enrolled subjects received colchicine, the subjects who were compliant with the protocol and without toleration issues were randomized 1:1 to either colchicine 0.5 mg once daily or matching placebo.

The primary efficacy endpoint was the composite of CV death, spontaneous MI, ischemic stroke, or UTVR.

The secondary endpoints, listed in order in which they were hierarchically tested at a significance level of 0.05, were: 1) composite of CV death, spontaneous MI, or ischemic stroke (*key secondary endpoint*); 2) composite of spontaneous MI or UTVR; 3) composite of CV death or spontaneous MI; 4) UTVR; 5) spontaneous MI; 6) ischemic stroke; 7) death from any cause; and 8) CV death.

Hierarchical testing of secondary endpoints was not included in the original planning, but rather incorporated in the 8th of 8 protocol amendments dated 22 JAN 2000. The last patient out occurred on 17 FEB 2020. The database was locked on 22 MAY 2020. Therefore, unblinding occurred after the last protocol amendment.

The trial was designed to accrue a minimum of 331 primary end-point events and to have a minimum follow-up of 1 year.

On the basis of a target enrollment of 6053 patients in the open-label run-in phase, with 5447 undergoing randomization after screening, the trial was estimated to have more than 90% power, at a two-sided alpha level of 0.05, to detect a 30% lower rate (i.e., a hazard ratio of 0.70) of the primary composite end-point event in the colchicine group than in the placebo group, assuming a 10% rate of discontinuation of colchicine or placebo and an annual rate of the primary end point in the placebo group of 2.6%.

A total of 6528 patients were enrolled in the open-label run-in period, of which 1006 did not undergo randomization (611 with side effects from which 437 experienced gastrointestinal side effects, and 395 for unspecified other reasons). A total of 5522 subjects were randomized (2762 in the colchicine arm and 2760 in the placebo arm).

Baseline characteristics between the colchicine and placebo arms (*i.e., age, gender, active smoking, hypertension, diabetes, renal function, prior acute coronary syndrome, time since last acute ischemic event, prior coronary revascularization, history of atrial fibrillation, history of gout, and listing of concomitant medications*) were well balanced. There were no data made available for review to evaluate the dependence of treatment effect on body weight.

The primary composite efficacy end-point event occurred in 187 subjects (6.8%) in the colchicine group and in 264 subjects (9.6%) in the placebo group, with incidence rates of 2.5 and 3.6 events, respectively, per 100 person-years (hazard ratio, 0.69; 95% CI, 0.57-0.83; P<0.001) The components of spontaneous MI and UTVR statistically significantly favored colchicine over placebo. The components of CV death and ischemic stroke trended in favor of colchicine over placebo but were not statistically significant.

The key secondary composite endpoint (*CV death, spontaneous MI, or ischemic stroke*) occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group, with incidence rates of 1.5 and 2.1 events, respectively, per 100 person-years (hazard ratio, 0.72; 95% CI, 0.57-0.92; P = 0.007).

In the prespecified hierarchical testing of the ranked secondary end points, the rates of the first five secondary end points were statistically significantly lower in the colchicine group than in the placebo group. There was no difference in the incidence of all-cause mortality between colchicine and placebo (*73 vs. 60 fatalities; incidence, 0.9 vs. 0.8 events per 100 person-years, respectively; hazard ratio, 1.21; 95% CI, 0.86-1.71*). It is noted that the ranked secondary efficacy endpoints were combinations of the components of the composite primary efficacy endpoint.

Safety evaluation from adverse events in the LoDoCo-2 trial did not show a safety signal. Adverse events were few (0.1%-5.2%) and equally distributed between the colchicine and placebo arms. The one exception was myalgia with the highest incidence (21% in the colchicine arm and 19% in the placebo arm; HR 1.15 (95% CI 1.01-1.31).

In the antecedent trial (LoDoCo), designed as a prospective randomized open blinded endpoint (PROBE) trial (*sample size of 532 subjects with stable coronary artery disease; n = 282 in the colchicine arm and n = 250 in the "no-colchicine" arm*), the hazard ratio was 0.33 (95% CI 0.18-0.59, p<0.001) for the composite primary efficacy endpoint of acute coronary syndrome, fatal / non-fatal out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke. The results were driven by acute coronary syndrome. These results adequately provided confirmatory evidence to satisfy the statutory requirement for substantial evidence of effectiveness.

Regarding safety in the LoDoCo PROBE trial, the publication specified that 32 subjects withdrew early from the trial and 30 subjects ceased colchicine therapy after a mean period of 2.36 years. Early withdrawal was reportedly based on intestinal intolerance and other side-effects, including myalgia that the authors attributed to concomitant statin therapy. Late withdrawal was reportedly caused by unrelated intercurrent illness in 11 patients, by choice in 5, and for a variety of possible drug-related effects in 14 patients. The PROBE design introduced

the possibility of bias, thus impacting an adequate safety assessment in this antecedent trial serving as confirmatory evidence.

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