CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212479Orig1s000
212479Orig2s000
212479Orig3s000
212479Orig4s000

PRODUCT QUALITY REVIEW(S)

Office of Pharmaceutical Quality

New Drug Application (NDA) 212479

Integrated Quality Assessment Template

Table of Contents

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 212479
Assessment #2

Drug Product Name	Methotrexate Oral Solution
Dosage Form	Oral solution
Strength	2 mg/mL
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Therakind Ltd.
US agent, if applicable	Dayton T. Reardan, PhD, RAC

Submission(s) Assessed	Document Date	Discipline(s) Affected
SD 18	3/3/2022	Drug Product/Manufacturing (Incomplete resubmission)
SD 21	5/31/2022	Drug Product (Resubmission)
SD 22	6/22/2022	Drug Product/Manufacturing

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	18-MAY-2021	
	III			Adequate		Referenced by approved products
	III			Adequate		Referenced by approved products
	III			Adequate		Referenced by approved products
	IV			Adequate	16-NOV-2021	

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	8085	Methotrexate Tablets

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

NDA Executive Summary

1. Application/Product Information

NDA Number.	212479
Applicant Name	Therakind Ltd.
Drug Product Name	JYLAMVO™ (methotrexate) Oral Solution
Dosage Form.	Solution
Proposed Strength(s)	2 mg/mL
Route of Administration	Oral
Maximum Daily Dose	75 mg once per week
Rx/OTC Dispensed	Rx
Proposed Indication	• Treatment of adults with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen • Treatment of adults with mycosis fungoides • Treatment of adults with relapsed or refractory non-Hodgkin lymphoma as part of a metronomic combination regimen • Treatment of adults with rheumatoid arthritis • Treatment of adults with severe psoriasis
Drug Product Description	The drug product is formulated with methotrexate (an antifolate), (b) (4) (Sucralose), citrate (b) (4), (b) (4) (ethylparaben, methylparaben sodium), and orange flavoring, in a solution of water, (b) (4), and glycerin. (b) (4), the potential for leachables is greater than for simple aqueous based formulations, albeit only the PE cap liner may contact the formulation for prolonged time.
Co-packaged product information	N/A
Device information:	The product is packaged with a bottle neck adaptor and a 10 mL syringe

Storage Temperature/ Conditions	Store JYLAMVO at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Lawrence Perez	Donna Christner
	Drug Product/ Labeling	Mike Theodorakis/ Craig M. Bertha	Hong Cai
	Manufacturing	Vickey He	Chengjiu Hu
	Biopharmaceutics	N/A	
	Microbiology	Kelly Ann Miller	Erika Pfeiler
	Other (specify):		
	RBPM	Oumou Barry/Teshara Bouie	
	ATL	Craig M. Bertha	
Consults	None		

2. Final Overall Recommendation Adequate.

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The applicant has amended the application to address the deficiencies that were outlined in the Complete Response Letter dated 12/22/2021.

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

Recommendation by Subdiscipline:

Drug Substance - N/A

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

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

5. Life-Cycle Considerations

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

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

Additional Lifecycle Comments:

N/A

CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: All of the changes that were recommended in the first review, with respect to the labeling, have been made, with the following exceptions:

- It had been recommended in the first review that patients [redacted (b) (4)] ” three months after first opening the bottle. DMEPA recommended that any remaining formulation not be disposed of in wastewater or the household waste and that patients should consult their caregiver or their pharmacist to obtain advise on how to dispose the remaining formulation due to its potential toxicity.

- It had been recommended in the first review that the pKa values be included in the DESCRIPTION section of the prescribing information. At the labeling meeting it was discussed and concluded that these values would have no practical use for prescribers and may be confusing. The pKa values for methotrexate have been removed.

Overall Assessment and Recommendation:

Adequate

Primary Labeling Assessor Name and Date: Craig M. Bertha, 10/24/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Craig Bertha

Digitally signed by Craig Bertha
Date: 10/24/2022 08:26:55AM
GUID: 50841a65000098a9383c817879a6a84d

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

/s/

CRAIG M BERTHA
10/26/2022 07:24:24 AM

Office of Pharmaceutical Quality

New Drug Application (NDA) 212479

Integrated Quality Assessment Template

Table of Contents

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 212479
Assessment #1

Drug Product Name	Methotrexate Oral Solution
Dosage Form	Oral solution
Strength	2 mg/mL
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Therakind Ltd.
US agent, if applicable	Dayton T. Reardan, PhD, RAC

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	01-MAR-2021	All
Amendment	14-APR-2021	Drug Product
Amendment	28-APR-2021	Microbiology and Manufacturing
Amendment	24-AUG-2021	Manufacturing
Amendment	19-OCT-2021	Manufacturing

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Lawrence Perez	Donna Christner
Drug Product	Michael Theodorakis	Hong Cai
Manufacturing	Vicky He	Chengjiu Hu
Microbiology	Kelly Ann Miller	Erika Pfeiler
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Oumou Barry/Teshara Bouie	
Application Technical Lead	Craig Bertha	
Laboratory (OTR)	N/A	
Environmental	Michael Theodorakis	Hong Cai

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
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	III			Adequate		Referenced by approved products
	IV			Adequate	16-NOV-2021	

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	8085	Methotrexate Tablets

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

A complete response action is recommended from OPQ. The main deficiencies are that the Overall Manufacturing Inspection Recommendation is WITHHOLD and the stability data and storage conditions proposed do not support the proposed expiration dating period for the drug product.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Methotrexate oral solution (2 mg/mL) is for oral administration and is indicated for the treatment neoplastic diseases, psoriasis, and rheumatoid arthritis in (b) (4) adults unable to swallow tablets. Therakind is filing under 505(b)(2) and references methotrexate tablets of NDA 8085. The drug product is formulated with methotrexate (an antifolate), (b) (4) (Sucralose), citrate (b) (4), (b) (4) (ethylparaben, methylparaben sodium), and orange flavoring, in a solution of water, (b) (4), and glycerin. (b) (4), the potential for leachables is greater than for simple aqueous-based formulations, albeit only the PE cap liner may contact the formulation for prolonged time. There is nothing unusual about the manufacturing, (b) (4). In-process controls include visual checks for (b) (4), pH, and minimum fill volume. It is noted that the product is packaged with a polypropylene oral dosing syringe and low density polyethylene bottle adapter.

Proposed Indication(s) including Intended Patient Population	• Treatment of adults with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen • Treatment of adults with mycosis fungoides • Treatment of adults with relapsed or refractory non-Hodgkin lymphoma as part of a metronomic combination regimen • Treatment of adults with rheumatoid arthritis • Treatment of adults with severe psoriasis
Duration of Treatment	Chronic
Maximum Daily Dose	75 mg once per week
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance Methotrexate is a well-established off-patent drug which has been used safely and effectively in humans for over 50 years and is currently authorized for long-term use in children and adults by oral and parenteral routes of administration. The manufacturer of the drug substance Methotrexate for this NDA is (b) (4) . Information on the manufacturer, method of manufacturing, characterization, specification, packaging and stability of Methotrexate is detailed in DMF (b) (4). The drug substance Methotrexate that is used in the manufacture of the drug product Methotrexate 2 mg/ml Oral Solution is tested by the drug substance manufacturer (b) (4) for compliance with the current USP monograph for "Methotrexate". Based on data in DMF (b) (4), a retest period of (b) (4) months can be granted for the drug substance Methotrexate when stored (b) (4)

Drug Product: Inadequate

The methotrexate oral solution is composed of compendial grade excipients, with the exception of the orange flavoring (see separate review of DMF (b) (4), which was determined to be adequate), and these are formulated in amounts that are acceptable as per the inactive ingredient report. As methotrexate is susceptible to photodegradation, the container used is an amber glass bottle. The final drug product is packaged with an oral dosing syringe and bottle adaptor. The specification applied to the drug product is acceptable and includes all parameters expected for an oral solution, however, the applicant will be asked to replace their in-house fill volume test with the USP <698> test for deliverable volume. Based on the method validation information in the application, the analytical methods have been validated appropriately and it was not necessary to request that the Office of Testing and Research perform any method verification. Stability studies have been undertaken with drug product under refrigerated (5°C), controlled room temperature (25°C/60%RH), intermediate (30°C/65%RH), and accelerated (40°C/75%RH) storage conditions. Under refrigerated conditions the product was observed to have adequate stability. However, the applicant proposes an unopened shelf-life of 18 months (including 3 months in-use) when the drug product is stored (b) (4). The controlled room temperature stability data do not support this proposed shelf-life, thus the applicant will need to either shorten the expiry period or propose alternate storage conditions.

Labeling: Inadequate

Revisions to the DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING, PATIENT INFORMATION, and CONTAINER LABELS are necessary.

Manufacturing: Inadequate

Facility Assessment Recommendation: Inadequate
Process Assessment Recommendation: Adequate

The drug product manufacturing process is divided into three main steps: (b) (4) (b) (4) For marketing, each bottle is co-packaged with a 10-mL oral dosing syringe and a bottleneck adaptor. Three registration batches, at (b) (4) each batch (equal to (b) (4) bottles (b) (4)), have been manufactured at (b) (4). The proposed commercial batches will be manufactured at (b) (4) at the same scale as the registration batches, i.e. at (b) (4) per batch, using the same equipment, manufacturing process, process parameters and controls. For both the registration batches and commercial manufacturing, the (b) (4) process is controlled by (b) (4), time, and in-process testing of appearance, assay, pH, and (b) (4). The proposed (b) (4) is supported by acceptable assay, related substances, and (b) (4) data. The commercial control for fill weight is also supported by registration batch data.

The drug product manufacturing facility (b) (4) has no profile code or commercial manufacturing history. A 704(a)(4) records request in lieu of PAI was recommended by ORA, since the facility has been inspected by MHRA in (b) (4) and (b) (4). The firm is authorized by MHRA to manufacture oral liquid products. Based on ORA and OPMA assessment of the firm's 704 (a)(4) records, AIL responses, and discussions with the CMC review team, a withhold recommendation has been made for the facility due to drug product stability issue and GMP deficiencies. The drug substance manufacturer and test facilities in the application have acceptable experiences and compliance status for the intended function, and are approved based on previous history.

Biopharmaceutics: N/A

Microbiology (if applicable): Adequate

The drug product is a non-sterile clear yellow oral solution that comes in a 75 mL amber glass bottle. Methotrexate is a multi-dose product that (b) (4) (b) (4). The applicant provided (b) (4) testing data that are consistent with USP (b) (4) (b) (4) and the applicant has met regulatory expectations for the product release specifications regarding microbiological tests. The applicant has also met regulatory expectations regarding the test method and verification for suitability of use for microbial limits and *Burkholderia Cepacia* Complex (BCC) testing. In addition, the applicant has met the regulatory expectations regarding microbiological tests and sampling frequencies for the stability program associated with the subject drug product. The stability data submitted to date support the microbiological quality of the drug product through the expiration period of (b) (4) months. The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling. There is no reconstitution or dilution prior to use, and stability data were provided in support of the storage conditions and expiration.

C. Final Risk Assessment

DP attribute/ CQA	Factors that may impact the CQA	O[1]	S[1, 2]	D[1]	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Comments/Lifecycle considerations
Appearance	• API precipitates	1	3	2	6	(b) (4)		
Identification	• incorrect drug formulated • no API formulated	2	3	3	18			
Assay	• incorrect amount of API formulated • high impurity level of input API • API degradation (b) (4)	3	3	2	18			
Degradation Products	• API degradation during manufacturing • API degradation in formulated drug product	3	3	2	18			

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of "3" will be used throughout)

						(b) (4)		
pH	• incorrect amounts of components formulated (i.e , citric acid, sodium citrate) • pH changes due to leachables and/or degradation	2	3	3	18			
Microbial limits	• lower than target amount (b) (4) formulated	2	3	2	12			
(b) (4)		2	3	3	18			
and elemental impurities	compounds leached from (b)(4) cap liner • leachables from oral dosing syringe/adapter • Elemental impurities from amber type III glass	2	3	5	30		1x3x5=15	(b) (4)

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

Refer to manufacturing deficiencies below.

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

1. Include the test for Deliverable Volume per USP <698> "Deliverable Volume" in the drug product specification.

2. The proposed 18 month expiration dating period is not supported by the stability data as two out of the six (6) commercial batches (THE/16/0273, THE/17/0330, THE/17/0331, THE/17/0332, THE/17/0356, THE/18/0407 and THE/19/0554) tested at 18 months, failed (THE/17/0331, THE/17/0332). Please provide your course of action to resolve this issue.

3. Provide additional stability data for batch THE/19/0554 manufactured on September 12, 2019 and for batch THE/20/0604 manufactured on February 2, 2020.

4. You state in your post approval stability protocol: (b) (4) Clarify whether you propose: (b) (4)

5. Provide appropriate in-use stability data to support the proposed 3-month period during patient use once the bottle is opened. You should use the aged stability sample (toward the end of the proposed shelf life) to represent the worst case scenario. See comment 4 above.

6. Revise the post approval stability protocol to include a testing station at 15 months.

7. Include the following statement in your post approval stability commitment: Withdraw from the market any batches found to fall outside the approved specifications for the drug product. If the applicant has evidence that the deviation is a single occurrence that

does not affect the safety and efficacy of the drug product, the applicant should discuss it with the agency as soon as possible and provide justification for the continued distribution of that batch. The change or deterioration in the distributed drug product must be reported under 21 CFR 314.81(b)(1)(ii).

4. Labeling Deficiencies

See the details in the final IQA labeling chapter IV, for CMC-related labeling deficiencies. As the recommended action is Complete Response, labeling negotiations will not be made in this first review cycle.

5. Manufacturing Deficiencies

During a review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, and provided by (b) (4) manufacturing facility, the FDA noted objectionable conditions. These objectionable conditions will be conveyed to the representative of the facility within 10 business days of this Complete Response Letter. Satisfactory resolution of these objectionable conditions is required (e.g., preapproval inspection and/or adequate facility responses addressing these conditions) before this application may be approved.

If it is determined that an inspection is needed to approve your application, please note that FDA continues to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies *(Specify discipline, such as Environmental)*

N/A

Application Technical Lead Name and Date:

Craig M. Bertha 18-NOV-2021

APPEARS THIS WAY IN ORIGINAL

109 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

List of Submissions Reviewed:

Documents Reviewed eCTD#)	Date Received
eCTD-0005 (SDN-5) (ORIG-1)	2021-03-01
eCTD-0004 (SDN-4) (ORIG-1)	2020-10-14

1.0 PRESCRIBING INFORMATION (PI)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights 201.57(a)(2)		
Proprietary name	JYLAMVO	**Acceptable**
Established name(s)	Methotrexate Oral Solution	**Acceptable**
Route(s) of administration	Oral	**Acceptable**
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval	1953	**Acceptable**. The NME methotrexate was initially approved in 1953 by FDA under NDA 008085 for

		Methotrexate Tablets, 2.5 mg for oral use.
Dosage Forms and Strengths: [201.57(a)(8)]		
Summary of the dosage form(s) and strength(s) in metric system.	Oral Solution, 2 mg/mL	**Acceptable**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

Assessment of Product Quality Related Aspects of the Prescribing Information: Acceptable.

API methotrexate is a free acid not a salt. (b) (4)

Methotrexate is an amphoteric compound and in solution exists in anionic, uncharged, zwitterionic (inner salt) and cationic forms. USP General Chapter <1121> Nomenclature, MAPP 5021.1 Rev 1., and Guidance Naming of Drug Products Containing Salt Drug Substances do not apply.

1.2 FULL PRESCRIBING INFORMATION (FPI)

1.2.1 Section 2 DOSAGE AND ADMINISTRATION

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
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)	No special instructions are needed for preparation of JYLAMVO (methotrexate) Oral Solution 2 mg/mL	**N/A**

Assessment: Section 2 DOSAGE AND ADMINISTRATION:
N/A

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Oral Solution	**Acceptable**
Strength(s) in metric system	2 mg/mL	**Acceptable**
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	JYLAMVO is a clear yellow solution.	**Acceptable**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Assessment of Section 3 DOSAGE FORMS AND STRENGTHS:

Acceptable.

1.2.3 Section 11 DESCRIPTION

tem	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	The proprietary name JYLAMVO does not appear in conjunction with the established name (methotrexate) in Section 11	**Not Acceptable** **The name "JYLAMBO (methotrexate) oral solution" should appear in the text of Section 11**
Dosage form(s) and route(s) of administration	The "Oral Solution" does not appear in the text of Section 11	**Not Acceptable** **The term "oral solution" should be inserted in the text of Section 11**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	The inactive ingredients are listed as: polyethylene glycol, glycerin, orange flavoring powder, sucralose, ethylparaben, methylparaben sodium, citric acid, sodium citrate and purified water.	**Not Acceptable** The inactive ingredients should be listed in alphabetical order as: citric acid, ethylparaben, glycerin, methylparaben sodium, orange flavoring powder, polyethylene glycol, purified water, sodium citrate and, sucralose. The revisions in the red font have been made in the PI at the SharePoint Dr.

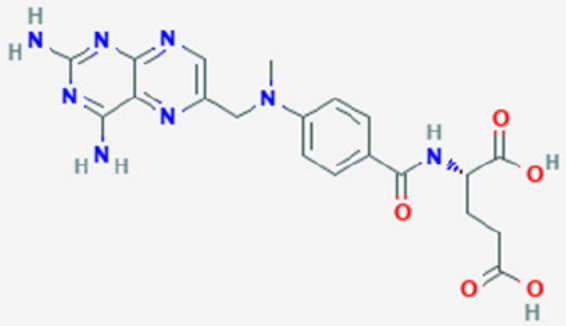
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A
Pharmacological/ therapeutic class	The pharmacological/ therapeutic class of methotrexate is a folate analog metabolic inhibitor. It is not included in Section 11.	**Not Acceptable.** Include in Section 11 methotrexate is a folate analog metabolic inhibitor
Chemical name, structural formula, molecular weight	See page 7 above	**Not acceptable,** see assessment below.
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	The pH of oral solution is 6.8 (b) (4) not included in Section 11.	**Not Acceptable** Include (b) (4) the pH value of 6.8 in Section 11.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	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	N/A

Assessment of Section 11 DESCRIPTION:
Not Acceptable.

a. The structural formula of methotrexate in PI, Section 11, appeared in NDA 008085 in 1953. This assessor recommends to replace by a more recent and better depicting the structure of the molecule such as:



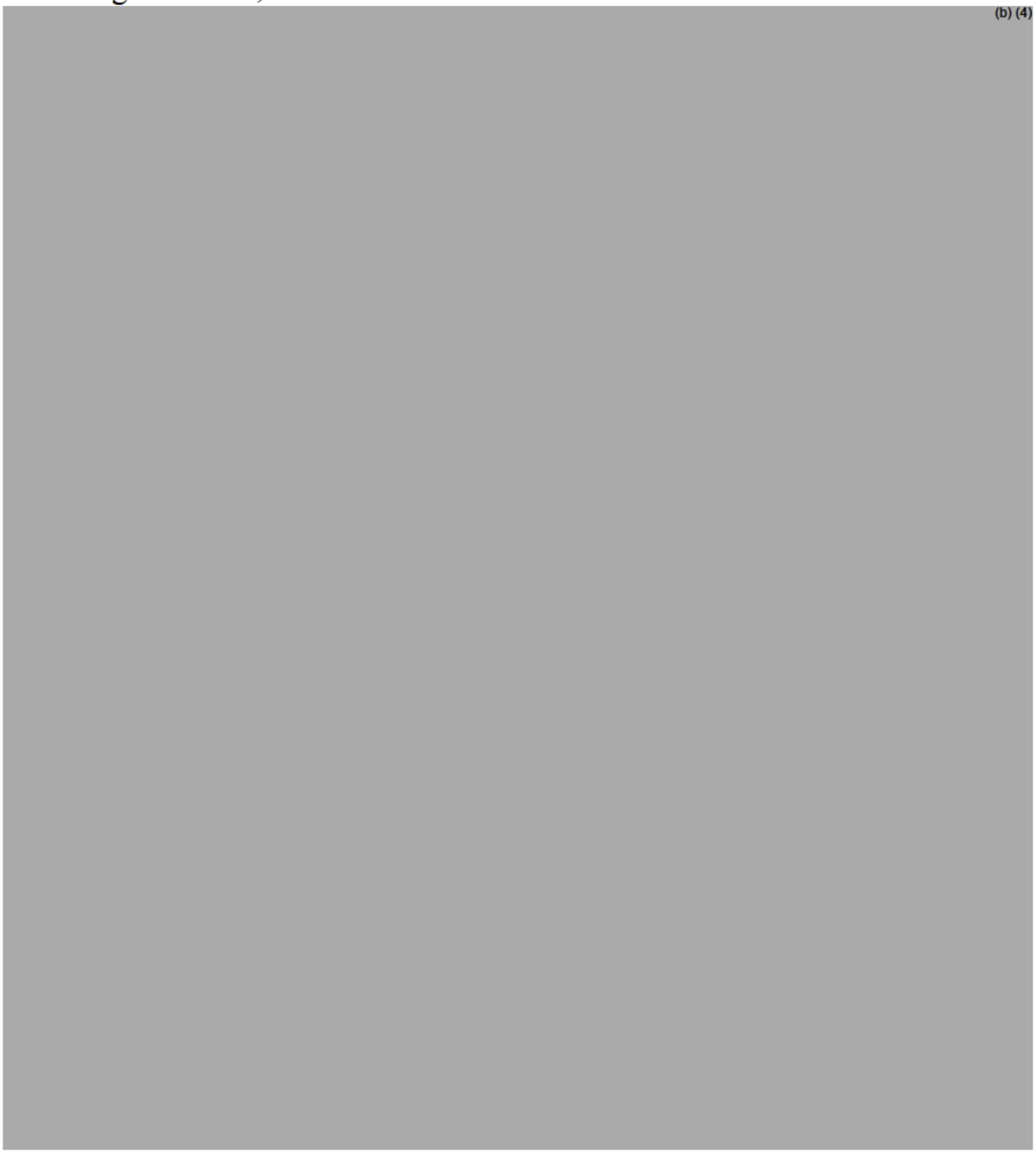
No color is needed.

b. Upon consultation with toxicologist, the Pharmacological Therapeutic Class for methotrexate is a folate analog metabolic inhibitor. The paragraph below is revised to read as follows:

(b) (4)

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Reviewer's Notes:
The components of the container and administration set are illustrated below:
Amber glass bottle, 75 mL Child resistant bottle closure



Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	oral solution	**Acceptable**
Strength(s) in metric system	2 mg of methotrexate per milliliter	**Acceptable**
Available units (e.g., bottles of 100 tablets)	Available in 75 mL Type III amber glass bottles, filled with 60 mL of oral solution.	**Acceptable**
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	A clear yellow oral solution NDC 55792-020-01	**Acceptable**
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	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	N/A

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

Item	Information Provided in the NDA	Assessor's Comments
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.)	The oral solution (60 mL) is packaged in a 75 mL a Type III amber glass bottle.	**Acceptable**
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F)	**Not acceptable** The Applicant should add excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature In USE storage conditions have been added to Section 16 and are present in Patient Information The revisions have been made in the PI at the SharePoint Dr.

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	N/A
Include information about child-resistant packaging	The closure of the bottle **is tampering evident child-resistant closure (polypropylene with expanded polyethylene liner).**	**Acceptable**

Assessment of Section 16 HOW SUPPLIED/STORAGE AND HANDLING:

Not Acceptable:

Section 16 has been revised to read as follows.

(b) (4)

(b) (4)

Note: The revisions in red font have been made in the PI at the SharePoint Dr.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

Assessment of Other Sections of Labeling:

Acceptable

None of the ingredients listed above are components of JYLAMVO (methotrexate) Oral Solution, 2 mg/mL.

1.2.5 Section 17: PATIENT COUNSELING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17 [21 CFR 201.1(h)(5)]		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer [21 CFR 201.1(h)(5)]	JYLAMVO is a registered trademark of Therakind Limited UK. Distributed by: Lukare Medical, LLC 4 Julia Court Scotch Plains, NJ 07076 1-908-834-2206.	**Acceptable**

Assessment of Section 17: PATIENT COUNSELING INFORMATION

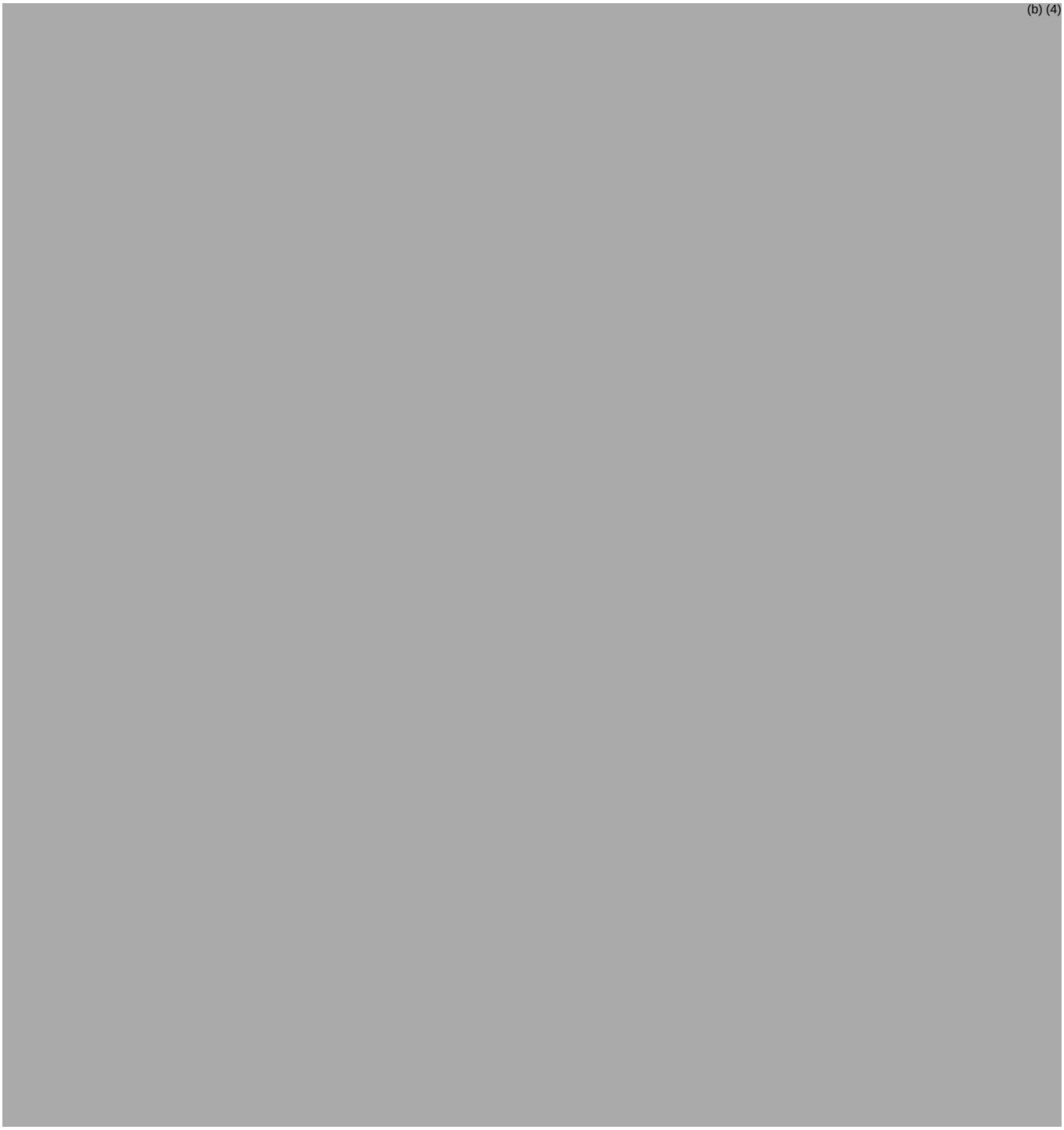
Acceptable

Manufacturer/distributor information in PATIENT COUNSELING INFORMATION meets the regulatory requirement.

2.0 INSTRUCTIONS FOR USE/PATIENT INFORMATION

The Patient Information, PI pages, 16, 18, 19 and 20 (submitted in eCTD-0009 (SDN-9) on 06/16/2021, should be revised to read as follows:

(b) (4)



Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Not Acceptable.

The Patient Information on PI pages, 16, 18, 19 and 20 should be revised to read as shown above.

The revisions in red font will be made in the PI at the SharePoint Dr.

4.0 CARTON AND CONTAINER LABELING

Documents Reviewed eCTD#)	Date Received
eCTD-0005 (SDN-5)	2021-03-01
eCTD-0004 (SDN-4) (ORIG-1)	2020-10-14

4.1 CONTAINER LABEL

Item	Information Provided in the NDA	Assessor's Comments about Container Label
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	**JYLAMVO (methotrexate) Oral Solution**	**Acceptable** In both the Container and Carton label the font size of established name is half of that for the proprietary name.
Dosage strength	2 mg/mL, exhibited on both container and carton labels	**Acceptable**
Route of administration if it is not for oral use [21 CFR 201.100(b)(3)]	Oral,	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	2 mg/mL	**Acceptable** Methotrexate is not a salt.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	60 mL (b)(4) (b)(4), exhibited on both container and carton labels	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR	Not provided in the container label	**Acceptable** Information on inactive ingredients is not required for the label of oral drugs.

201.10(i)(2)]; [Quantitative ingredient information is required for injectables per 21 CFR 201.100(b)(5)(iii)]		
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Rx, exhibited on container label	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 55792-020-01.	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	No space has been allocated explicitly for Lot No and expiration date. In the annotated version of the container label there is an area for 2D Data matrix barcode (Batch No./Lot No. and Expiry date)	**Not acceptable** Define the space on the container label where the Lot No and Expiry date will be printed numerically.
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store JYLAMVO at 20° to 25°C (68° to 77°F) Keep the bottle tightly closed. Shake Well Before Using. (b) (4) There is a space explicitly allocated for writing the new BUD.	**Not Acceptable** Revise "Store JYLAMVO at 20° to 25°C (68° to 77°F)" to read "Store JYLAMVO at 20°C to 25°C (68°F to 77°F)"
Bar code [21CFR 201.25(c)(2)]	Space has been allocated on the container label for bar code	**Acceptable**
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose,	N/A	N/A

multiple-dose, single-patient-use)		
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A

Assessment of Container Label:

Not Acceptable

1. Define the area on the container label where the numerical values of Batch No/Lot No and Expiry date will be printed.

2. Revise the phrase "Store JYLAMVO at 20° to 25°C (68° to 77°F)" to read "Store JYLAMVO at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]"

4.2 CARTON LABEL

Item	Information Provided in the NDA	Assessor's Comments about Carton Label
Proprietary name, established name [FD&C Act 502(e)(1)(A)(i)] [font size at least half as large as the proprietary name, and prominence per FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2)]	**JYLAMVO (methotrexate) Oral Solution**	**Acceptable** In both the Container and Carton label the font size of established name is more than half of that for the proprietary name.
Dosage strength	2 mg/mL, exhibited on both container and carton labels	**Acceptable**
Route of administration if it is not for oral use [21 CFR 201.100(b)(3)]	Oral	**Acceptable**
Active moiety expression of strength with equivalence statement (if applicable) [FD&C Act 502(e)(1)(ii), 21 CFR 201.10(d)(1); 21 CFR 201.100(b)(4), USP <1121>]	2 mg/mL	**Acceptable** Methotrexate is not a salt.
Net content [FD&C Act 502(b)(2), 21 CFR 201.51(a)]	60 mL is exhibited on carton label.	**Acceptable**
Name of all inactive ingredients, in alphabetical order required for OTC drugs [FD&C Act 502(e)(1)(A)(iii), 21 CFR 201.10(a)] [except for oral drug per 21 CFR 201.100(b)(5) or limited space per 21 CFR 201.10(i)(2)]; [Quantitative ingredient	Not provided in the carton label.	**Acceptable** Information on inactive ingredients is not required for the label of orally administered drugs.

information is required for injectables per 21 CFR 201.100(b)(5)(iii)]		
"Rx only" displayed on the main panel [21 CFR 201.100(b)(1)]	Rx, is exhibited on carton label	**Acceptable**
NDC number [per 21 CFR 201.2, requested, but not required for all labels or labeling, also see 21 CFR 207.35(b)(3)(i)]	NDC 55792-020-01	**Acceptable**
Lot number (21 CFR 201.18) and expiration date (21 CFR 201.17)	No space has been allocated explicitly for Lot No and expiration date. In the annotated version of the container label there is an area for 2D Data matrix barcode (Batch No./Lot No. and Expiry date)	**Not acceptable** Define the space on the carton label where the Lot No and Expiry date will be printed numerically

Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store JYLAMVO at 20° to 25°C (68° to 77°F) [redacted (b)(4)] Shake Well Before Using. [redacted (b)(4)] There is not a space explicitly allocated for writing the new BUD.	**Not Acceptable** Revise the temperature range to read: Store JYLAMVO at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature] Define a space to write the BUD
Bar code [21CFR 201.25(c)(2)]	Space has been allocated on the carton label for bar code	**Acceptable**
Adequate directions for use [FD&C Act 502(f)(1), 21 CFR 201.5] or "Recommended Dosage and Administration: Prescribing Information" (21 CFR 201.55)	See Prescribing Information for dosage and administration	**Acceptable**
"Keep out of reach of children" (Required for OTC in CFR. Optional for Rx drugs)	Provided	**Acceptable**
Name of manufacturer/distributor [502(b)(1), 21 CFR 201.1(a), 21 CFR 201.1(h)(5)]	Distributed by : Lukare Medical LLC, 4 Julia Court, Scotch Plains, NJ 07076 1-908-834-2206	**Acceptable**
No text on Ferrule and Cap overseal unless a cautionary statement is required.	No text	**Acceptable**

If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	N/A Currently the USP-NF does not include a monograph for methotrexate oral solution
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	**N/A**
And others if space is available	There is not a space explicitly allocated for writing the new BUD.	**Not Acceptable**

Assessment of Carton Label:
Not Acceptable

1. Define the area on the carton label where the numerical values of Batch No/Lot No and Expiry date will be printed.

2. Include a space on the carton label to write the new beyond-use-date (BUD).

3. Revise the phrase "Store JYLAMVO at 20° to 25°C (68° to 77°F)" to read "Store JYLAMVO at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]"

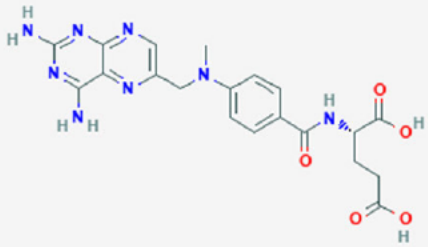
ITEMS FOR ADDITIONAL ASSESSMENT
Chemistry Comments about Labeling Deficiencies to be Conveyed to Applicant

Section 3 DOSAGE FORMS AND STRENGTHS:

The sentence [redacted] (b) (4) **should be revised to read** [redacted] (b) (4)

Section 11 DESCRIPTION

The structural formula of methotrexate in PI, Section 11, appeared in NDA 008085 in 1953. We recommend you replace with a more recent and better depiction of the structural formula of methotrexate such as shown below. No need for color.



Revise the 1st paragraph to read:

[redacted] (b) (4)

The ingredients in the paragraph below should be in alphabetical order. The 2nd paragraph should be revised as follows: [redacted] (b) (4) (b) (4)

(b) (4)

[redacted]

Section16. **HOW SUPPLIED / STORAGE AND HANDLING**

Revise Section 16 to read as follows:

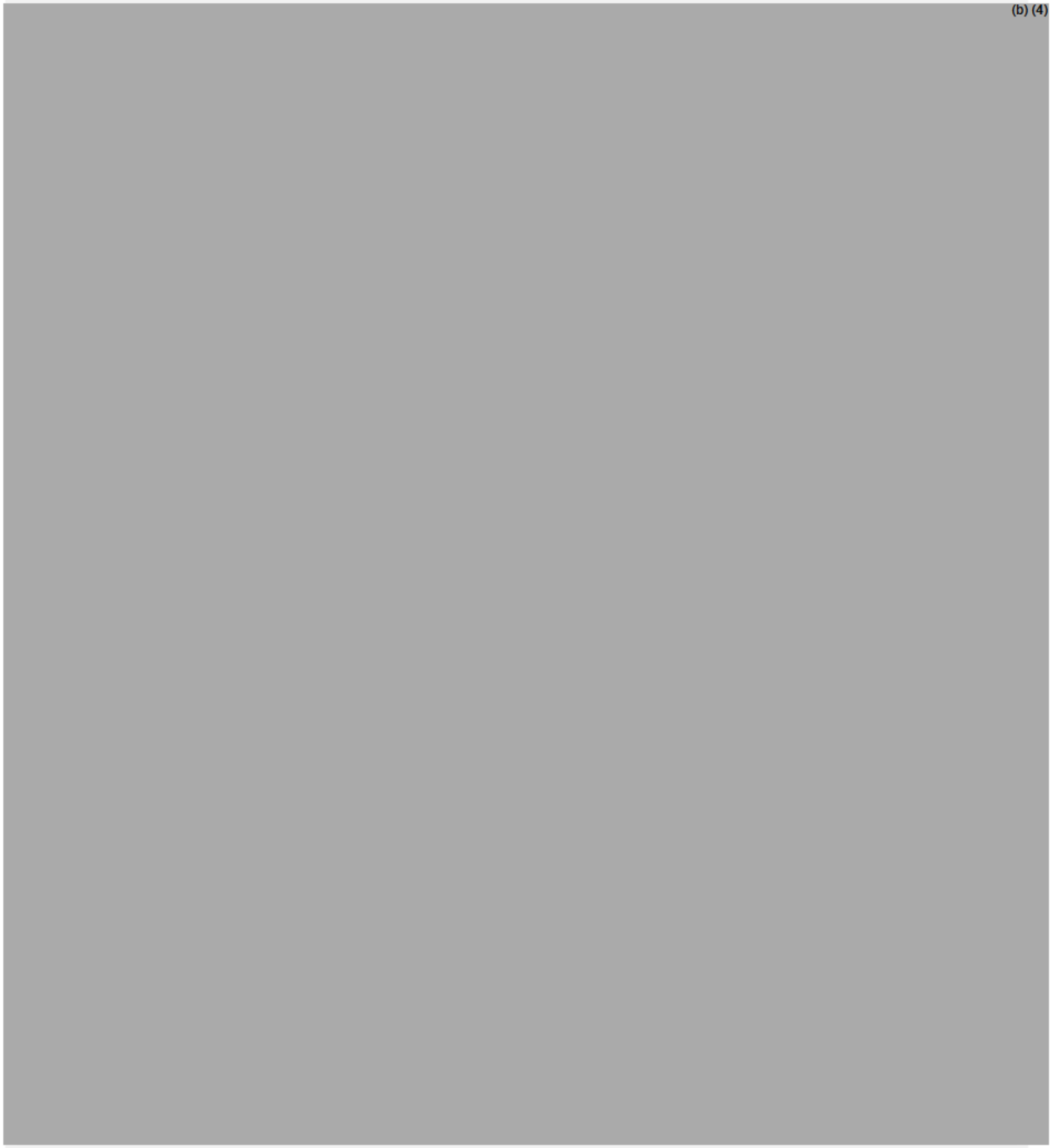
(b) (4)

[redacted]

PATIENT COUNSELING INFORMATION

The Patient Information on PI pages, 16 to 20, should be revised to read as follows:

(b) (4)



CONTAINER LABEL:

1. Define the area on the container label where the numerical values of Batch No/Lot No and Expiry date will be printed.

2. Revise the phrase "Store JYLAMVO at 20° to 25°C (68° to 77°F)" to read "Store JYLAMVO at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]"

CARTON LABEL:

1. Define the area on the container label where the numerical values of Batch No/Lot No and Expiry date will be printed.

2. Include a space on the carton label to write the new beyond-use-date (BUD).

3. Revise the phrase "Store JYLAMVO at 20° to 25°C (68° to 77°F)" to read "Store JYLAMVO at 20°C to 25°C (68°F to 77°F) excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]"

Overall Assessment and Recommendation

Overall, the labeling is not sufficient from the CMC perspective with deficiencies identified.

The deficiencies should be conveyed to the Applicant.

From the ONDP perspective, this application is **not** ready for approval in its present form per 21 CFR 314.125(b)(6) until the deficiencies delineated above are satisfactorily resolved. Once the prescribing information, carton and container labels are corrected then a labeling review amendment will be written.

Michael C. Theodorakis 6/30/2021
Primary Labeling Assessor Name and Date:

Hong Cai
Secondary Assessor Name and Date (and Secondary Summary, as needed):

Michael Theodorakis

Digitally signed by Michael Theodorakis
Date: 6/30/2021 08:48:07PM
GUID: 508da7410002ba4531dbeead99c8bf49

Hong Cai

Digitally signed by Hong Cai
Date: 6/30/2021 08:59:05PM
GUID: 55919d6500e16bdaad5825645e4f22ff

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	212479
Assessment Cycle Number	01
Drug Product Name/ Strength	Methotrexate/ 2mg/mL
Route of Administration	Oral Solution
Applicant Name	Therakind Limited
Therapeutic Classification/ OND Division	CDER/OND/OII/DRTM
Manufacturing Site	(b) (4)
Method of Sterilization	N/A; non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary: The application is adequate from the standpoint of product quality microbiology.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
0005 SD 5	03/01/2021
0007 SD7	04/28/2021

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

Remarks: The drug product is a non-sterile clear yellow oral solution indicated for use in combination chemotherapy that comes in a 75 mL amber glass bottle. Methotrexate is a multi-dose product (b) (4)

Concise Description of Outstanding Issues: N/A

Supporting Documents:

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- **Description of drug product –** Section 3.2.P.1. The drug product is a multi-dose non-sterile oral solution that contains 2 mg/mL methotrexate.

- **Drug product composition –** Section 3.2.P.1

Ingredient	Quantity per (mg/mL)	Function
Methotrexate, USP	2	Active ingredient
Polyethylene glycol (b) (4) USP-NF	(b) (4)	
Ethylparaben, USP-NF		
Methylparaben Sodium, USP-NF		
Glycerin, USP-NF		
Orange flavoring powder		
Sucralose, USP-NF		
Citric Acid, USP-NF		
Sodium Citrate, USP-NF		
Purified Water, USP-NF		

- **Description of container closure system –** Section 3.2.P.1, p.4 of 4. 3.2.P.7

Component	Description	Manufacturer
Bottle	75 mL amber glass bottle with 25 mm opening	(b) (4)
Cap	White, child-resistant, screw cap	
Neck Adaptor	LDPE, used with the oral dosing syringe	
Syringe	10 mL dosing polypropylene syringe with white HDPE plunger	

Assessment: Adequate
The applicant provided an adequate description of the drug product composition and container closure system.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity: N/A

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information
Section 1.14.1.3

The oral solution is ready to use and is not reconstituted or diluted.

Assessment: Adequate
The applicant has met regulatory expectations with regard to the information related to issues of product quality microbiology that is provided in the product labeling. There is no reconstitution or dilution prior to use, and stability data was provided in support of the storage conditions and expiration.

MICROBIOLOGY LIST OF DEFICIENCIES: N/A

Primary Microbiology Assessor Name and Date: KellyAnn Miller, PhD, 4/29/2021
Secondary Assessor Name and Date (and Secondary Summary, as needed): Erika Pfeiler, PhD, 4/29/2021

KellyAnn Miller

Digitally signed by KellyAnn Miller
Date: 5/19/2021 07:11:58AM
GUID: 5e1f6620004382592e50464168938fab

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 5/19/2021 07:14:25AM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

DOCUMENT HISTORY

Authors: **OPQ/ONDP:** Wendy Wilson, Ramesh Sood, David Claffey **OND/ONDP:** Eric Brodsky, Debra Beitzell **OPQ/OPPQ:** Jibril Abdus-Samad, Richard Lostritto, Yana Mille **OPQ/OPMA:** Derek Smith, Joanne Wang **OPQ/OPRO:** Jason C. Crawford	[redacted]

Clearance Statement:

This document is sponsored by the Office of Program and Regulatory Operations (OPRO). Don Henry (OPRO/IO) and the authors listed above have cleared this document for use.

The CDER OPQ Integrated Quality Assessment Template will be assessed approximately 1 year from date issued (April 8, 2021) and updated as needed.

Version	**Date Issued** **Summary of Changes**
04	01/17/2017: Content update
05	10/15/2017: GDUFA II Drop-down option added
06	1/3/2019: 1. The previous template and assessment guide contained information relevant to both ANDA and NDA. The document is now separated into two documents for each application type. 2. Replaced distinct Process and Facilities chapters with the new integrated Manufacturing chapter. 3. Made content updates to NDA Labeling chapter. 4. Added Maximum Daily Dose (MDD) field.
07	4/8/2021: 1. COVID-19 option added to dropdown menus in Executive Summary and relevant chapters 2. Content and formatting revisions completed for the following chapters: • Labeling • Manufacturing • Microbiology

APPEARS THIS WAY IN ORIGINAL

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

/s/

CRAIG M BERTHA
11/18/2021 08:57:12 AM