CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215727Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	215727		
Applicant Name	Agepha Pharma Middle East Trading LLC		
Drug Product Name	LODOCO (colchicine) tablets		
Dosage Form.	Tablet		
Proposed Strength(s)	0.5 mg		
Route of Administration	Oral		
Maximum Daily Dose	0.5 mg		
Rx/OTC Dispensed	Rx		
Proposed 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.		
Drug Product Description	White to slightly yellow, round, biconvex tablets, debossed with 'L1' on one side and plain on the other side.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	20°C to 25°C (68°F to 77°F), in carton to protect from light.		
Review Team	**Discipline**	**Primary**	**Secondary**

	Drug Substance	Ben Zhang OPQ/ONDP/DNDAPI/NDB3	Zhengfu Wang OPQ/ONDP/DNDAPI/NDB3
	Drug Product/ Labeling	Rao Kambhampati OPQ/ONDP/DNDPIII/NDPB5	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5
	Manufacturing	Nancy Waites OPQ/OPMA/DPMAIII/PMB7	Alexander Gontcharov OPQ/OPMA/DPMAIII/PMB7
	Biopharmaceutics	Nadia Ahmed OPQ/ONDP/DB/BB3	Haritha Mandula OPQ/ONDP/DB/BB3
	Microbiology	N/A	
	Other (specify):	N/A	
	RBPM	Grafton Adams OPQ/OPRO/DRBPMI/RBPMB2	
	ATL	Theodore Carver OPQ/ONDP/DNDPIII/NDPB5	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating:

A shelf life of 18 months is granted for the drug product when stored at 20 to 25 °C in the original package to protect from light.

b. Additional Comments for Action: None.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

1.) Background

The Applicant, Agepha Pharma, has submitted a 505(b)(2) NDA seeking marketing approval for LODOCO (Colchicine tablets), 0.5 mg, which is indicated to reduce the risk of myocardial infarction (MI), stroke, coronary

revascularization, [redacted], and cardiovascular death among patients with established atherosclerotic disease or with multiple risk factors for cardiovascular disease. The application relies on published literature, FDA's previous findings for approved products including published clinical studies, and in vitro bridging data. NDA 215727 was initially submitted on April 13, 2022, and a refusal-to-file was issued for this NDA on June 11, 2022, due to nonclinical and labeling deficiencies. The Applicant resubmitted NDA 215727 on September 19, 2022. On February 23, 2023, the FDA extended the review goal date by three months due to a major CMC amendment submitted by the Applicant, which included information addressing deficiencies identified during the review (see drug product review summary below).

2.) Drug Substance (Colchicine)

Colchicine is a small molecule, a single diastereomer extracted from Gloriosa Superba seeds [redacted] using a well-established manufacturing process. The [redacted] polymorphism and particle size of the drug substance are not critical quality attributes with respect to the drug product. The proposed drug substance 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 [redacted] which has been reviewed and found adequate to support this NDA, including all recent amendments.

3.) Drug Product (Colchicine Tablets)

The drug product is immediate-release tablets containing colchicine, lactose monohydrate, gelatin, potato starch, talc, and magnesium stearate. All excipients are manufactured to compendial standards and animal-derived excipients are from appropriate sources certified to be BSE/TSE-free. The specification includes appropriate tests and acceptance criteria to confirm the drug product quality. 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 [redacted]. In response to information requests and teleconference held on February 10th, 2023, the Applicant agreed to add [redacted] to the drug product manufacturing process and submitted an amendment including the [redacted] batch data [redacted], which was reviewed and found to be adequate after an extension of the review period. The drug product primary packaging is a 30-count blister card contained in a

carton as the secondary packaging. Based on 18 months long-term stability data for three drug product batches manufactured at commercial scale, the drug product is stable for 18 months when stored at 25 °C and protected from light by storing the blister pack in the carton.

4.) Manufacturing

Process - The manufacturing process for the 0.5 mg tablets was developed based on a well-established process (b) (4) The manufacturing process consists of (b) (4) . As indicated above, the manufacturing process was revised (b) (4). Overall, 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).

Facilities – 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. See the Table 2, Facilities Table, on page 2 of the manufacturing review in the Integrated Quality Assessment.

5.) Biopharmaceutics

The biopharmaceutics review included review of the proposed dissolution method and review of physicochemical data to support a scientific bridge between the proposed and reference drug products. With regards to the dissolution method, the method was found to be adequate based on the Applicant's responses to information requests, clarification regarding the proposed BCS classification, and revised dissolution acceptance criteria. The biopharmaceutics review concluded that comparative dissolution profiles for test and reference drug product demonstrate rapid dissolution for all drug products tested. The review recommended approval from the biopharmaceutics perspective.

6.) Quality Labeling

The prescribing information and container labeling were found to be adequate based on the Applicant's agreement to implement changes recommended by the review team, which will be confirmed in the final labeling to be submitted by the Applicant.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations: None.

Established Conditions per ICH Q12: No
Comments: N/A

Comparability Protocols (PACMP): No
Comments: N/A

Additional Lifecycle Comments:

None.

LABELING REVIEW
NDA 215727 Revised Final Review 4-14-2023

Note: This review is based on the labeling documents submitted in the resubmitted NDA 215727, Seq. # 0006 (9/19/2022) and revised documents submitted later to the NDA. The proposed proprietary name (tradename) "Lodoco" was conditionally accepted by the Division of Medication Error Prevention and Analysis 2 (DARRTS review 12/7/2022).

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The comments shown in the following tables related to the Prescribing Information were incorporated into the sharepoint document, which was communicated to the applicant by the OND PM and the applicant agreed to incorporate them into the final printed labeling.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s)[1]	Adequate	LODOCO (colchicine) tablets, for oral use.
Route(s) of administration	Adequate	Oral use.
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Adequate	Tablets: 0.5 mg
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored".	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

[1] Established name = [Drug] [Route of Administration] [Dosage Form]

If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: *"Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit"*	N/A	
If there is a USP monograph for the drug product and it contains a	Adequate	

labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).		
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement *"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.*[x]*"* with x numerical citation to "OSHA Hazardous Drugs".	N/A	

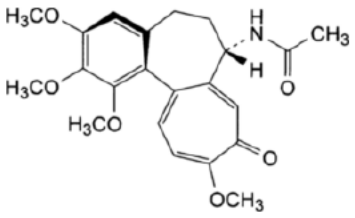
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Tablets
Strength in metric system	Adequate	0.5 mg
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	Tablets: 0.5 mg - White to slightly yellow, biconvex tablets debossed with "L1" on one side and plain on the other side.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	LODOCO contains colchicine
Dosage form(s) and route(s) of administration	Adequate	Tablet, Oral
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP. For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Adequate	LODOCO (colchicine USP) tablets are supplied for oral administration as white to slightly yellow, round, biconvex tablets containing 0.5 mg of colchicine USP as the active ingredient and the following inactive ingredients: gelatin, lactose monohydrate, magnesium stearate, potato starch, and talc.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	Alkaloid

Chemical name, structural formula, molecular weight	Adequate	Acetamide, N-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[a]heptalen-7-yl)-, (S) with a molecular formula of $C_{22}H_{25}NO_6$ and a molecular weight of 399.4 g/mol. The structural formula of colchicine is given below. 
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	Adequate	Statement was included in How Supplied Section.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

APPEARS THIS WAY ON ORIGINAL

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	Tablets.
Strength(s) in metric system	Adequate	0.5 mg
Available units (e.g., bottles of 100 tablets)	Adequate	Aluminum/PVC blister of 30 tablets: NDC 82867-001-01
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	LODOCO (colchicine USP) tablets 0.5 mg are white to slightly yellow, biconvex tablets with "L1" on one side and plain on other side and available as single Aluminum/PVC blister pack of 30 tablets, which is secondary packaged in a carton: NDC 82867-001-01
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.[x]" with x numerical citation to "OSHA Hazardous Drugs."	Adequate	Store LODOCO in the original package in order to protect from light.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Adequate	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].
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: *"Not made with natural rubber latex. Avoid statements such as "latex-free."*	N/A	
Include information about child-resistant packaging	N/A	

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Adequate	Distributed by: AGEPHA Pharma USA LLC Parsippany New Jersey 07054

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information): In the NDA, applicant submitted a Medication Guide and the quality (CMC) related comments were incorporated into the sharepoint document along with other disciplines and then it was sent to the applicant for revision by the OND PM. Applicant agreed to revise in the final printed labeling.

3.0 CONTAINER AND CARTON LABELING

Note: The proposed primary container is a blister card configuration, which is secondary packaged in a carton.

Blister Card (30-count) Label:

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

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Blister Card and Carton Labels (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name[2], (font size and prominence)	Adequate	LODOCO (Colchicine)
Strength(s) in metric system	Adequate	0.5 mg
Route(s) of administration	N/A	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP.	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	Not shown on blister card. Carton contains: 30 tablets.
"Rx only" displayed on the principal display	Adequate	Not shown on blister card. Carton contains: Rx only
NDC	Adequate	Included: 82867-001-01
Lot number and expiration date	Adequate	Included
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Adequate	Not shown on the blister card. Carton contains: Store at 20°C to 25°C (68°F to 77°F); [see USP Controlled Room Temperature]. Protect from light.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	Included

[2] Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	Distributed by: AGEPHA Pharma USA LLC Parsippany New Jersey 07054
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	Protect from light statement was included.
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Container Labeling: Adequate.

Overall Assessment and Recommendation: Adequate. All the comments regarding prescribing information, Medication Guide, and container and carton labels were communicated to the applicant and the applicant agreed to incorporate them in the final printed labeling.

ITEMS FOR ADDITIONAL ASSESSMENT: None

Primary Labeling Assessor Name and Date: Rao V. Kambhampati, Ph.D. 4/14/2023

Rao Kambhampati

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Theodore Carver

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U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

Product Information	Colchicine Tablet
NDA Number	215727
Assessment Cycle Number	1
Drug Product Name/ Strength	Lodoco (Colchicine)/0.5 mg
Route of Administration	Oral
Applicant Name	Agepha Pharma Middle East Trading LLC
Therapeutic Classification/ OND Division	CDER/OND/OCHEN/DCN
RLD/RS Number	NDA 022353 (NDA) and Australian-approved Reference 27909 (Colgout)
Proposed Indication	To reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, (b) (4) , and cardiovascular death among patients with atherosclerotic disease or with multiple risk factors for cardiovascular disease.

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant submitted NDA 215727 for the marketing approval of Lodoco (Colchicine) 0.5 mg in the US, indicated to reduce the risk of myocardial infarction (MI), stroke, coronary revascularization, (b) (4) , and cardiovascular death. The current submission is a resubmission, following a refuse to file issued by the Agency due to insufficient information submitted in the Nonclinical section. This Application refers to one US RLD for safety (Colcrys 0.6 mg, NDA 022352) and three non-US approved references for efficacy (Colgout tablets, 0.5 mg, approved in Australia, Colchicine Tiofarma 0.5 mg tabletten, approved in the Netherlands, and Colchicine Teva 0.5 mg tabletten, approved in the Netherlands). In a meeting package[1] dated 09/08/2020, the Agency agreed that two BE studies (one fed and one fasting) against one of the three Foreign-approved RLDs may be enough to demonstrate effectiveness. In the current submission, the Applicant claims that Colchicine is a high solubility drug substance belonging to BCS Class III. Based on its high solubility, the Applicant claims that the risk is low.

[1] \\CDSESUB1\EVSPROD\nda215727\0006\m1\us\prenda-typeb-meet-2020sept08.pdf

The Applicant has not requested a biowaiver. Instead, the Applicant has proposed a scientific bridge to the reference products. In addition to the provided literature and BE study with one of the three foreign reference products, the Applicant has provided multimedia comparative dissolution using purified water, 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer as supportive information for the bridge. Although all submitted dissolution profiles demonstrate rapid dissolution (> (b) (4) in 15 minutes), the adequacy of using in vitro dissolution to support the efficacy studies is under the purview of the Clinical Pharmacology Reviewer.

To support the bridge to the US RLD for demonstration of safety, the Applicant has provided multimedia comparative dissolution using purified water, 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. Although all submitted dissolution profiles demonstrate rapid dissolution (> (b) (4) in 15 minutes), the adequacy of the bridge to the US RLD is under the purview of the PharmTox Reviewer.

The Applicant had not originally submitted a dissolution method development report, nor had they provided BCS solubility data. Based on the Applicant's claim of high solubility, the Agency recommended that the Applicant propose a dissolution method consistent with the High Solubility guidance and submit solubility data via IR. However, upon receipt of the IR, the Applicant's original data demonstrated that their drug substance was not soluble in under 250 mL under any tested conditions. Additionally, the Applicant claimed that their drug product is (b) (4). However, per communications with the Clinical Pharmacology Team, the Agency does not consider this an (b) (4). [2]

Based on the Applicant's originally submitted solubility data, the Applicant was asked to confirm that equilibrium solubility has been performed adequately and provide a full dissolution development report via IR. Literature supports that colchicine is a highly soluble drug substance, and the drug release results using 0.1N HCl (consistent with the High Solubility guidance) demonstrate rapid and similar drug release to the Applicant's proposed dissolution method. Therefore, the risk is low. The Applicant's proposed in vitro dissolution method is adequate. However, based on the submitted in vitro dissolution data, the Applicant was recommended via IR to adopt the acceptance criterion of "Q= (b) (4) in 15 minutes".

In response to the Agency's IR, the Applicant has redone the solubility studies, noting that the previously submitted solubility studies were not conducted

[2] (b) (4)

under equilibrium conditions. Under equilibrium solubility conditions, the Applicant has demonstrated that Colchicine is highly soluble in various media over a pH range of 1 to 6.8 (water, 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). It is noted that the highest dose, 0.5 mg, is soluble in less than 250 ml of media under all conditions tested. Colchicine is considered a highly soluble drug as per BCS classification.

The Applicant's proposed dissolution method is not consistent with the method in the guidance for High Solubility drug substances. However, the drug release results using 0.1N HCl demonstrates rapid solubility and similar drug release to the Applicant's proposed dissolution method. (b) (4) (b) (4). For further details, see the drug substance, drug product, and manufacturing reviews. The dissolution consistently demonstrates very rapid dissolution (> (b) (4) drug release in 15 minutes). The Applicant's proposed dissolution method is adequate.

The Applicant accepted the Agency's recommended acceptance criterion for release but requested to maintain their originally proposed acceptance criterion for stability, based on their accelerated stability batches. The Applicant's previously proposed dissolution specifications are shown in Table A1. However, the Applicant was reminded via IR that the dissolution acceptance criterion is based on initial rather than stability data and was recommended to implement the acceptance criterion of "Q= (b) (4) in 15 minutes" for both the release and stability specifications. In response to the Agency's IR, the Applicant has adopted the recommended acceptance criterion for release and stability specifications and updated the stability specifications accordingly. The approved dissolution method and acceptance criterion are shown in Table 1. Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 215727 for Lodoco (Colchicine) Tablets, 0.5 mg is Adequate and recommended for APPROVAL.

Table 1: Dissolution Method and Acceptance Criterion

USP Apparatus	Speed	Medium	Volume/ Temperature	Acceptance Criterion
Type I (Basket)	100 RPM	Water	500 mL; 37°C ± 0.5°C	Q= (b) (4) in 15 min

List Submissions being assessed:

Document(s) Assessed	Date Received
NDA-215727-ORIG-1 Seq 0006	09/20/2022
NDA-215727-ORIG-1 Seq 0008	01/05/2023
NDA-215727-ORIG-1 Seq 0013	02/03/2023
NDA-215727-ORIG-1 Seq 0016	02/08/2023
NDA-215727-ORIG-1 Seq 0017	02/13/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

B.1 BCS DESIGNATION

Assessment: The Applicant did not originally submit solubility data, but they claimed that their drug substance demonstrated high solubility and belonged to BCS Class III. Therefore, the Applicant was asked to submit solubility data via IR. In response to the IR, the Applicant provided solubility data, which demonstrated that the drug substance is not highly soluble per BCS classification. However, in response to a second IR asking if the solubility experiments had been conducted under equilibrium conditions, the Applicant has submitted new solubility data, conducted under equilibrium conditions, demonstrating that the drug substance, Colchicine, is highly soluble per BCS classification.

Solubility: Based on the originally provided solubility data of the drug substance over the physiological pH range, the Applicant demonstrated that Colchicine is not highly soluble in various media over pH range of 1 to 6.8 (water, 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). In response to the Agency's IR, the Applicant has redone the solubility studies, noting that the previously submitted solubility studies were not conducted under equilibrium conditions. Under equilibrium solubility conditions, the Applicant has demonstrated that Colchicine is highly soluble in various media over a pH range of 1 to 6.8 (water, 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer). It is noted that the highest dose, 0.5 mg, is soluble in less than 250 ml of media under all conditions tested. Colchicine is considered a highly soluble drug as per BCS classification.

Permeability: The Applicant has not submitted any permeability data.

Dissolution: The Applicant's proposed dissolution method is not consistent with the method in the guidance for High Solubility drug substances. However, the drug release results using 0.1N HCl demonstrates rapid solubility and similar drug release to the Applicant's proposed dissolution method. Additionally, the (b) (4) dissolution consistently demonstrates very rapid dissolution (> (b) (4) drug release in 15 minutes). For further details on the manufacturing process, see the drug substance, drug product, and manufacturing reviews. Based on the previous information, the risk is low.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***{Adequate}***

The Applicant had originally claimed that the drug substance was a BCS Class III substance, demonstrating high solubility. Therefore, the Agency had originally recommended that the Applicant propose a dissolution method consistent with the FDA Guidance titled, "Dissolution Testing and Acceptance

Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances" via IR. In response to the Agency's IR, the Applicant has claimed that the before-mentioned guidance is not applicable to their drug product because colchicine is (b) (4) (b) (4). The Clinical Pharmacology Reviewer has determined that Colchicine 0.5 mg is not considered (b) (4) per the Agency.[2]

Although the Applicant's original solubility data does not demonstrate high solubility, the drug substance (b) (4) dissolution consistently demonstrates very rapid dissolution (> (b) (4) drug release in 15 minutes). Furthermore, literature supports that colchicine is a highly soluble drug substance, and the drug release results using 0.1N HCl (consistent with the High Solubility guidance) demonstrate rapid solubility and similar drug release to the Applicant's proposed dissolution method. Therefore, the risk is low. Based on the submitted in vitro dissolution Exhibit Batch Data, the Applicant was recommended via IR to adopt the acceptance criterion of "Q= (b) (4) in 15 minutes". Additionally, based on the Applicant's originally submitted solubility data, the Applicant was asked to confirm that equilibrium solubility has been performed adequately and provide a full dissolution development report.

In response to the Agency's IR, the Applicant has redone the solubility studies, noting that the previously submitted solubility studies were not conducted under equilibrium conditions. Under equilibrium solubility conditions, the Applicant has demonstrated that Colchicine is considered a highly soluble drug as per BCS classification. Additionally, Appears this way on original the Applicant accepted the Agency's recommended acceptance criterion for release, (b) (4) (b) (4), based on their accelerated stability batches. The Applicant's proposed dissolution method is adequate. However, the Applicant was reminded via IR that the dissolution acceptance criterion is based on initial (b) (4) data and was recommended to implement the acceptance criterion of "Q= (b) (4) in 15 minutes" for both the release and stability specifications via IR.

In response to the Agency's IR, the Applicant has accepted the Agency's recommended acceptance criterion for release and stability and updated their specifications accordingly. A summary of the approved dissolution method and acceptance criterion is shown in Table 1.

B.12 BRIDGING OF FORMULATIONS

Assessment: The in vitro dissolution data submitted for bridging is supportive information for the two scientific bridges: 1. Supportive information to bridge to the three foreign reference drugs in the LoDoCo-2 trial and 2. Supportive information to bridge to Colcrys, the US RLD. The adequacy of the first bridge

will be determined by the Clinical Pharmacology Reviewer. The adequacy of the second bridge will be determined by the Pharm Tox Reviewer.

In-vitro comparisons between Lodoco, Colgout, Colchicine Tiofarma, and Colchicine Teva (Foreign Reference Products used in LoDoCo2 trial):
In addition to the provided literature and BE study with one of the three foreign reference products, the Applicant has provided multimedia comparative dissolution between the three foreign reference products (Colgout, Colchicine Tiofarma, and Colchicine Teva) using purified water, 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer, as shown in Tables 2a-c. Additionally, the Applicant has provided multimedia comparative dissolution between the test and reference products used in the in vivo BE studies (Lodoco and Colgout) using purified water, 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer as supportive information for the bridge, as shown in Table 3. All dissolution profile comparisons across all pH's demonstrate rapid and similar dissolution (> (b) (4) release in 15 minutes).

Table 2a: Multimedia Dissolution of Colgout

500 ml media using USP apparatus I (Basket) at 100 rpm (Colgout®- DA601)							
Purified Water		0.1 N HCl		pH 4.5 (Acetate buffer)		pH 6.8 (Phosphate buffer)	
Time (min)	% Colchicine dissolved	Time (min)	% Colchicine dissolved	Time (min)	% Colchicine dissolved	Time (min)	% Colchicine dissolved
0	(b) (4)	0	(b) (4)	0	(b) (4)	0	(b) (4)
5		5		5		5	
10		10		10		10	
15		15		15		15	
30		30		30		30	
45		45		45		45	

Table 2b: Multimedia Dissolution of Teva Colchicine

500 ml media using USP apparatus I (Basket) at 100 rpm (Teva-19B26E)							
Purified Water		0.1 N HCl		pH 4.5 (Acetate buffer)		pH 6.8 (Phosphate buffer)	
Time (min)	% Colchicine dissolved	Time (min)	% Colchicine dissolved	Time (min)	% Colchicine dissolved	Time (min)	% Colchicine dissolved
0	(b) (4)	0	(b) (4)	0	(b) (4)	0	(b) (4)
5		5		5		5	
10		10		10		10	
15		15		15		15	
30		30		30		30	
45		45		45		45	

Table 2c: Multimedia Dissolution of Tiofarma Colchicine

500 ml media using USP apparatus I (Basket) at 100 rpm (Tiofarma-19F10/D)							
Purified Water		**0.1 N HCl**		**pH 4.5 (Acetate buffer)**		**pH 6.8 (Phosphate buffer)**	
Time (min)	% Colchicine dissolved	Time (min)	% Colchicine dissolved	Time (min)	% Colchicine dissolved	Time (min)	% Colchicine dissolved
0	(b) (4)	0	(b) (4)	0	(b) (4)	0	(b) (4)
5		5		5		5	
10		10		10		10	
15		15		15		15	
30		30		30		30	
45		45		45		45	

Table 3: Comparative Multimedia Dissolution Profiles between Colgout (Reference used in in vivo BE study) and LoDoCo (Proposed Drug Product)

Dissolution Conditions			**Apparatus:**		Basket					
			Speed of Rotation:		100 rpm					
			Volume:		500 ml					
			Temperature:		37°C ± 0.5°C					
			Applicants proposed specification		(b) (4) Q % of labeled amount of Colchicine is dissolved in 15 minutes.					
Dissolution testing site and address			(b) (4)							
Product ID/ batch no. (Test-Manufacturing date and Reference expiration date)	**Medium**	**Dosage form**	**No. of dosage units**	**Dosage Strength & Form**	-	**Collection times**				
						5 mins	10 mins	15 mins	30 mins	45 mins
Test product-1E3547 (04.05.2021)	Purified water	Tablet	12	0.5 mg tablet	Mean (%)	100	99	99	98	98
					Range (%)	(b) (4)				
					%RSD	2	1	1	1	1
Reference product-DH258 (10/2022)		Tablet	12	0.5 mg tablet	Mean (%)	71	98	98	98	98
					Range (%)	(b) (4)				
					%RSD	3	2	1	1	1
Test product-1E3547 (04.05.2021)	0.1 N HCl	Tablet	12	0.5 mg tablet	Mean (%)	94	95	95	94	93
					Range (%)	(b) (4)				
					%RSD	1	1	1	1	1
Reference product-DH258		Tablet	12	0.5 mg tablet	Mean (%)	65	90	94	93	92
					Range (%)	(b) (4)				
(10/2022)					%RSD	5	4	2	2	2
Test product-1E3547 (04.05.2021)	pH 4.5 Acetate buffer	Tablet	12	0.5 mg tablet	Mean (%)	97	98	98	98	98
					Range (%)	(b) (4)				
					%RSD	1	1	1	1	1
Reference product-DH258 (10/2022)		Tablet	12	0.5 mg tablet	Mean (%)	41	81	98	99	99
					Range (%)	(b) (4)				
					%RSD	7	5	2	2	2
Test product-1E3547 (04.05.2021)	pH 6.8 Phosphate buffer	Tablet	12	0.5 mg tablet	Mean (%)	97	98	98	98	98
					Range (%)	(b) (4)				
					%RSD	2	2	2	2	2
Reference product-DH258 (10/2022)		Tablet	12	0.5 mg tablet	Mean (%)	72	98	98	98	99
					Range (%)	(b) (4)				
					%RSD	6	2	2	2	2

As further supportive information, the Applicant has provided formulation comparisons between the proposed product (Lodoco) and the three foreign reference products (Colgout, Colchicine Tiofarma, and Colchicine Teva). See Table 4. Per the comparative in vitro dissolution studies provided, the differences

in inactive ingredients do not affect the in vitro drug release, and drug release is similar between all tested products.

Table 4: Formulation Comparisons between the Proposed Product and the three reference products (Colgout, Colchicine Tiofarma, and Colchicine Teva)

Sr. No.	Product Ingredients	Colchicine Tablets 0.5 mg (AGEPHA Pharma)	Colgout® 0.5 mg (Aspen Pharmacare Australia Pty Ltd)	Colchicine TioFarma 0,5 mg, tabletten (TioFarma B.V.)	Colchicine Teva 0,5 mg, tabletten (Teva Nederland B.V.)	Justification
Active ingredient						
1	Colchicine	0.5 mg	0.5 mg	0.5 mg	0.5 mg	No change
Inactive ingredients						
2	Lactose monohydrate (b) (4)	(b) (4)	NA	(b) (4)	(b) (4)	Colchicine is a highly soluble and poorly permeable drug. Lactose does not impact colchicine permeability/ absorption.
3	(b) (4)	--	--	NA	NA	(b) (4)
4	Gelatin (b) (4)	(b) (4)	--	--	--	Gelatin does not impact colchicine permeability/ absorption.
5	(b) (4)	--	NA	--	--	(b) (4) does not impact colchicine permeability/ absorption.
6	Potato starch (b) (4)	(b) (4)	--	--	--	Potato starch does not impact colchicine permeability/ absorption.
7	(b) (4)	--	NA	--	--	(b) (4)
8	(b) (4)	--	--	NA	NA	
9	Magnesium stearate (b) (4)	(b) (4)	NA	NA	NA	Magnesium stearate does not impact colchicine permeability/ absorption.
10	Talc (b) (4)	(b) (4)	--	--	--	Talc does not impact colchicine permeability/ absorption.
11	(b) (4)	(b) (4)	--	(b) (4)	(b) (4)	(b) (4)
--	Total amount*	(b) (4)				Tablet weight does not impact colchicine permeability/ absorption.

Additionally, the Applicant has provided physiochemical comparisons between the proposed product (Lodoco) and the three foreign reference products (Colgout, Colchicine Tiofarma, and Colchicine Teva). See Table 5. The comparisons are similar. For further analysis on these physiochemical comparisons, please see the drug product and drug substance Reviews.

Table 5: Physiochemical Comparisons between the Proposed Product and the reference products (Colgout, Colchicine Tiofarma, and Colchicine Teva)

Parameter	LODOCO (Colchicine Tablets, USP, 0.5 mg) (AGEPHA Pharma)	Colgout® 0.5 mg tablets (Aspen Pharmacare Australia Pty Ltd)	Colchicine 0.5 mg, tabletten (Teva)	Colchicine 0.5 mg, tabletten (Tiofarma)
Proprietary Name	LODOCO	Colgout® 0.5 mg	Colchicine Teva 0,5 mg, tabletten	Colchicine Tiofarma 0,5 mg, tabletten
Batch No/Lot No	1E3547	DA601	19B26/E	19F10/D
Expiry Date	-	May 2021	February 2022	June 2022
Dosage form	Immediate release tablet	Immediate release tablet	Immediate release tablet	Immediate release tablet
Description	White, biconvex tablets	Round, white, tablets embossed "C" on the upper side, and plain on the bottom face.	Cream-white, round, flat tablets with the inscription "0.5" on one side.	Cream-white, round, flat tablets with the inscription "0.5" on one side.
Shape	Biconvex	Round	Round	Round
Coated/Uncoated	Uncoated	Uncoated	Uncoated	Uncoated
Scoring/ Break line	Unscored	Unscored	Unscored	Unscored
Label claim	Each tablet contains 0.5 mg of Colchicine	Each tablet contains 0.5 mg of Colchicine	Each tablet contains 0.5 mg of Colchicine	Each tablet contains 0.5 mg of Colchicine
Inactive ingredients	Lactose Monohydrate (b) (4) Gelatin, Potato starch, Talc, Magnesium stearate, (b) (4)	Lactose monohydrate, Maize starch, Povidone, and Magnesium stearate	Lactose, Magnesium stearate, Microcrystalline cellulose, (b) (4)	Lactose monohydrate, Magnesium stearate, Microcrystalline cellulose, Sodium starch glycolate, (b) (4)
Diameter (mm)	6.04	6.40	6.03	6.03
Thickness (mm)	3.08 - 3.17	2.87-2.95	3.15-3.23	3.12-3.19
Average Weight (mg)	100.2	103.2	120.9	120.4
Disintegration Time (s)	(b) (4)			
Hardness (N)				
Dissolution (Purified water medium in 15 minutes)				
Assay				

Although all submitted dissolution profiles demonstrate rapid dissolution, the adequacy of using in vitro dissolution to support the efficacy studies is under the purview of the Clinical Pharmacology Reviewer.

In-vitro comparisons between Lodoco (proposed drug product) and Colcrys (US RLD):

As per the Agency's recommendation to the Applicant, the Applicant has submitted comparative in vitro dissolution between Colcrys (US RLD) and Lodoco (proposed drug product). As supportive information for the bridge to the US RLD for demonstration of safety, the Applicant has provided multimedia comparative dissolution between Colcrys (US RLD) and LoDoCo (proposed drug product) using purified water, 0.1N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer as supportive information for the bridge. See Table 6. Comparisons across all pH's demonstrate rapid and similar dissolution (> (b) (4) release in 15 minutes). Although all submitted dissolution profiles demonstrate rapid and similar dissolution, the adequacy of this bridge is under the purview of the PharmTox Reviewer.

Table 6: Comparative Multimedia Dissolution Profiles between Colcrys (US RLD) and LoDoCo (Proposed Drug Product)

500 ml media using USP apparatus I (Basket) at 100 rpm (Colcrys-A26695 and LODOCO-1E3547)											
Purified Water			0.1 N HCl			pH 4.5 (Acetate buffer)			pH 6.8 (Phosphate buffer)		
Time (min)	% Colchicine dissolved		Time (min)	% Colchicine dissolved		Time (min)	% Colchicine dissolved		Time (min)	% Colchicine dissolved	
	Colcr-ys	LODOCO		Colcr-ys	LODOCO		Colcr-ys	LODOCO		Colcr-ys	LODOCO
0	(b) (4)										
5											
10											
15											
30											
45											

B. 13 BIOWAIVER REQUEST

Assessment: N/A

The Applicant has not submitted a biowaiver request.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None.

Primary Biopharmaceutics Assessor's Name and Date: Nadia Ahmed, Pharm D 2/13/23

Secondary Assessor Name and Date (and Secondary Summary, as needed): Haritha Mandula, PhD 2/13/23

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