CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215727Orig1s000

OTHER REVIEW(S)

DIVISION OF CARDIOLOGY AND NEPHROLOGY

Regulatory Project Manager Review

NDA:	215727
Drug:	Lodoco (colchicine)
Dosage Form:	Tablet, 0.5mg
Applicant:	Agepha Pharma FZ LLC
Application Description:	This Application provides for the following for colchicine: ▪ A new indication: 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 ▪ A new dosage strength: 0.5mg
Approved Indication:	To reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease
Date of Submission:	September 19, 2022
FDA Received Date:	September 20, 2022
Original PDUFA Date:	March 20, 2023
Major Amendment Received:	February 17, 2023
New PDUFA Date:	June 20, 2023
Date of Action:	June 16, 2023

❖ REVIEW TEAM

Center for Drug Evaluation and Research

❖ Office of New Drugs
- *Office of Cardiology, Hematology, Endocrinology and Nephrology, Division of Cardiology and Nephrology*
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  - Mary Ross Southworth, PharmD – Deputy Director for Safety
  - Michael Monteleone, MS, RAC – Associate Director for Labeling
  - Fortunato Senatore, MD, PhD – Cross Discipline Team Leader
  - Rosalyn Adigun, MD, PharmD – Physician

- Selena DeConti, PharmD – Clinical Analyst

- *Office of Cardiology, Hematology, Endocrinology and Nephrology, Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology and Nephrology (DPT-OCHEN)*
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  - Xuan Chi, MD, PhD – Team Leader
  - Philip Gatti, PhD – Reviewer

- *Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine, Division of Pediatric and Maternal Health (DPMH)*
  - Lynne Yao, MD – Director
  - Tamara Johnson, MD, MS – Team Leader
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❖ Office of Pharmaceutical Quality
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  - Nadia Ahmed, PhD – Primary Reviewer

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- *Office of Pharmaceutical Manufacturing Assessment, Division of Pharmaceutical Manufacturing Assessment III*
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  - Jody Kundreskas, PharmD – Reviewer
- *Office of Medical Error Prevention and Risk Management, Division of Risk Management*
  - Yasmeen Abou-Sayed, PharmD – Team Leader
  - Courtney Cunningham, PharmD – Reviewer
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  - Heather Lee, PharmD – Reviewer
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  - Christian Cao, MPAS, PA-C – Cross Discipline Safety Advisor
- *Project Management Staff*
  - Monique Killen, PharmD – Senior Regulatory Health Project Manager

❖ Office of Medical Policy
- *Office of Prescription Drug Promotion*
  - Susannah O'Donnell, MPH, RAC – Team Leader
  - Meena Savani, PharmD – Regulatory Review Officer
- *Office of Medical Policy Initiatives, Division of Medical Policy Programs, Patient Labeling Team*
  - LaShawn Griffiths, MSHS-PH, BSN, RN – Associate Director for Patient Labeling
  - Barbara Fuller, RN, MSN – Team Leader
  - Jessica Chung, PharmD, MS – Reviewer

❖ BACKGROUND

Regulatory History of Colchicine

Colchicine is an anti-inflammatory, microtubule polymerization inhibitor. In 1961, colchicine was first approved by the FDA as part of a combination with probenecid for the chronic treatment of gout (ColBenemid, colchicine 0.5 mg/probenecid 500 mg). ColBenemid underwent review through the Drug Efficacy Study Implementation (DESI) process (FR Vol.37, No.146, 28 July 1972) which deemed the combination effective for the treatment of "chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout". The following is a list of non-generic colchicine products currently approved in the United States as of June 16, 2023 (date of action for NDA 215727):

- NDA 022351 (0.6 mg tablet, oral; AR Holding Co. Inc.)
- NDA 022352 (0.6 mg tablet, oral; Takeda Pharmaceuticals USA, Inc.)
- NDA 022353 (0.6 mg tablet, oral; AR Holding Co. Inc.)
- NDA 210942 (0.6 mg/5ml solution, oral; Romeg Therapeutics, LLC)
- NDA 204820 (0.6 mg capsule, oral; Hikma International Pharmaceuticals, LLC)
- **NDA 215727 (0.5 mg tablets, oral; Agepha Pharma FZ LLC)**

Development History for Lodoco (colchicine) tablets, 0.5 mg

Cumulus Pharmaceuticals (Cumulus) first developed a 0.5 mg colchicine tablet indicated for the treatment of secondary prevention of coronary artery disease and had several interactions with the Division under Pre-IND 119015. In January 2014, Cumulus met with the Division to discuss the validity of the LoDoCo clinical trial to support a future literature-based 505(b)(2) application. The LoDoCo trial employed a prospective, randomized, observer-blinded endpoint design; the objective of the study was to determine whether a lower dose of colchicine (0.5 mg/day) could reduce the risk of cardiovascular events in patients with clinically stable CAD. According to the published results, colchicine 0.5 mg/day administered in addition to other standard secondary prevention therapies reduced the risk of major acute cardiovascular (CV) events by 67%. At the meeting, the Division indicated that the study had the potential to provide evidence of effectiveness for marketing approval but also noted there were general issues that would have to be addressed. Ultimately, the Division concluded that the findings from the LoDoCo study alone would not provide sufficient support for Cumulus's proposed NDA and indicated that a phase 3 confirmatory trial would be needed to support approval.

In June 2014, Cumulus submitted a request for a Special Protocol Assessment of a phase 3 clinical trial; the Division responded with a No Agreement Letter in July 2014. In its letter, the Division indicated that while the general protocol seemed reasonable, the protocol lacked important details. Cumulus subsequently determined that it would not be feasible to conduct a large trial.

In 2017, Cumulus submitted a meeting request to discuss using (b) (4) (b) (4) to qualify for Accelerated Approval. Following an informal teleconference with the Division, Cumulus decided not to pursue the (b) (4) approach.

The Sponsor met with the Division in December 2019, to discuss the use of Real-World Data (RWD) to generate additional efficacy data to support the safety and efficacy of colchicine for the proposed indication. Specifically, Cumulus proposed to conduct 2 observational studies to support a 505(b)(2) marketing application for a new dose and indication. Following submission of the meeting background package, Cumulus alerted the Division to the results of the COLCOT trial, a randomized, double-blind trial of colchicine 0.5 mg/day in patients recruited within 30 days after a myocardial infarction. The Division informed Cumulus that it was too late to submit a revised briefing document or alter their meeting questions and advised Cumulus to cancel the meeting request and submit a new request with the new materials. Cumulus indicated that they preferred to move forward with the scheduled meeting. During this meeting, Cumulus proposed a new strategy for submitting a 505(b)(2) NDA – a literature-based application, relying on COLCOT, LoDoCO, and LoDoCo-2 studies. The Division agreed that two blinded trials with supportive evidence may be sufficient to approve a future 505(b)(2) NDA; however, the Division explained that patient-level data is desired, the Sponsor will need to provide evidence that supports bridging their proposed marketing product to the product used in the LoDoCo2 trial, and the Sponsor should provide additional information on products used in the cited studies (e.g., precise composition, active and inactive ingredients, release mechanism, in vitro dissolution, etc.).

In September 2020, the Division held a Pre-NDA meeting with Cumulus to discuss the results of published clinical trial data, mainly study results of LoDoCo-2, and the appropriateness of comparative bridging data for proposed test products and products used in LoDoCo-2 trial. Additionally, Cumulus requested feedback from the Agency regarding the sufficiency of the overall approach to support the submission of a 505(b)(2) NDA for the new dose of colchicine (0.5 mg) and the new indication (b) (4) (b) (4). On March 30, 2021, Cumulus notified the Division that PIND 119015 was transferred to AGEPHA Pharma Middle East Trading LLC (AGEPHA).

Review Cycle #1

On April 13, 2022, the Applicant submitted NDA 215727. On June 11, 2022, the Division refused to file NDA 215727. The following statement was included within the Refusal to File correspondence sent to the Applicant:

> Adequate information to support the nonclinical sections of the proposed Prescribing Information has not been provided in your NDA submission. Therefore, your application is not complete, and we are unable to conduct a substantive review. You cannot rely upon foreign labeling for findings of safety and effectiveness to support your application.
>
> You need to provide information to support proposed labeling regarding risks of reproductive toxicity, developmental toxicity, carcinogenesis, mutagenesis, and impairment of fertility. This information might come from the literature or reliance upon findings from an FDA-approved product. We can provide more detailed requirements in a subsequent advice letter.

A General Advice letter was sent to the Applicant on June 30, 2022, requesting additional clinical pharmacology and product quality information. On August 5, 2022, the Division held a Type A Meeting with the Applicant (minutes dated August 31, 2022) to discuss deficiencies outlined in the Refuse to File Letter, dated June 11, 2022, and the General Advice Letter, dated June 30, 2022.

Review Cycle #2

On September 20, 2022, the Applicant resubmitted NDA 215727. This application was subsequently filed on November 19, 2022. The Division deemed this application to be a Priority Review with a PDUFA date of March 20, 2023. Pursuant to §21 CFR 314.54, the Applicant's 505(b)(2) submission relied on FDA findings of clinical pharmacology, clinical safety, and nonclinical safety for the listed drug (LD), Colcrys tablets, 0.6 mg (NDA 022352), as well as published literature on the single pivotal LoDoCo2 trial with confirmatory evidence from the antecedent LoDoCo trial.

Safety

With respect to nonclinical and clinical safety, an adequate bridge was established between the proposed product (Lodoco) and Colcrys based on the following rationale:

- Colcrys is approved for use at daily doses up to 1.8 mg. Given the absolute bioavailability of Colcrys to be 45%, the area under the plasma concentration time curve (AUC) for 1.8 mg Colcrys is expected to be higher compared to that for Lodoco at the proposed 0.5 mg dose daily dose even if a 100% absolute bioavailability is assumed for Lodoco.
- The applicant conducted an *in-vitro* multi-media dissolution analysis between Lodoco and the LD. The rapid dissolution profile of Colcrys and Lodoco, as well as the proposed lower strength of Lodoco (0.5 mg) compared to Colcrys, reduce the risk of a higher peak plasma concentration (Cmax) for Lodoco compared to Colcrys.

With respect to the reviewed clinical pharmacology information, an adequate scientific bridge was established between the proposed product (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.
- 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.

Efficacy

Substantial evidence of effectiveness was based on the single pivotal LoDoCo2 trial with confirmatory evidence from the antecedent LoDoCo trial. This application relied on published literature without patient level datasets. The randomized, double-blind, placebo-controlled LoDoCo2 trial evaluated 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.

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

Major Amendment (3-month PDUFA extension)

During the review, the CMC review team noted the submitted manufacturing process did not include a (b) (4). In response to information requests and the teleconference held on February 10, 2023, the Applicant agreed to add (b) (4) to the drug product manufacturing process. On February 17, 2023, the Applicant submitted a major amendment (b) (4) and batch data (b) (4) which extended the review period by three months (June 20, 2023). The major amendment was reviewed and found to be adequate to support approval.

Lastly, on April 6, 2023, the Applicant notified the Division of the change of ownership of NDA 215727 from Agepha Pharma Middle East Trading LLC to Agepha Pharma FZ LLC.

Please see Discipline Review Section for recommendations.

❖ REGULATORY TIMELINE & APPLICATION DETAILS

- Pre-NDA Meeting: September 8, 2020 (Minutes dated October 1, 2020)
- NDA Submission Date: April 13, 2022
- NDA Received Date: April 13, 2022
- Filing Meeting #1: May 31, 2022
- Team Meeting #1: June 10, 2022
- Refuse to File (RTF) Letter Issued: June 11, 2022
- Type A Meeting (Post-RTF): August 5, 2022 (Minutes dated August 31, 2022)
- NDA Resubmission Date: September 19, 2022
- NDA Received Date: September 20, 2022
- Filing Meeting #2: November 3, 2022
- Filing Letter Issued: November 17, 2022
- Team Meeting #2: November 10, 2022
- Team Meeting #3: December 15, 2022
- Midcycle Meeting: January 4, 2023
- Team Meeting #4: January 23, 2023

- Team Meeting #5: January 25, 2023
- Labeling Meeting #1: February 3, 2023
- Team Meeting #6: February 8, 2023
- Team Meeting #7: February 9, 2023
- Teleconference with Applicant: February 10, 2023
- Labeling Meeting #2: February 13, 2023
- Major Amendment Received: February 17, 2023
- PeRC Meeting: February 28, 2023
- Major Amendment Letter Issued: February 28, 2023
- Labeling Meeting #3: May 4, 2023
- Labeling Negotiations Initiated: April 4, 2023
- Wrap-Up Meeting: May 22, 2023
- Labeling Negotiations Completed: June 14, 2023
- Action Date: June 16, 2023
- PDUFA Date: June 20, 2023

User Fee

User Fee I.D. Number is PD3018236. The Applicant requested a small business user fee waiver. The Division of User Fee Management granted their request on February 14, 2022. Form FDA 3397 was signed by the Applicant on July 9, 2022.

Proprietary Name

Under Pre-IND 119015, the proprietary name Lodoco was conditionally accepted on May 27, 2021. The Applicant submitted a Proprietary Name Request to the NDA on April 13, 2022, and was found conditionally acceptable on June 7, 2022. However, on June 11, 2022, the Division issued a refuse to file letter for NDA 215727. On September 20, 2022, the Applicant resubmitted their request and Lodoco was again found conditionally acceptable on December 5, 2022.

Facilities Inspection

The Facilities Inspection review was part of the OPQ integrated review and was signed on April 14, 2023. All the sites were approved based on previous inspection history.

Office of Study Integrity and Surveillance (OSIS)

A request for Biopharmaceutical Inspections (clinical & analytical) was submitted on November 21, 2022. On December 9, 2022, OSIS determined that inspections were not needed as previous inspections for the analytical site and clinical site occurred in (b) (4) and May 2022, respectively. OSIS concluded that each inspection sufficiently falls within the surveillance interval.

Pediatric Review Committee (PeRC)

This application triggered PREA. The Applicant submitted a request for a full waiver for pediatric studies because necessary studies are impossible or highly impracticable considering the pathophysiology of the proposed indication occurs mostly in the adult population. Furthermore, this product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients (Agreed iPSP, May 5, 2021; Pre-IND 119015). PeRC agreed with the Applicant's request for a full waiver on February 28, 2023.

Advisory Committee

The Division determined an Advisory Committee was not required for this application.

❖ DISCIPLINE REVIEWS

Below are the conclusions reached by the primary review team. Please refer to DARRTS for the complete reviews.

❖ Cross Discipline Team Leader (CDTL) Review with Division Concurrence (Senatore, Stockbridge; June 15, 2023)

Recommended Action: Approval

The Executive Summary provided by Drs. Senatore (CDTL) and Stockbridge (Division Director), evaluated each disciplines review and endorsement for approval. Reviews from Clinical, Clinical Pharmacology, Pharmacology-Toxicology, CMC, and Labeling all recommend approval of Lodoco. The CDTL and Division Director concur with the review team's recommendation for approval.

❖ Primary Reviews

Clinical/Biostatistics (Adigun, Zhou, Zhang, Senatore; June 15, 2023)

Recommended Action: Approval

A joint collaborative review was written by the clinical and statistical teams. Dr.'s Adigun (clinical) and Zhou (biostatistics) focused on efficacy and safety data. Dr. Senatore (CDTL) provided the Executive Summary within the review.

Substantial evidence of effectiveness was based on the single pivotal LoDoCo-2 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 published literature without patient-level datasets. LoDoCo-2 was a randomized, double-blind, placebo-controlled study that evaluated 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), which 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.

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

Given these findings, the review team concluded that sufficient evidence was present to endorse an approval of Lodoco for the following indication: to reduce the risk of myocardial infarction

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

(MI), stroke, coronary revascularization, and cardiovascular death in adult patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease

Clinical Pharmacology (Kronfol, Samant; March 3, 2023)
Recommended Action: Approval
Dr. Kronfol's review found that NDA 215727 is adequate to support approval of Lodoco for the proposed indication. The application relied on Colcrys for clinical pharmacology information where colchicine is the victim drug in a drug-drug interaction. This was 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 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 (Gatti, Chi; May 1, 2023)
Recommended Action: Approval
Dr. Gatti's primary review focused on the adequacy of the nonclinical bridge to support labeling for nonclinical sections 8.1 (pregnancy), 12.1 (mechanism of action), and 13.1 (carcinogenesis, mutagenesis, and fertility impairment). The basis for this nonclinical bridge pertained to data generated from the comparative in vitro dissolution study and CMC characterization findings of the Applicant's proposed product (Lodoco). These data were evaluated by the Biopharmaceutics and Drug Product Reviewer respectively.

To support the bridge to the RLD (Colcrys) for demonstration of nonclinical safety, the Applicant provided multimedia comparative dissolution between Colcrys (US RLD) and the proposed drug product (Lodoco) using purified water, 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. All submitted dissolution profiles demonstrate rapid dissolution (> (b) (4) in 15 minutes). This dissolution profile and the methods utilized by the Applicant were deemed adequate by the Biopharmaceutics reviewer (see Biopharmaceutics review in OPQ Integrated Quality Review in DARRTS dated 4/14/23).

Regarding the drug product formulation of Lodoco, the CMC reviewer stated "*The formulation contains USP quality colchicine that is manufactured as according to the DMF* (b) (4) *which was found to be adequate by the drug substance reviewer and, commonly used excipients. The excipient levels present in the tablet were adequately justified based on eIID. The 0.5 mg strength tablet is based upon the decades of applicant's experience with the 0.375 mg colchicine tablets"* (see OPQ Integrated Quality Review in DARRTS dated 4/14/23).

Based on the aforementioned reviews, Pharm/Tox concluded that an adequate scientific bridge to Colcrys has been established to support reliance on Colcrys labeling for nonclinical safety.

Office of Pharmaceutical Quality (OPQ) - CMC Integrated Review (Carver; April 14, 2023)
Recommended Action: Approval
OPQ provided an integrated review. They recommended approval of the application with a shelf life of 18 months when stored at 20°C to 25°C. The review stated that Environmental Assessment was submitted and the request for Categorical Exclusion is adequate. Manufacturing sites were acceptable based on previous history.

On February 23, 2023, the FDA extended the review goal date by three months due to a major CMC amendment submitted by the Applicant. During the review, the review team noted the manufacturing process submitted did not include (b) (4) (b) (4). In response to information requests and teleconference held on February 10th, 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), which was reviewed and found to be adequate after the extension of the review period.

Division of Medical Error Prevention and Analysis (Kundreskas, Mehta; March 8, 2023 and May 10, 2023)
Recommended Action: Approval
Drs. Kundreskas and Mehta reviewed the proposed Prescribing Information (PI), (b) (4) (b) (4) and carton and container labels for areas of vulnerability that may lead to medication errors. During the review it was determined a Patient Package Insert (PPI) was required (b) (4) (b) (4). They identified areas of concern in the PI and carton and container labels and performed a risk assessment for areas of vulnerability with regard to medication error. The Applicant submitted revised carton and container labeling on May 8, 2023. Drs. Kundreskas and Mehta reviewed the revised carton and container labeling and concluded the submitted labeling is acceptable from a medication error perspective.

❖ **Consult Reviews**

Division of Pediatric and Maternal Health (Mastroyannis, Johnson, Yao; February 7, 2023)
Recommended Action: Approval with Recommendations
The Division consulted DPMH on January 5, 2023, to assist with the labeling subsections *Pregnancy, Lactation, and Females and Males of Reproductive Potential* to ensure that the labeling complies with the PLLR content and format. DPMH revised subsections 8.1, 8.2 and 8.3 for compliance with PLLR and recommended the Division align labeling with previously approved labeling for Colcrys.

Division of Medical Policy Programs, Patient Labeling Team (Chung, Savani, Fuller, Griffiths; May 18, 2023)
Recommended Action: Approval with Recommendations
The patient labeling team, in collaboration with the Office of Prescription Drug Promotion (OPDP), conducted a review of the proposed (b) (4) PPI, PI, and Colcrys comparator labeling. Recommendations made to the Division included simplified wording and clarified concepts where possible. They removed unnecessary or redundant information, proposed revisions to ensure that the PI and PPI were free of promotional language and ensured that the PI

and PPI met the criteria as specified in the guidance for industry *Useful Written Consumer Medication Information (CMI)*[3].

Office of Prescription Drug Promotion (Savani, O'Donnell; May 24, 2023)
Recommended Action: Approval with Recommendations
OPDP reviewed the proposed PI, PPI, and carton and container labeling for Lodoco. A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under the review dated May 18, 2023. OPDP's review of the proposed carton and container labeling was based on the draft labeling submitted by the Applicant on May 8, 2023, where no further comments were provided. OPDP's review of the proposed PI was based on the draft labeling dated May 23, 2023, where comments and recommendations were provided throughout the document.

❖ LABELING

Labeling discussions occurred with the Applicant from April 4, 2023, to June 14, 2023. During negotiations, the Division determined they did not support the inclusion of a (b) (4) but were open to the inclusion of a Patient Package Insert (PPI). The final agreed upon labeling is attached to the Approval Letter.

❖ CONCLUSION

After taking into consideration all primary and consult reviews, the Division issued an Approval Letter for NDA 215727, signed by Norman Stockbridge, Director for the Division of Cardiology and Nephrology, on June 16, 2023.

[3] https://www.fda.gov/media/72574/download

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/s/

BRIAN T COONEY
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 24, 2023

To: Brian Cooney, Regulatory Project Manager
Division of Cardiology and Nephrology (DCN)

Michael Monteleone, MS, RAC
Associate Director for Labeling, DCN

From: Meena Savani, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for LODOCO (colchicine) tablets, for oral use

NDA: 215727

Background:
In response to DCN's consult request dated November 17, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for Lodoco.

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling downloaded from SharePoint on May 23, 2023, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on May 18, 2023.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on May 8, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Meena Savani at 240-402-1348 or Meena.Savani@fda.hhs.gov.

22 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

MEENA R SAVANI
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 18, 2023
To:	Brian Cooney, MS, PSM Regulatory Health Project Manager **Division of Cardiology and Nephrology (DCN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meena Savani, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	LODOCO (colchicine)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 215727
Applicant:	AGEPHA Pharma Middle East Trading, LLC

1 INTRODUCTION

On September 20, 2022, AGEPHA Pharma Middle East Trading, LLC resubmitted for the Agency's review a (505)(b)(2) New Drug Application (NDA) 215727 for LODOCO (colchicine) tablets in response to the Agency's Refuse to File letter dated June 11, 2022. The reference list drug (RLD) for this submission is NDA 022352 for COLCRYS (colchicine, USP) tablets, for oral use. The proposed indication for LODOCO (colchicine) tablets is 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on November 17, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for LODOCO (colchicine) tablets. The Applicant revised the MG to a Patient Package Insert (PPI) after DCN communicated to the Applicant by mail on April 4, 2023, that they do not support the inclusion of a MG but are open to the inclusion of a PPI.

2 MATERIAL REVIEWED

- Draft LODOCO (colchicine) tablets MG received on September 20, 2022.
- Draft LODOCO (colchicine) tablets PPI received by email on April 11, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 11, 2023.
- Draft LODOCO (colchicine) tablets Prescribing Information (PI) received on September 20, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 11, 2023.
- Approved COLCRYS (colchicine, USP) tablets, for oral use comparator labeling dated May 14, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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05/18/2023 10:28:09 AM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 9, 2023
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 215727
Product Name, Dosage Form, and Strength:	Lodoco (colchicine) tablets, 0.5 mg
Applicant/Sponsor Name:	Agepha Pharma FZ LLC
TTT ID #:	2022-2100-1
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 8, 2023 for Lodoco. We reviewed the revised container label and carton labeling for Lodoco (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kundreskas, Jody. Label and Labeling Review for Lodoco (NDA 215727). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2023 MAR 08. TTT ID No.: 2022-2100.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	03/08/2023
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 215727
Product Name, Dosage Form, and Strength:	Lodoco (colchicine) tablets, 0.5 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	AGEPHA Pharma Middle East Trading LLC
FDA Received Date:	June 28, 2022, September 20, 2022, January 16, 2023, January 25, 2023, January 30, 2023, and February 8, 2023
TTT ID #:	2022-777
DMEPA 2 Safety Evaluator:	Jody Kundreskas, PharmD
DMEPA 2 Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

As part of the approval process for Lodoco (colchicine) tablets, we reviewed the proposed Lodoco Prescribing Information (PI), Medication Guide, container labels and carton labels for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

On April 13, 2022, AGEPHA Pharma Middle East Trading LLC submitted NDA 215727 for Lodoco (colchicine) tablets, 0.5 mg, 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. Due to inadequate information to support the nonclinical sections of the proposed Prescribing Information, the Agency issued a Refuse-to-File (RTF) letter on June 11, 2022. The Applicant resubmitted the NDA on September 20, 2022, as a 505(b)(2) referencing NDA 022352, Colcrys 0.6 mg tablets.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed PI, Medication Guide, and carton and container labels to identify deficiencies that may lead to medication errors and other areas of improvement. We note that the proposed container labels (b) (4) . We sent an Information Request (see Appendix F) on January 11, 2023 to the Applicant, to clarify the proposed blister packaging and labeling design. The Applicant

responded (see Appendix F and G) on January 16, 2023, [redacted]. The Applicant further clarified that after reviewing FDA guidance they were submitting updated container labels with [redacted]. After further correspondence, on January 30, 2023, the Applicant submitted a container label with labeling information printed across the foil on the back of the blister pack twice (see Appendix F).

We note there was no information in the proposed PI regarding [redacted]. As such we sent a communication to the Office of Pharmaceutical Quality (OPQ) regarding this information. Per OPQ, the Applicant has committed to [redacted] prior to commercialization. OPQ also determined that the tablets cannot be stored outside of the blister pack and the carton due to light sensitivity of the product. As such, the entire blister pack and carton would have to dispensed at once. Thus, we provide a recommendation below for the carton labeling stating the product must be stored and dispensed in original container.

We identified areas of concern in the PI and carton and container labels that should be revised to improve the clarity of the information presented. We provide recommendations for the Division in Section 4.1 and the Applicant in Section 4.2 to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the proposed PI and carton and container labels that can be improved to increase readability and prominence of important information and promote the safe use of the product. We provide specific recommendations in Sections 4.1 and 4.2, below.

4.1 RECOMMENDATIONS FOR DIVISION OF CARDIOLOGY AND NEPHROLOGY (DCN)

A. Highlights of Prescribing Information

1. Dosage and Administration

   a. We recommend revising the first statement to remove "[redacted]". Revise the first sentence to "The recommended dosage is 0.5 mg orally once daily.".

   b. We recommend removing [redacted].

2. Dosage Forms and Strengths

   a. We recommend removing the word "[redacted] as it is not needed as part of the statement.

B. Prescribing Information

1. Dosage and Administration Section

   a. In Section 2.1, Recommended Dosage, we recommend rewording the first sentence to include the route of administration and to remove unnecessary information. Revise to "The recommended dosage of LODOCO is 0.5 mg orally once daily.".

b. We recommend removing [redacted].

c. We recommend adding instructions for missed/late dosages. Add:
   - If the dose of LODOCO is missed, take the missed dose as soon as possible and return to the normal dosing schedule.
   - If a dose is skipped the patient should not the double the next dose.

2. Dosage Forms and Strengths

   a. We recommend removing the word "[redacted]" from this section as it is not needed.

3. How Supplied/Storage and Handling Section

   a. In Section 16.1, How Supplied, we recommend revising "Aluminum/PVC blister of 30 tablets:" to "Carton containing 1 blister pack of 30 tablets:" for clarity.

   b. In Section 16.2, Storage, the F is missing following 68° and should be added for clarity.

4. Patient Counseling Information Section

   a. Revise the first bullet under Dosing Instructions to state "…should not alter the dose or discontinue the medication without consulting the provider.".

   b. We recommend removing the last bullet in the Dosing Instructions section regarding handling skipped dose as this does not appear to pertain to this product which is dosed once a day.

4.2 RECOMMENDATIONS FOR AGEPHA PHARMA MIDDLE EAST TRADING LLC

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container Labels & Carton Labeling)

1. As currently presented, there is inconsistency between the presentation of the proprietary name, established name, and dosage form in the blister pack container label and carton labeling with respect to the parenthesis. We also recommend removing "[redacted]" from the product name and labeling. For consistency with the PI, revise the presentation of the information as follows:

   LODOCO

   (colchicine) tablets

B. Container Labels

1. As proposed, the product strength statement on the blister pack does not clearly communicate the strength is per unit. Revise the strength statement to make it clear that the designated strength is per tablet. Revise to “0.5 mg per tablet”.
2. As currently presented, the product strength is not clearly separated from the proprietary name. We recommend moving the strength statement underneath the statement of established name and dosage form.
3. We recommend debolding “AGEPHA Pharma USA, LLC” as this competes for prominence with the drug name and strength.
4. Per the Prescribing Information, the product must be stored in the original package to protect from light. To ensure this important information is not missed we recommend including the statement “Store in original carton packaging to protect from light.” on the blister pack.
5. We recommend including a statement regarding contents. Please include “Each tablet contains 0.5 mg of colchicine.”.

C. Carton Labeling

1. As presented the net quantity lacks clarity and is missing information such as number of blister packs. We recommend revising the net quantity to “One blister pack containing 30 tablets”. In addition, the net quantity appears in close proximity to the product strength which may increase the risk of numerical confusion. We recommend moving the net quantity away from the product strength to prevent confusion.
2. We recommend debolding the net quantity statement and the statement “Rx only” as these statements compete for prominence on the principal display panel with the drug name and strength.
3. We recommend removing [redacted] (b) (4) as a [redacted] (b) (4) will not be required with this product.
4. As currently presented the dosage statement should be revised from [redacted] (b) (4) to “Recommended Dosage: See Prescribing Information.” for consistency across all products.
5. Per the Prescribing information the product must be stored in the original package to protect from light. To ensure this important information is not missed we recommend including the statement “Attention: Dispense and store Lodoco in original blister pack and carton packaging to protect from light.” on the principal display panel.
6. We recommend revising the storage statement for consistency with the Prescribing Information. Revise to “Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled

Room Temperature]. Store in original blister pack and carton packaging to protect from light.”.

7. We recommend including a statement regarding contents. Please include “Each tablet contains 0.5 mg of colchicine.” on the back panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Lodoco received on 09/20/2022 from AGEPHA Pharma Middle East Trading LLC, and the listed drug (LD).

Table 2. Relevant Product Information for Lodoco and the Listed Drug		
Product Name	Lodoco (NDA 215727)	Colcrys[a] (NDA 022352)
Initial Approval Date	N/A	07/29/2009
Active Ingredient	colchicine	colchicine
Indication	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.	In adults and children 4 years or older for treatment of familial Mediterranean fever (FMF).
Route of Administration	Oral	Oral
Dosage Form	tablets	Tablets
Strength	0.5 mg	0.6 mg
Dose and Frequency	0.5 mg once daily	Children: 0.3 mg to 2.4 mg once daily Adults: 1.2 mg to 2.4 mg daily
How Supplied	White to slightly yellow biconvex tablets Aluminum/PVC blister of 30 tablets	Purple, film-coated, capsule shaped tablets, debossed with 'AR 374' on one side and scored on the other side. Bottles of 30, 60, 100, 250, 500 or 1,000
Storage	Store at 20 to 25C (68 to 77F) [See USP Controlled Room Temperature]	Store at 20 to 25C (68 to 77F) [See USP Controlled Room Temperature]

[a] Colcrys [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2009 JUL [accessed 11/07/2022]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022352lbl.pdf

	Store LODOCO in the original package in order to protect from light	Dispense in tight, light-resistant container
Container Closure	The primary packaging material is composed of (b) (4) . The blister is packed in an outer package of carton. Each box contains a single Alu/PVC blister containing 30 tablets.	(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On November 10, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 'LODOCO' and 'NDA 215727'. Our search did not identify any relevant previous reviews.

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APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Lodoco labels and labeling submitted by AGEPHA Pharma Middle East Trading LLC.

- Container label received on February 8, 2023
- Carton labeling received on February 8, 2023
- Sample Unit-Dose Carton Labeling received on June 28, 2022
- Sample Blister Pack received on June 28, 2022
- Prescribing Information (Image not shown) received on 09/20/2022, available from \\CDSESUB1\EVSPROD\nda215727\0006\m1\us\pi-draft-label-text-20220919-lodoco-v1.pdf
- Medication Guide received on 09/20/2022, available from \\CDSESUB1\EVSPROD\nda215727\0006\m1\us\colchicine-medication-guide.pdf

G.2 Label and Labeling Images

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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HINA S MEHTA
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatrics and Maternal Health Memorandum

Date: February 6, 2023 **Date Consulted:** January 5, 2023

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, Director, DPMH

To: Division of Cardiology and Nephrology (DCN)

Drug: Lodoco (Colchicine Tablets)

NDA: 215727

Indication: To reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, (b) (4) , and CV death among patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease.

Applicant: AGEPHA Pharma Middle East Trading LLC

Subject: Pregnancy and Lactation labeling as per PLLR

Materials Reviewed:

- NDA 215727 submitted on September 20, 2022
- Gloperba (colchicine oral solution) labeling review by Kristie Baisden, DO, DPMH of January 10, 2019, in DARRTS and

Reference ID: 4373586[1]

- Colcrys (colchicine tablets for oral use) labeling review by Christos Mastroyannis, M.D., DPMH of February 28, 2020, in DARRTS and Reference ID: 4568250
- DCN's consult request to DPMH for Lodoco Tablets, for Oral Use, of January 5, 2023, in DARRTS, Reference ID: 5104658

Consult Question: DCN has requested DPMH to ensure that the labeling for this new NDA 215727 complies with the PLLR content and format.

INTRODUCTION

On September 20, 2022, the applicant, AGEPHA Pharma Middle East Trading
LLC, submitted an original new drug application (NDA) for Lodoco (Colchicine Tablets, for Oral Use) via the 505 (b) (2) regulatory pathway. The applicant provides this NDA based on literature and FDA's findings of safety and effectiveness for the US approved products containing colchicine, specifically with Colcrys oral tablets as the listed drug relied upon. The proposed indication for Lodoco is 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. This indication for Lodoco is different from the approved indications for Colcrys, the drug the applicant relied upon. Colcrys is indicated for:

- Prophylaxis and treatment of gout flares in adults
- Familial Mediterranean fever (FMF) in adults and children 4 years or older

DCN consulted the DPMH on January 5, 2023, to assist with the labeling subsections for the *Pregnancy*, *Lactation, and Females and Males of Reproductive Potential* and to ensure that the labeling complies with the PLLR content and format.

BACKGROUND

Regulatory History

- The applicant is relying on the FDA-approved drug Colcrys Tablets for Oral Use, NDA 022352, as the listed drug relied

[1] DPMH did not rely on data in the Gloperba (Colchicine Oral Solution) NDA or the Agency's finding of safety and effectiveness for Gloperba to support labeling sections of this Lodoco NDA. Rather, the cross-reference to the Gloperba consults are included to avoid duplicating background information relevant to this class of products.

upon.

- Colcrys was approved on July 29, 2009 for:
    - Prophylaxis and treatment of gout flares in adults
    - Familial Mediterranean fever (FMF) in adults and children 4 years or older

Colchicine Drug Characteristics[2]

- *Drug Class:* antigout/ Alkaloid/ Mitotic Inhibitor
- *Molecular weight:* 399 Daltons
- *Bioavailability:* 45%
- *Protein binding:* (b) (4)-44%
- *Half-life:* 27-31 hours
- *Adverse reactions:* (b) (4) muscle weakness, nausea, vomiting, abdominal pain, diarrhea, (b) (4), aplastic anemia, agranulocytosis (b) (4) purpura, alopecia

- **Mode of Action[3]:**
  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.

Reviewer Comment:

LODOCO is to be administered at lower doses that the use of the same drug in Gout and FMF.

LODOCO should be administered as single oral dose of 0.5 mg once daily. The approved dosages for gout and FMF (Familial Mediterranean fever) are:

- ***Prophylaxis of Gout Flares:*** *0.6 mg once or twice daily in adults and adolescents older than 16 years of age. Maximum dose 1.2 mg/day.*
  Treatment of Gout Flares: *1.2 mg (two tablets) at the first sign of a gout flare followed by 0.6 mg (one tablet) one hour later*
- ***FMF:*** *Adults and children older than 12 years 1.2 – 2.4 mg; children 6 to 12 years 0.9 – 1.8 mg; children 4 to 6 years 0.3 – 1.8 mg*
    - *Give total daily dose in one or two divided doses*
    - *Increase or decrease the dose as indicated and as tolerated, not*

[2] Colcrys (Colchicine Tablets for Oral Use) existing labelings of May 14, 2020.
[3] Lodoco labeling as edited by non-clinical reviewer Philip Gatti, Ph.D.

to exceed the maximum daily dose

APPEARS THIS WAY ON ORIGINAL

CURRENT STATE OF THE COLCRYS LABELING of May 14, 2020

The labeling is in PLR and PLLR format.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

• Females and Males of Reproductive Potential: Advise males that COLCRYS may transiently
impair fertility (8.3).

FULL PRESCRIBING INFORMATION: CONTENTS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

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

Data

Human Data

Available data from published observational studies, case series, and case reports over several decades do not suggest an increased risk for major birth defects or miscarriage in pregnant women with rheumatic diseases (such as rheumatoid arthritis, Behcet’s disease, or familial Mediterranean fever (FMF)) treated with colchicine at therapeutic doses during pregnancy. Limitations of these data include the lack of randomization and inability to control for confounders such as underlying maternal disease and maternal use of concomitant medications.

8.2 Lactation

Risk Summary

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

Data

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

8.3 Females and Males of Reproductive Potential

Infertility

Case reports and epidemiology studies in human male subjects on colchicine therapy indicated that infertility from colchicine is rare and may be reversible. A case report indicated that azoospermia was reversed when therapy was stopped. Case reports and epidemiology studies in female subjects on colchicine therapy have not established a clear relationship between colchicine use and female infertility. However, since the progression of FMF without treatment may result in infertility, the use of colchicine needs to be weighed against the potential risks *[see Nonclinical Toxicology (13.1)]*.

17 PATIENT COUNSELING

Infertility

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

REVIEW

Data

There were no clinical or nonclinical studies conducted in this development program. The applicant's NDA relies upon information from the US approved drug, Colcrys.

The applicant provided a literature review for colchicine use during pregnancy.[4,5,6] The identified publications have been previously reviewed by DPMH. The reader is referred to the extensive review of the literature provided by DPMH in the previous review of Colcrys, by this reviewer, dated February 28, 2020. The applicant relies on the Colcrys labeling for Lactation. They did not provide any additional literature search except for animal data. Some of the applicant's publications regarding the effects of colchicine on human fertility have been previously reviewed. Additional publications provided by the applicant state:

- Yu ,T[7] 1982: There is no evidence of chromosomal aberration or infertility in humans.
- The publication by Bruce and Heddle of 1979 is not relevant.

No additional safety issues relevant to colchicine exposure during pregnancy or lactation, or its effects on human fertility were identified.

Applicant's Proposed Labeling

The applicant is referencing the Colcrys labeling, but they did not follow the PLLR format eventhough they include the Colcrys labeling's content. In addition, the applicant's proposed recommendations for use in Pregnancy and Lactation do not align with those in Colcrys labeling.

In subsection 8.1 Pregnancy, the applicant states:

> Available data from published literature on colchicine use in pregnancy over several decades have not identified any drug associated risks for major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data). (b) (4)

Reviewer Comment

(b) (4)

[4] Diav-Citrin, O., Shechtman, S *et.al*. Pregnancy outcome after in utero exposure to colchicine. Am J of OB-GYN, 203.(2), 144-e1, 2010

[5] Duman NC, Karabacak M, *et. al*. Colchicine use during pregnancy: case reports, Annals of the Rheumatic Diseases, 78:2082-2083:2019

[6] Indraratna PL *et. al*. Use of colchicine in pregnancy: a systemic review and meta-analysis. Rheumatology (Oxford). :4(12), 977-987:2005

[7] Yu, T The efficacy of colchicine prophylaxis in articular gout--a reappraisal after 20 years. Semin Arthritis Rheum
1982 Nov;12(2):256-64.

[redacted]. *It is the opinion of this reviewer that extensive human data on colchicine use during pregnancy over several decades supersedes the data from animal studies. Colcrys labeling does not include this recommendation. In addition, this drug is to be administered at lower doses than the use of the same drug in Gout and FMF. Therefore, the sentence:* [redacted] *should be deleted.*

In subsection 8.2 Lactation, the applicant states:

> Limited published data from case reports and a small lactation study demonstrate that colchicine is [redacted] in breast milk. Adverse events in breastfed infants have not been reported in the published literature after administration of Colchicine to lactating women. There are no data on the effects of colchicine on milk production. [redacted]

Reviewer Comment

[redacted] *Human data has not indicated any adverse reactions to colchicine use during lactation over the years, and therefore, this sentence should be deleted.*

In subsection 8.3 Females and Males of Reproductive Potential,

[redacted]

- Infertility: This paragraph is identical to Colcrys labeling.

The applicant has not provided any additional information that requires inclusion in the labeling or revision to the safety messaging regarding colchicine use during pregnancy or lactation, or in patients of reproductive potential.

DISCUSSION and CONCLUSIONS

Because this 505(b)(2) NDA is seeking approval with drug relied upon Colcrys, and depends on published literature, DPMH recommends that the labeling for Lodoco aligns with previously approved labeling for Colcrys.

Also, DPMH does not recommend a PMR for a Descriptive Pregnancy Safety Study or a lactation milk only study because there is extensive published literature on colchicine use in humans over several decades including observational studies, case series and case reports that do not suggest an increased risk for major birth defects, miscarriage or adverse maternal or fetal outcomes when colchicine was used in pregnant women. Colchicine is present in human milk and no adverse events in breastfed infants have been reported in the published literature after administration of colchicine to lactating women. In a prospective observational cohort study, no gastrointestinal or other symptoms were reported in 38 colchicine-exposed breastfed infants.

LABELING RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2 and 8.3 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

CHRISTOS MASTROYANNIS
02/06/2023 05:31:57 PM

TAMARA N JOHNSON
02/07/2023 10:33:53 AM

LYNNE P YAO
02/07/2023 12:42:37 PM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12/9/2022

TO: Division of Cardiology and Nephrology (DCN)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 215727

The Office of Study Integrity and Surveillance (OSIS) determined that inspections are not needed at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) conducted an inspection for the clinical site in May 2022, which falls within the surveillance interval. The inspection was conducted under the following submission: NON-RESPONSIVE

OSIS concluded that data from the reviewed studies were reliable.

OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4), which falls within the surveillance interval. The RRA was conducted under the following submissions: Non-Responsive

Sites

Facility Type	Facility Name	Facility Address
Clinical	Axis Clinicals, Ltd.	Atharva, Opposite Rajpath Club, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad, Gujarat, India)

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

JOSHUA L PEREZ
12/12/2022 10:12:59 AM