CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212479Orig1s000
212479Orig2s000
212479Orig3s000
212479Orig4s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

Cross-Discipline Team Leader Review/Division Summary

Date	11/17/2022
Cross-Disciplinary Team Leader	Jianmeng Chen, MD, PhD
Division Director (or designated signatory authority)	Nikolay Nikolov, MD
Subject	Cross-Discipline Team Leader Review/Division Summary
NDA/BLA # and Supplement#	NDA 212479
Applicant	Therakind Limited
Date of Submission	5/31/2022
PDUFA Goal Date	11/30/2022
Proprietary Name	Jylamvo
Established or Proper Name	Methotrexate
Dosage Form(s)	Oral solution
Applicant Proposed Indication(s)/Population(s)	• 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

Applicant Proposed Dosing Regimen(s)	• Neoplastic diseases:
	  ▪ Acute lymphoblastic leukemia: Starting dosage is 20 mg/m^2 once weekly as part of a combination chemotherapy maintenance regimen
	  ▪ Mycosis fungoides: Dosage is 25 to 75 mg once weekly as monotherapy; 10 mg/m^2 twice weekly as part of combination chemotherapy regimen
	  ▪ Relapsed or refractory non-Hodgkin lymphoma: Dosage is 2.5 mg two to four times per week (maximum 10 mg per week) as part of metronomic combination chemotherapy regimen
	• Rheumatoid arthritis: Starting dosage is 7.5 mg once weekly with escalation to achieve an optimal response
	• Psoriasis: Dosage is 10 to 25 mg once weekly until adequate response is achieved (do not exceed a dose of 30 mg per week)

Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	• 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

Recommended Dosing Regimen(s) (if applicable)	• Neoplastic diseases:
	  • Acute lymphoblastic leukemia: Starting dosage is 20 mg/m^2 once weekly as part of a combination chemotherapy maintenance regimen
	  • Mycosis fungoides: Dosage is 25 to 75 mg once weekly as monotherapy; 10 mg/m^2 twice weekly as part of combination chemotherapy regimen
	  • Relapsed or refractory non-Hodgkin lymphoma: Dosage is 2.5 mg two to four times per week (maximum 10 mg per week) as part of metronomic combination chemotherapy regimen
	• Rheumatoid arthritis: Starting dosage is 7.5 mg once weekly with escalation to achieve an optimal response
	• Psoriasis: Dosage is 10 to 25 mg once weekly until adequate response is achieved (do not exceed a dose of 30 mg per week)

1. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

This is a 505(b)(2) new drug application (NDA) for an oral methotrexate (MTX) solution. The application was originally submitted on Mar 01, 2021, and received a complete response (CR) on Dec 22, 2021, due to facility deficiencies and deficiencies of drug product stability data. On May 31, 2022, Therakind submitted a response to the CR.

In this NDA, the Applicant is seeking approval of their product for the treatment of neoplastic diseases, psoriasis and rheumatoid arthritis. The efficacy and safety of the Applicant's methotrexate product has been based on the Agency's previous findings of safety and effectiveness of methotrexate for the listed drug, Methotrexate Sodium Tablets (NDA 08085). The proposed dosing regimens are the same as currently approved MTX dosing regimens, as outlined below:

- **Neoplastic diseases:**
  - Acute lymphoblastic leukemia: Starting dosage is 20 mg/m^2 once weekly as part of a combination chemotherapy maintenance regimen
  - Mycosis fungoides: Dosage is 25 to 75 mg once weekly as monotherapy; 10 mg/m^2 twice weekly as part of combination chemotherapy regimen
  - Relapsed or refractory non-Hodgkin lymphoma: Dosage is 2.5 mg two to four times per week (maximum 10 mg per week) as part of metronomic combination chemotherapy regimen
- **Rheumatoid arthritis:** Starting dosage is 7.5 mg once weekly with escalation to achieve an optimal response
- **Psoriasis:** Dosage is 10 to 25 mg once weekly until adequate response is achieved (do not exceed a dose of 30 mg per week)

See the unireview dated Dec 17, 2021, for additional details of the first review cycle, including discussion of the clinical issues related to RA and review of the bioavailability study. Please see the Division of Dermatology and Dentistry, Dr. Tabatabai's review for the plaque psoriasis indication (DARRTS date 12/6/2021), and the Division of Hematologic Malignancies I, Dr. Godder (DARRTS date 12/1/2021) and the Division of Hematologic Malignancies II, Dr. Seam's review (DARRTS date 12/6/2021) for the neoplastic diseases. The focus of the current review cycle was the labeling and CMC issues related to the complete response.

The benefit-risk profile of methotrexate for the proposed indications is favorable. The efficacy and safety of the Applicant's methotrexate product has been based on the Agency's previous findings of safety and efficacy with methotrexate. The submitted bioavailability data demonstrate bioequivalence between the proposed methotrexate oral solution and the listed drug, methotrexate tablets. The deficiencies identified in the previous complete response letter have been adequately addressed by the Applicant in this submission. Therefore, the regulatory action for this submission is approval.

2. Background

The Applicant, Therakind Limited, submitted a 505(b)(2) new drug application (NDA) for methotrexate (MTX) 2 mg/mL oral solution for treatment of neoplastic diseases, rheumatoid arthritis, and psoriasis in adults. The product is presented in amber type III glass bottles with tamper evident child-resistant closures containing 60 ml of oral solution. Each pack contains one bottle, a bottle adaptor and one 10 mL graduated oral dosing syringe. Methotrexate is a dihydrofolate reductase inhibitor.

Methotrexate tablets have been marketed since December of 1953 (NDA 08085, Dava Pharmaceuticals Inc.) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, MTX is approved as an injection for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intra-thecal (IT) administration. Methotrexate is currently available in 2.5 mg tablets (multiple companies), and 5, 7.5, 10, and 15 mg tablets. Injectable MTX is available from multiple companies in varying quantities of 25 mg/mL solution. At the time of submission of this NDA, approved indications and routes of administration for MTX included neoplastic diseases (oral, IM, IV, IA, and IT routes), rheumatoid arthritis (oral, SC route), polyarticular juvenile idiopathic arthritis (oral, IM, SC routes), and severe psoriasis (oral, IM, SC, IV routes). The Applicant is only seeking approval for indications in adults with neoplastic diseases (ALL, Mycosis fungoides, and refractory non-Hodgkin lymphomas), adults with RA, and adults with psoriasis with the rationale that an alternative MTX oral liquid (XATMEP) was approved in 2017 and has exclusivity for use in children with ALL and children with JIA.

Regulatory history
See the unireview dated Dec 17, 2021, for relevant regulatory history.
Therakind received a complete response on Dec 22, 2021 due to facility deficiencies and deficiencies of drug product stability data.

On May 31, 2022, Therakind submitted this response to the complete response action.

3. Product Quality

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

- Based on the updated stability data provided in the 6/22/2022 amendment, the Applicant's proposed drug product expiration dating period of 18 months can be granted.

- In the previous review cycle, the FDA review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, and provided by (b) (4) drug product manufacturing facility, noted objectionable conditions. These objectionable conditions have been resolved.

The overall recommendation is approval from the CMC perspective. For additional details, refer to the Integrated Quality Assessment in DARRTS dated 26-Oct-2022. The Signatory agrees with this recommendation.

4. Nonclinical Pharmacology/Toxicology

No new data or information was needed or submitted. See the unireview dated Dec 17, 2021.

5. Clinical Pharmacology

No new data or information was needed or submitted. See the unireview dated Dec 17, 2021.

6. Clinical Microbiology

No new data or information was needed or submitted.

7. Clinical/Statistical- Efficacy

No new data or information was needed or submitted. See the unireview dated Dec 17, 2021.

8. Safety

No new data or information was needed or submitted. See the unireview dated Dec 17, 2021.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this application. Methotrexate is an approved drug and no issues were identified that would warrant advisory committee input.

10. Pediatrics

No new data or information was needed or submitted. See the unireview dated Dec 17, 2021.

During this review cycle, DRTM submitted a consult request to DPMH on June 23, 2022, requesting input on the labeling for this resubmission. Specifically, the Division requested DPMH to determine if there was outstanding protected exclusivities or patents that would require disclaimer language to be added in place of the carved-out information. During the review, DPMH consulted with OCC to discuss the appropriateness for a carveout. DPMH recommended to not include a carveout as the Applicant was not proposing to label for any pediatric indication and there is no information that would be protected under the currently proposed label. As such, the label does not have the same regulatory requirements as the label requiring a carveout for protected information and therefore a disclaimer is not appropriate.

OCC concurred with DPMH's recommendation that disclaimer language is not needed in the labeling. See review by Dr. Jacquline Yancy for details (DARRTS date 10/26/2022).

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** Not applicable.
- **Exclusivity or patent issues of concern:** The Applicant submitted the required patent certification with respect to the listed drug.
- **Financial disclosures:** No issues.
- **Other Good Clinical Practice (GCP) issues:** No issues.
- **Office of Scientific Investigations (OSI) audits:** No issues.
- **Any other outstanding regulatory issues:** None.

12. Labeling

- **Proprietary name**

On May 31, 2022, the Applicant requested the proposed proprietary name, Jylamvo, which was found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) review team.

- **Prescribing Information**

In the current application, given the demonstration of bioequivalence between the test product (methotrexate oral solution) and the listed drug (LD) (NDA 008085 Methotrexate Tablets, Dava) establishing the scientific bridge to the LD, the Applicant proposed labeling with similar content to the LD, but limited to the following indications: neoplastic diseases, rheumatoid arthritis, and psoriasis. FDA updated the submitted labeling for consistency with regulations and current labeling guidances recommendations, and also included language for the safe use of the proposed oral solution as the LD is a tablet dosage form. All labeling has been agreed upon with the Applicant.

- **Carton and immediate container labels**

Acceptable with FDA's recommended changes. See details in review by Dr. Teresa McMillan (DARRTS date 11/1/2022).

- **Patient Labeling/Medication Guide**

The Patient Information is acceptable with FDA's recommended changes. See details in review by Dr. Nyedra Booker (DARRTS date 10/31/2022).

13. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

No postmarketing risk evaluation and management strategies are recommended.

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No postmarketing requirements or commitments are recommended.

14. Recommended Comments to the Applicant

None.

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/

JIANMENG CHEN
11/17/2022 09:08:42 AM

NIKOLAY P NIKOLOV
11/17/2022 09:26:47 AM

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	212479
Supporting document/s:	SDN 4 (eCTD 0004)
Applicant's letter date:	October 14, 2020
CDER stamp date:	October 14, 2020
Product:	Methotrexate oral solution (2 mg/mL)-JYLAMVO
Indication:	Rheumatoid Arthritis (RA), Psoriasis, Relapsed or refractory non-Hodgkin lymphoma, Acute lymphoblastic leukemia (ALL), Mycosis fungoides
Applicant:	Therakind Ltd.
Review Division:	Division of Rheumatology and Transplant Medicine (DRTM)
Pharm/Tox Division	Division of Pharm/Tox for Immunology and Inflammation (DPT-II)
Reviewer:	Anup Srivastava, PhD
Supervisor/Team Leader:	Carol Galvis, PhD
Division Director:	Nikolay Nikolov, MD
Project Manager:	Cindy Chee

Template Version: September 1, 2010

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Therakind Ltd. submitted a 505(b)(2) NDA 212479 application on March 1, 2021, for the use of JYLAMVO (methotrexate) 2mg/mL oral solution for the treatment of adults with acute lymphoblastic leukemia (ALL) as part of combination chemotherapy maintenance regimen, and treatment of adults with relapsed non-Hodgkin lymphoma as part of a metronomic combination regimen. It is also indicated for treatment of mycosis fungoides, rheumatoid arthritis, and severe psoriasis.

This review evaluates the labeling content for JYLAMVO (Methotrexate oral solution-2mg/mL). Labeling recommendations were provided for Indications and Usage (under Highlights of Prescribing Information), Section 8.1 “Pregnancy”, Section 8.2 “Lactation”, Section 8.3 “Females and Males of Reproductive Potential”, and Section 13 “Nonclinical Toxicology”. Additions are denoted as underlined text. Deletions are denoted as strikeout ~~text~~. The recommendations were based on labeling language for other methotrexate products, to ensure consistency.

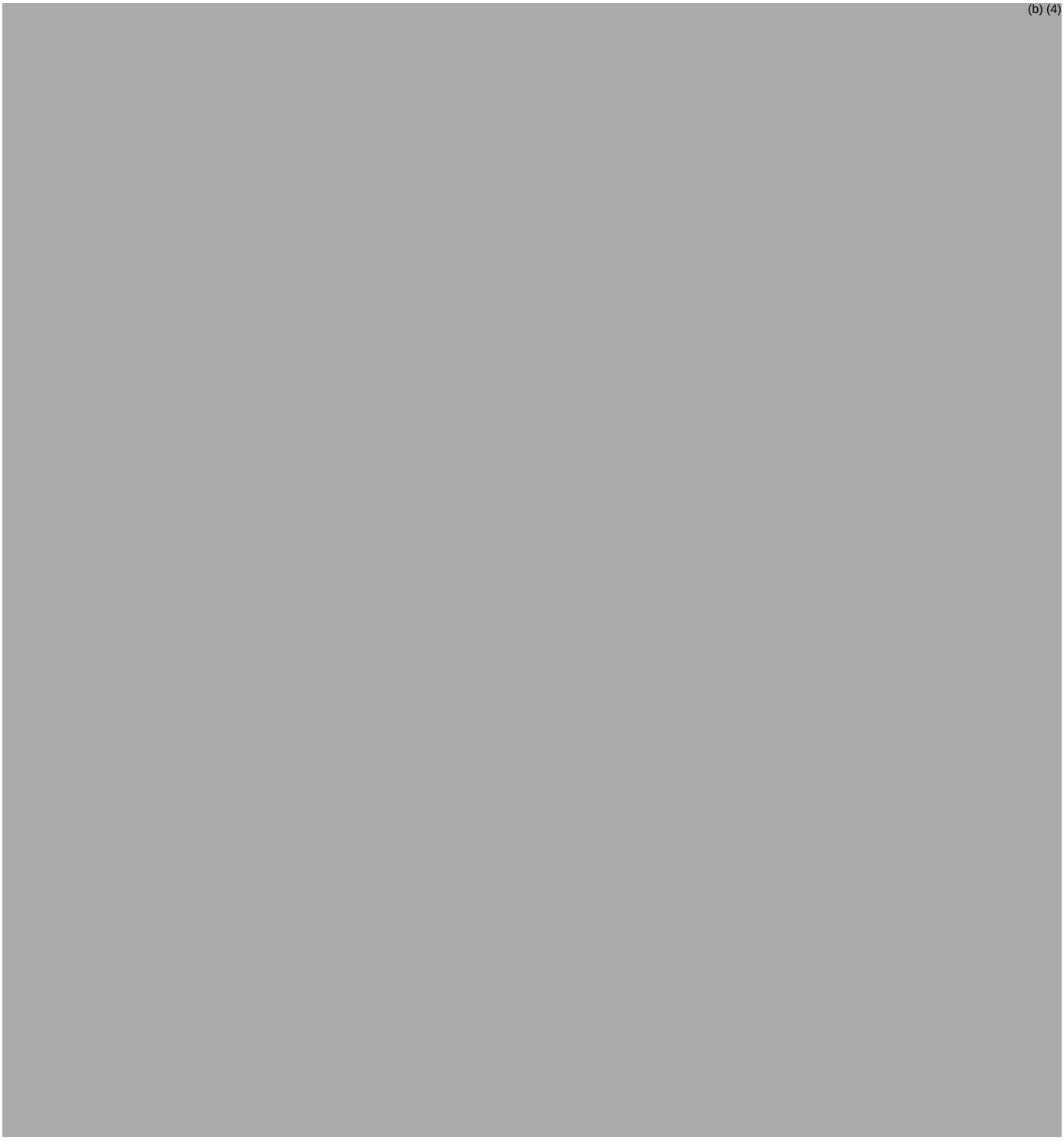
1.3 Recommendations

1.3.1 Approvability

NDA 212479 is recommended for approval from the nonclinical perspective.

1.3.3 Final Labeling

(b) (4)



11 Integrated Summary and Safety Evaluation

Labeling recommendations were provided for Section 8.1 “Pregnancy”, Section 8.2 “Lactation”, Section 8.3 “Females and Males of Reproductive Potential”, and Section 13 “Nonclinical Toxicology”. Additions are denoted as underlined text. Deletions are denoted as strikeout ~~text~~.

(b) (4)

Reviewer’s evaluation: *The Established Pharmacologic Class (EPC) was changed to reflect the updated version of EPC text phrases (updated on October 2021).*

(b) (4)

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

---

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/

ANUP K SRIVASTAVA
10/26/2022 03:48:47 PM

CAROL M GALVIS
10/26/2022 03:57:01 PM

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	212479
Priority or Standard	Standard
Submit Date(s)	March 1, 2021
Received Date(s)	March 1, 2021
PDUFA Goal Date	January 1, 2022
Division/Office	DRTM
Review Completion Date	See electronic stamp date
Established/Proper Name	Methotrexate
(Proposed) Trade Name	Jylamvo
Pharmacologic Class	Anti-folate medication
Code name	N/A
Applicant	Therakind Limited
Doseage form	Oral solution

Applicant proposed Dosing Regimen	• Neoplastic diseases:
	  • Acute lymphoblastic leukemia: Starting dosage is 20 mg/m2 once weekly as part of a combination chemotherapy maintenance regimen
	  • Mycosis fungoides: Dosage is 25 to 75 mg once weekly as monotherapy; 10 mg/m2 twice weekly as part of combination chemotherapy regimen
	  • Relapsed or refractory non-Hodgkin lymphoma: Dosage is 2.5 mg two to four times per week (maximum 10 mg per week) as part of metronomic combination chemotherapy regimen
	• Rheumatoid arthritis: Starting dosage is 7.5 mg once weekly with escalation to achieve an optimal response
	• Psoriasis: Dosage is 10 to 25 mg once weekly until adequate response is achieved (do not exceed a dose of 30 mg per week)

Applicant Proposed Indication(s)/Population(s)	• 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
Recommendation on Regulatory Action	Complete response

Recommended Indication(s)/Population(s) (if applicable)	Not applicable due to Complete Response action
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable due to Complete Response action
Recommended Dosing Regimen	Not applicable due to Complete Response action

Table of Contents

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Cindy Chee, PharmD
Nonclinical Reviewer	Anup Srivastava, PhD
Nonclinical Team Leader	Carol Galvis, PhD
Office of Clinical Pharmacology Reviewer(s)	Shalini Wickramaratne Senarath Yapa, PhD
Office of Clinical Pharmacology Team Leader(s)	Jianmeng Chen, MD, PhD
Clinical Reviewer	Keith Hull, MD, PhD
Clinical Team Leader	Anil Rajpal, MD, MPH
Statistical Reviewer	N/A
Statistical Team Leader	N/A
Cross-Disciplinary Team Leader	Jianmeng Chen, MD, PhD
Office Director (or designated signatory authority)	Nikolay Nikolov, MD

Additional Reviewers of Application

OPQ	Craig Bertha, PhD
Microbiology	Kelly Ann Miller
OPDP	Lynn Panholzer
OSE/DEPI	Marie Bradley
OSE/DMEPA	Teresa McMillan
Other	DDD Hamid Tabatabai DHM1 Kamar Godder DHM2 Pam Seam

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Anup Srivastava	OII/DPTII	Sections: 5	**Select one:** _X__ Authored ___ Approved
	Signature: Anup K. Srivastava -S Digitally signed by Anup K. Srivastava -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001943361, cn=Anup K. Srivastava -S Date: 2021.12.15 15:11:58 -05'00'			
Nonclinical Supervisor	Carol Galvis	OII/DPTII	Sections: 5	**Select one:** ___ Authored _X__ Approved
	Signature: Carol Galvis -S Digitally signed by Carol Galvis -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Carol Galvis -S, 0.9.2342.19200300.100.1.1=2000329778 Date: 2021.12.15 15:55:06 -05'00'			
Clinical Pharmacology Reviewer	Shalini Wickramaratne Senarath Yapa	OCP/DIIP	Section: 6	**Select one:** _X__ Authored ___ Approved
	Signature: Shalini Wickramaratne -S Digitally signed by Shalini Wickramaratne -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001808888, cn=Shalini Wickramaratne -S Date: 2021.12.15 15:42:45 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Team Leader and CDTL	Jianmeng Chen, MD, PhD	OCP/DIIP	Section: 1, 6	**Select one:** _ x _ Authored _x_ Approved
	Signature: Jianmeng Chen Digitally signed by Jianmeng Chen DN: cn=Jianmeng Chen, o=FDA/CDER/OTS/OCP, ou, email=JIANMENG.CHEN@FDA.HHS.GOV, c=US Date: 2021.12.15 15:06:14 -05'00'			
Clinical Reviewer	Keith M. Hull, MD, PhD	OII/DRTM	Sections:2, 7, 8	**Select one:** _x_ Authored ___ Approved
	Signature: Keith M. Hull -S Digitally signed by Keith M. Hull -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Keith M. Hull -S, 0.9.2342.19200300.100.1.1=1300218445 Date: 2021.12.15 15:36:52 -05'00'			
Clinical Team Leader	Anil Rajpal, MD	OII/DRTM	Sections: 2, 7, 8	**Select one:** ___ Authored _x_ Approved
	Signature: Anil K. Rajpal -S Digitally signed by Anil K. Rajpal -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Anil K. Rajpal -S, 0.9.2342.19200300.100.1.1=1300170204 Date: 2021.12.15 15:15:03 -05'00'			
Division Director (Clinical)	Nikolay Nikolov, MD	OII/DRTM	Sections: All	**Select one:** ___ Authored _X__ Approved
	Signature: Nikolay P. Nikolov -S Digitally signed by Nikolay P. Nikolov -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011314790, cn=Nikolay P. Nikolov -S Date: 2021.12.15 15:40:00 -05'00'			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The Applicant, Therakind Limited, submitted a 505(b)(2) new drug application (NDA) for methotrexate (MTX) 2 mg/mL oral solution for treatment of neoplastic diseases, rheumatoid arthritis, and psoriasis in adults. The product is presented in amber type III glass bottles with tamper evident child-resistant closures containing 60 ml of oral solution. Each pack contains one bottle, a bottle adaptor and one 10 mL graduated oral dosing syringe. Methotrexate is a dihydrofolate reductase inhibitor. The proposed dosing regimens are the same as currently approved MTX dosing regimens, as outlined below:

- **Neoplastic diseases:**
  - Acute lymphoblastic leukemia: Starting dosage is 20 mg/m^2 once weekly as part of a combination chemotherapy maintenance regimen
  - Mycosis fungoides: Dosage is 25 to 75 mg once weekly as monotherapy; 10 mg/m^2 twice weekly as part of combination chemotherapy regimen
  - Relapsed or refractory non-Hodgkin lymphoma: Dosage is 2.5 mg two to four times per week (maximum 10 mg per week) as part of metronomic combination chemotherapy regimen
- **Rheumatoid arthritis:** Starting dosage is 7.5 mg once weekly with escalation to achieve an optimal response
- **Psoriasis:** Dosage is 10 to 25 mg once weekly until adequate response is achieved (do not exceed a dose of 30 mg per week)

Methotrexate tablets have been marketed since December of 1953 (NDA 08085, Dava Pharmaceuticals Inc.) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, MTX is approved as an injection for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intra-thecal (IT) administration. Methotrexate is currently available in 2.5 mg tablets (multiple companies), and 5, 7.5, 10, and 15 mg tablets. Injectable MTX is available from multiple companies in varying quantities of 25 mg/mL solution. At the time of submission of this NDA, approved indications and routes of administration for MTX included neoplastic diseases (oral, IM, IV, IA, and IT routes), rheumatoid arthritis (oral, SC route), polyarticular juvenile idiopathic arthritis (oral, IM, SC routes), and severe psoriasis (oral, IM, SC, IV routes). The Applicant will only seek approval for indications in adults with neoplastic diseases (ALL, cutaneous T-cell lymphoma, and refractory non-Hodgkin lymphomas), adults with RA, and adults with psoriasis since an alternative MTX oral liquid (XATMEP) was approved in 2017 and has exclusivity for use in children with ALL and children with JIA.

This review covers the RA indication. Please see the Division of Dermatology and Dentistry, Dr. Tabatabai's review for the plaque psoriasis indication, and the Division of Hematologic Malignancies I, Dr. Godder and the Division of Hematologic Malignancies II, Dr. Seam's reviews

for the neoplastic diseases.

1.2. Conclusions on the Substantial Evidence of Effectiveness

To support approval of their product for the RA indication, the Applicant is relying on:

- The Agency's previous findings of safety and effectiveness of methotrexate in RA for the listed drug, Methotrexate Sodium Tablets (NDA 008085)
- One comparative bioavailability (BA) study comparing the proposed oral solution with Dava's methotrexate sodium tablets and assessment of food-effect to evaluate methotrexate oral solution in the fasted and fed state
- Information in the published literature supporting the safety and efficacy of methotrexate for RA

The primary data to support this NDA submission is from the BA study comparing the proposed methotrexate oral solution to oral methotrexate (Study MTX003). Based on the study, methotrexate Cmax and AUC of the proposed oral solution are similar to those of the immediate release tablet. The geometric mean ratio (GMR) of 10 mg MTX oral solution (proposed drug product, T) and 10 mg MTX tablets (reference product, R) for systemic exposure (AUC and Cmax) was within the bioequivalence limits of 80 to 125%. Therefore, the Applicant could rely on Agency's previous findings of safety and effectiveness of MTX for the listed drug.

However, Complete Response is recommended for this application given the CMC deficiencies. Refer to the Integrated Quality Assessment in DARRTS dated 18-NOV-2021 for details.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Methotrexate is a folate analog metabolic inhibitor currently indicated for the treatment of neoplastic diseases, severe psoriasis, and rheumatoid arthritis (RA). Methotrexate is marketed in various dosage forms including oral preparations and solutions for injection. The proposed product is a 2 mg/ml Oral Solution.

The efficacy and safety of the Applicant's methotrexate product has been based on the Agency's previous findings of safety and effectiveness of methotrexate for methotrexate tablets. The submitted bioavailability data demonstrate bioequivalence between the proposed methotrexate oral solution and the listed drug, methotrexate tablets. Information in the published literature also supports the safety and efficacy of methotrexate for RA. However, the CMC deficiencies preclude approval during this review cycle.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Rheumatoid arthritis is an autoimmune disease that causes chronic systemic inflammation of the joints. RA can impact patients due to pain, decreased physical function, and irreversible joint damage.	**Rheumatoid arthritis is a serious condition and common type of inflammatory arthritis. Most patients have a chronic progressive disease that is associated with morbidity and increased mortality.**
Current Treatment Options	• There are multiple drugs approved for RA. Methotrexate, a disease modifying antirheumatic drug (DMARD), is typically the first line of therapy for RA. There are multiple classes of medications approved for RA if a patient continues to have disease activity with methotrexate.	**There are multiple current treatment options for patients with RA. However, despite the availability of multiple therapies for RA, there remains unmet medical need for alternative, effective medications.**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The benefit of methotrexate has been established with multiple methotrexate products. The Applicant has provided a rationale that their product is similar to an already approved product, Methotrexate Sodium Tablets (NDA 008085). The Applicant has also provided additional literature review supporting the benefit of methotrexate for RA.	**Methotrexate has established effectiveness for the treatment of RA.**
Risk and Risk Management	• The safety of methotrexate has been established with multiple methotrexate products. The Applicant has provided a rationale that their product is similar to an already approved product, Methotrexate Sodium Tablets (NDA 008085). The Applicant has also provided additional literature review regarding the safety of methotrexate for RA. Risks can be managed with labeling.	**Methotrexate has an established safety profile in patients with RA. Risks can be managed with labeling.**

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
☐	**The patient experience data that were submitted as part of the application include:**			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that primarily affects diarthrodial joints but frequently involves other organs as well. Approximately 1% of the general population is affected worldwide and although RA may occur at any age, the peak incidence of onset is usually between the 4th and 6th decades with females being 2-3 times more likely affected than males. The etiology of RA is unknown but there clearly appears to be a combination of both genetic and environmental factors that allow for the onset and progression of the disease. Evidence suggests that a major portion of the pathogenesis of RA is mediated by antigen-driven T cells and macrophages which produce proinflammatory cytokines including IL-1 and tumor necrosis factor-α (TNFα). This process contributes to osteoclast activation and proliferation of synoviocytes surrounding the joint that can ultimately expand and resorb cartilage and bone and present radiographically as erosions.

The initial clinical presentation of RA can be extremely variable but the majority of patients develop symmetrical polyarticular pain and/or stiffness of the proximal interphalangeal, metacarpophalangeal, wrist, shoulder, knee, ankle, and metatarsophalangeal joints over the course of weeks to months which then develop into frank synovitis and joint swelling. As the disease progresses most patients develop joint deformities caused by bone erosions and tendon/ligament damage that limit physical function resulting in deformity, early disability, and even death.

2.2. Analysis of Current Treatment Options

Table 1: Currently approved csDMARDs marketed in the US for the treatment of Rheumatoid Arthritis

Product Name (Trade Name) [Sponsor]	Year of First Approval for RA	Dosing/ Administration	Mechanism of Action in RA
Sulfasalazine (AZULFIDINE) [Pfizer]	1950	Oral	Anti-inflammatory and antimicrobial
Methotrexate sodium (METHOTREXATE SODIUM) [Multiple]	1988	Oral, SC (autoinjectors)	Anti-metabolite
Hydroxychloroquine (PLAQUENIL) [Sanofi-Aventis]	1955	Oral	Interference with antigen processing (?)
Azathioprine (IMURAN) [Prometheus Labs]	1968	Oral	Cytostatic
Penicillamine (CUPRIMINE) [Alton]	1970	Oral	Unknown
Auranofin (RIDAURA) [Prometheus Labs]	1985	Oral	Unknown
Cyclosporine (NEORAL) Cyclosporine (SANDIMMUNE) [Novartis]	1995 1990	Oral	T-cell activation inhibitor
Leflunomide (ARAVA) [Sanofi-Aventis]	1998	Oral	Anti-metabolite
Steroids and NSAIDs are approved for the reduction of the signs and symptoms of RA. csDMARDs: conventional synthetic disease modifying antirheumatic drugs			

Table 2: Summary of Approved bDMARD and tsDMARD Drugs Available for the Treatment of Rheumatoid Arthritis

Product Name (Trade Name)	Year approved for RA	BLA/NDA (sponsor)	ROA	Description	MOA
Etanercept (ENBREL)	1998	103795 Immunex/Amgen)	SC	Fusion protein TNFR:IgG1 Fc	TNF inhibitor
Infliximab (REMICADE)	1999	103772 (Centocor)	IV	Chimeric IgG1k mAb	TNF inhibitor
Anakinra (KINERET)	2001	103950 (Amgen)	SC	Recombinant polypeptide	IL-1r antagonist
Adalimumab (HUMIRA)	2002	125057 (Abbott/Abbvie)	SC	Human IgG1k mAb	TNF inhibitor
Abatacept (ORENCIA)	2005 2011	125118 (Bristol-Myers Squibb)	IV SC	Fusion protein consisting of CTLA-4 and human IgG1 Fc	T cell activation inhibitor
Rituximab (RITUXAN)	2006	103705 (Genentech & Biogen Idec)	IV	Chimeric murine/human IgG1k mAb	AntiCD20, B cell depleter
Golimumab (SIMPONI)	2009	125289 (Centocor & Janssen)	SC	Humanized IgG1k mAb	TNF inhibitor
Certolizumab Pegol (CIMZIA)	2009	125160 (UCB Inc)	SC	Humanized Fab fragment	TNF inhibitor
Tocilizumab (ACTEMRA)	2010 2013	125276 125472 (Genentech/Roche)	IV SC	Humanized IgG1k mAb	IL-6 receptor inhibitor
Tofacitinib (XELJANZ)	2012	203214 (Pfizer/PF Prism CV)	PO	Citrate salt	JAK inhibitor
Golimumab IV (SIMPONI ARIA)	2013	125433 (Janssen)	IV	Humanized IgG1k mAb	TNF inhibitor
Tofacitinib (XELJANZ XR)	2016	208246 (Pfizer/PF Prism CV)	PO	Citrate salt	JAK inhibitor
Sarilumab (KEVZARA)	2017	761037 (Sanofi)	SC	Humanized IgG1k mAB	IL-6 receptor inhibitor
Baricitinib (OLUMIANT)	2018	207924 (Eli Lilly and Co)	PO	-	JAK inhibitor
Upadacitinib (RINVOQ)	2019	211675 (Abbvie)	PO	-	JAK inhibitor
Biosimilars					
Infliximab-DYYB (INFLECTRA)	2016	125544 (Celltrion Inc)	IV	Chimeric IgG1k mAb	TNF inhibitor
Etanercept-szzs (ERELZI)	2016	761042 (Sandoz)	SC	Fusion protein consisting of TNFR linked to human IgG1 Fc	TNF inhibitor
Adalimumab-atto (AMJEVITA)	2016	761024 (Amgen)	SC	Human IgG1k mAb	TNF inhibitor
Infliximab-abda (RENFLEXIS)	2017	761054 (Samsung)	IV	Chimeric IgG1k mAb	TNF inhibitor
Adalimumab-adbm (CYLTEZO)	2017	761058 (Boehringer-Ingelheim)	SC	Human IgG1k mAb	TNF inhibitor

Product Name (Trade Name)	Year approved for RA	BLA/NDA (sponsor)	ROA	Description	MOA
Infliximab-qbtx (IXIFI)	2017	761072 (Pfizer)	IV	Chimeric IgG1k mAb	TNF inhibitor
Adalimumab-adaz (HYRIMOZ)	2018	761071 (Sandoz)	SC	Human IgG1k mAb	TNF inhibitor
Etanercept-ykro (ETICOVO)	2019	761066 (Samsung)	SC	Fusion protein TNFR:IgG1 Fc	TNF inhibitor

Abbreviations: ROA = Route of administration; MOA= Mechanism of action; TNF=tumor necrosis factor; TNFR=tumor necrosis factor receptor; IL=interleukin; JAK=Janus kinase; mAb=monoclonal antibody; CTLA-4=cytotoxic T-lymphocyte-associated protein 4; SC=subcutaneous; IV=intravenous; bDMARDs=biologic DMARDS; tsDMARDs=targeted synthetic DMARDs such as tofacitinib and baricitinib

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

JYLAMVO has not currently approved for use in the US. JYLAMVO was granted a European Centralised Marketing Authorisation by the European Medicines Agency (EMA) on 29 March 2017 for the treatment of neoplastic diseases, psoriasis, and rheumatoid arthritis.

3.2. Summary of Presubmission/Submission Regulatory Activity

A pre-NDA meeting was held between the Agency and the Applicant on October 16, 2018. At the Pre-NDA meeting, it was agreed that the Applicant will conduct an in vivo relative BA study with their proposed drug product and a US-approved listed drug under fasting conditions. The Agency recommended that a food-effect study with their proposed drug product be conducted and that the to-be-marketed drug product be used in all clinical studies.

The Initial Pediatric Study Plan requesting full pediatric waiver for JYLAMVO™ (methotrexate) 2 mg/ml Oral Solution was submitted to FDA on April 17, 2020. On July 16, 2020, FDA informed the Applicant that the proposed product did not trigger PREA (see Section 10, Pediatrics); therefore, a withdrawal request for the iPSP was submitted to the Agency on July 22, 2020.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and analytical sites for Study MTX003. OSIS declined to conducted inspection for both sites since a Remote Record Review for the site (b) (4) was conducted in (b) (4), which falls within the surveillance interval (refer to OSIS review by Dr. Ting Wang archived on August 2, 2021).

4.2. Product Quality

The FDA review of records requested under section 704(a)(4) of the Federal Food, Drug, and Cosmetic Act, and provided by (b) (4) drug product manufacturing facility, noted objectionable conditions. These objectionable conditions will need to be resolved before this application may be approved.

In addition, there are other drug product related deficiencies that will need to be addressed before approval can be recommended. In summary, the currently available stability data do not support the proposed expiration dating period of 18 months and additional testing and acceptance criteria for deliverable volume should be added to the drug product specificiation. For additional details, refer to the Integrated Quality Assessment in DARRTS dated 18-NOV-2021.

4.3. Clinical Microbiology

OPQ microbiology review team concluded that the information of the drug product microbial quality control is adequate. For additional details, refer to the Integrated Quality Assessment in DARRTS dated 18-NOV-2021.

4.4. Devices and Companion Diagnostic Issues

Not Applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies were submitted or required to support this application. Relevant pharmacology/toxicology information is contained in the listed drug, Methotrexate Sodium Tablets (NDA 008085).

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant, Therakind Limited, submitted a 505(b)(2) new drug application (NDA) for methotrexate (MTX) 2 mg/mL oral solution for treatment of neoplastic diseases, rheumatoid arthritis, and psoriasis in adults. Methotrexate is a dihydrofolate reductase inhibitor. This NDA presents a new dosage form. The proposed dosing regimens are outlined below:

- **Neoplastic diseases:**
  - Acute lymphoblastic leukemia: Starting dosage is 20 mg/m^2 once weekly as part of a combination chemotherapy maintenance regimen
  - Mycosis fungoides: Dosage is 25 to 75 mg once weekly as monotherapy; 10 mg/m^2 twice weekly as part of combination chemotherapy regimen
  - Relapsed or refractory non-Hodgkin lymphoma: Dosage is 2.5 mg two to four times per week (maximum 10 mg per week) as part of metronomic combination chemotherapy regimen
- **Rheumatoid arthritis:** Starting dosage is 7.5 mg once weekly with escalation to achieve an optimal response
- **Psoriasis:** Dosage is 10 to 25 mg once weekly until adequate response is achieved (do not exceed a dose of 30 mg per week)

The Applicant has referenced Methotrexate 2.5 mg tablets USP (NDA 008085, Dava Pharmaceuticals, Inc.) for this 505(b)(2) NDA. The clinical development program to bridge the proposed MTX oral solution drug product to FDA's finding of clinical efficacy and safety of MTX 2.5 mg tablets includes a phase 1 relative bioavailability (BA) and food-effect study in healthy male subjects (Study MTX003).

6.2. Summary of Clinical Pharmacology Assessment

The Office of Clinical Pharmacology/Division of Inflammation and Immune Pharmacology (OCP/DIIP) has reviewed the clinical pharmacology data submitted under NDA 212479. This NDA is recommended for approval from a clinical pharmacology perspective for the treatment of adult patients with neoplastic diseases, rheumatoid arthritis, and psoriasis. The Division Signatory agrees with this assessment and recommendations.

6.2.1. Pharmacology and Clinical Pharmacokinetics

The following are the major clinical pharmacology findings from the current review:

1) Following a single-dose administration under fasted conditions in healthy male subjects (18 to 50 years of age), the 90% confidence interval (CI) for the test/reference (T/R) geometric mean ratio (GMR) of 10 mg MTX oral solution (proposed drug product, T) and 10 mg MTX tablets (reference product, R) for systemic exposure (area under the curve (AUC)) and peak concentration (C_{max}) was within the bioequivalence limits of 80 to

125%. Therefore, the Applicant could rely on Agency's previous findings of safety and effectiveness of MTX for the listed drug, MTX 2.5 mg tablets (NDA 008085). In addition, relevant information for MTX, including pharmacokinetics (PK), drug interaction, renal and hepatic impairment, and others, could rely on the approved U.S. labeling for MTX 2.5 mg tablets USP (NDA 008085).

2) MTX has nonlinear PK. The relative BA assessment was conducted at a lower dose of 10 mg compared to the proposed doses for the proposed indications. A literature reference[1] has shown that intravenous MTX prepared as an oral solution has comparable exposure to that of MTX tablets up to doses of 25 mg/m^2. Therefore, the relative BA findings at the 10 mg dose were deemed representative of the relative BA of MTX at the proposed doses for all proposed indications.

3) Following 10 mg single-dose administration of MTX oral solution under fed and fasted conditions in healthy male subject (18 to 50 years of age), the 90% CI for the fed state/fasted state GMR for systemic exposure (AUC) was within the limits of 80 to 125%. Geometric mean peak concentration (C_{max}) was ~28% lower and time to peak concentration (T_{max}) was delayed (1.25 hours vs. 1 hour) under fed state compared to the fasted state. Similar observations for the effect of food on the absorption of MTX has been reported in the U.S. Prescribing Information (PI) for the reference drug, MTX 2.5 mg tablets. These findings are not considered to be clinically relevant, therefore MTX oral solution can be taken without regard for food.

4) The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and analytical sites for Study MTX003, and they declined to inspect based on past inspection history.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The following dosing regimens of MTX oral solution is recommended for adults with neoplastic diseases, rheumatoid arthritis, and psoriasis.

(b) (4)

[redacted]

[1] Harvey VJ, et al. Cancer Chemother Pharmacol 1984;13:91-4.

Source: Proposed Jylamvo (methotrexate) oral solution USPI

(b) (4)

Therapeutic Individualization

Not applicable.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Methotrexate inhibits dihydrofolic acid reductase. Dihydrofolates must be reduced to tetrahydrofolates by this enzyme before they can be utilized as carriers of one-carbon groups in the synthesis of purine nucleotides and thymidylate. Therefore, MTX interferes with DNA synthesis, repair, and cellular replication. Following oral administration, peak plasma concentrations of MTX are reached within 0.75 to 6 hours. Food has been shown to delay the absorption and reduce peak concentrations of MTX. Methotrexate primarily undergoes renal excretion by glomerular filtration and active tubular secretion that is depended upon dosage and route of administration. Non-linear elimination due to saturation of renal tubular reabsorption has been observed in studies in psoriasis patients receiving MTX doses between 7.5 mg and 30 mg. For metabolism, MTX primarily undergoes hepatic and intracellular metabolism and is partially metabolized by intestinal flora after oral administration. The terminal half-life of MTX is ~ 3 to 10 hours. The terminal half-life of MTX is variable and increases with the severity of renal impairment. The effect of hepatic impairment on the PK of MTX is unknown. For further details, refer to the MTX 2.5 mg tablets USPI (NDA 008085).

The clinical development program for MTX oral solution included one phase 1 relative BA and food-effect study in healthy male subjects (Study MTX003). Study MTX003 was a randomized, open-label, laboratory-blind, three-period, three-sequence, single-dose, crossover study in healthy male subjects (n=27) to assess the relative BA of MTX 10 mg oral solution relative to MTX 10 mg tablet (reference product: MTX 2.5 mg tablets USP, NDA 008085, Dava Pharmaceuticals, Inc.) under fasting conditions and to assess the effect of food on the BA of MTX 10 mg oral solution (fed and fasted conditions). The fasted and fed conditions were in line with the recommendations outlined in the FDA Guidance for Industry[2].

Study MTX003 evaluated the relative BA of MTX oral solution to MTX tablets (fasted conditions) and the effect of food on the BA of MTX oral solution (fasted and fed conditions) following a 10 mg single-dose in healthy male subjects. For the relative BA assessment, the 90% CI for the T/R GMR for AUC and C_{max} was within the bioequivalence limits of 80 to 125%. For the effect of food on the BA of MTX oral solution, the 90% CI for the fed state/fasted state GMR for AUC was within the limits of 80 to 125%. For C_{max}, geometric mean was ~28% lower and time to peak concentration (T_{max}) was delayed (1.25 hours vs. 1 hour) under fed state when compared to the fasted state. These findings are not considered to be clinically relevant, therefore MTX oral solution can be taken without regard for food.

Two anomaly plasma profiles with low plasma MTX concentrations were identified in the relative BA assessment for Subject (b) (6) following administration of the reference product, MTX tablet, and in the food-effect assessment for Subject (b) (6) following administration of MTX oral solution under fed conditions. Clinical and bioanalytical investigations confirmed that the study procedures were performed accordingly to the study protocol. For Subject (b) (6), no plausible explanation could be established for the observed anomaly profile, while Subject (b) (6) confirmed that he had vomited after receiving his treatment (MTX oral solution in the fed state) but had failed to report this adverse event to the clinical staff at the time of event. Both the anomaly plasma profiles were determined to be outlier profiles and were excluded from the relative BA and food-effect assessments.

6.3.2. Clinical Pharmacology Questions

Describe the relevant regulatory history for the review of this 505(b)(2) NDA

The regulatory interactions with the Agency during the clinical development program for MTX oral solution are listed in Section 3 of the review. Key regulatory interactions with the Agency relevant to clinical pharmacology are outlined below:

- Type B Pre-NDA meeting (NDA 212479, dated October 16, 2018): At the Pre-NDA meeting it was agreed that the Applicant will conduct an in vivo relative BA study with

[2] Draft Guidance, Guidance for Industry 'Assessing the effects of food on drugs in INDs and NDAs – Clinical pharmacology considerations (February 2019)'

their proposed drug product and a US-approved listed drug under fasting conditions. The Agency recommended that a food-effect study with their proposed drug product be conducted and that the to-be-marketed drug product be used in all clinical studies.

What are the clinical studies submitted under this NDA?

The clinical studies conducted in the MTX oral solution development program that are relevant to support NDA submission in the US are presented in Table 4. Two additional relative BA clinical studies, Studies MTX001 and MTX002, were conducted in the overall development program, however these studies did not use a US-approved reference drug product and therefore will not be discussed further in the current review.

Table 4: Overview of the Clinical Studies in the Methotrexate Oral Solution Clinical Development Program

Study	Design/Objectives	Patient Population	Dosing Regimen
MTX003	Randomized, open-label, laboratory-blind, 3-period, 3-sequence, single-dose, crossover study Objectives: To assess the relative BA of MTX oral solution relative to MTX tablet (Reference product: MTX 2.5 mg tablets USP, NDA 008085, Dava Pharmaceuticals, Inc.) under fasted condition To assess the effect of food on the BA of MTX oral solution (fasted and fed conditions)	Healthy male subjects (n=27, randomized); 18 to 50 years of age (inclusive)	MTX 2 mg/mL oral solution, 10 mg oral single-dose MTX 2.5 mg tablets USP, NDA 008085, Dava Pharmaceuticals, Inc. (Reference product), 10 mg oral single-dose

Source: Information collated from CSR for Study MTX003
Abbreviations: BA: Bioavailability; MTX: Methotrexate; PK: Pharmacokinetic

Was the to-be-marketed methotrexate oral solution used in Study MTX003?

The to-be-marketed drug product of MTX 2 mg/mL oral solution was used in Study MTX003. The drug product is a clear yellow solution containing 2 mg of MTX per mL. The drug product solution is presented in a standard amber glass bottle with a standard closure and a separate 10 mL oral dosage syringe (with major and minor graduations at every 1 mL and 0.25 mL, respectively) and bottle neck adapter. The composition of the MTX 2 mg/mL oral solution is presented in Table 5.

Table 5: Composition of Methotrexate 2 mg/mL Oral Solution

Name of Ingredient	Quantity		Function	Reference to Standards
	(%w/w)	(mg/ml)		
Methotrexate	0.2	2	Active ingredient	USP
Polyethylene Glycol (b) (4) (b) (4)	(b) (4)			USP-NF
Ethylparaben				USP-NF
Methylparaben Sodium				USP-NF
Glycerin				USP-NF
Orange Flavouring Powder				In-house
Sucralose				USP-NF
Citric Acid[1]				USP-NF
Sodium Citrate[1]				USP-NF
Purified Water				USP-NF

Source: Table 1 of Quality Overall Summary – Drug Product (Module 2.3.P)

What are the findings from OSIS inspection?

OSIS inspection was requested for the clinical and analytical sites for Study MTX003. OSIS declined to conducted inspection for both sites since a Remote Record Review for the site ((b) (4) was conducted in (b) (4), which falls within the surveillance interval (refer to OSIS review archived August 2, 2021).

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

The proposed dosing regimens of MTX oral solution outlined in Table 3 (Section 6.2.2) in adults for the treatment of neoplastic diseases, rheumatoid arthritis, and psoriasis is reasonable from a clinical pharmacology perspective.

For Study MTX003, the relative BA in the fasted state between MTX oral solution and MTX tablet (Reference product: MTX 2.5 mg tablets USP, NDA 008085, Dava Pharmaceuticals, Inc.) following a 10 mg single-dose in healthy male subjects is presented in Table 6. The 90% CI for the T/R GMR for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were within the bioequivalence limits of 80 to 125%. These relative BA results from the reviewer's analysis were consistent with the Applicant's relative BA results.

Table 6: Comparison of Geometric Mean Pharmacokinetic Parameters: Methotrexate Oral Solution 10 mg vs. Methotrexate Tablet 10 mg (Methotrexate 2.5 mg tablets USP, NDA 008085) (Study MTX003, n=26-27)

Comparison	PK Parameter	Geometric Mean Ratio (90% CI)
MTX Oral Solution (T) vs.	C_{max}	100.55 (88.19, 114.64)
	AUC_{0-t}	96.24 (84.02, 110.23)

MTX Tablet (R)	$AUC_{0-\infty}$	96.57 (84.59, 110.24)

Results based on an ANOVA model with treatment, sequence, period as fixed effects and subject(sequence) as a random effect
Source: Reviewer's analysis

Twenty-seven subjects were randomized in the study and all subjects were included in the PK analysis dataset (n=27). The Applicant reports that for the relative BA assessment, it was noted that Subject (b) (6) in treatment period 1 who was administered MTX tablet (reference product) showed lower plasma MTX concentrations when compared to his other treatment periods. To determine the cause of this anomaly plasma profile, the Applicant conducted extensive clinical and bioanalytical investigations which confirmed that the study procedures were performed as specified in the study protocol. The Applicant reports that such observations are unlikely to be due to a 'product failure' of the MTX tablet and that there is no evidence in the literature of 'subject-by-formulation interaction' for MTX. No plausible explanation could be established for the anomaly plasma profile for Subject (b) (6). The plasma profile for Subject (b) (6) following MTX tablet administration was determined to be an outlier profile and was excluded from the relative BA assessment (Table 6).

For the relative BA assessment, the reviewer considers the exclusion of Subject (b) (6) plasma profile following treatment with MTX tablet to be reasonable given that it is unlikely to be due to study conduct integrity and given that this observation is not related to the quality of the proposed drug product (MTX oral solution).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

There is no clinically relevant effect of food on the BA of MTX oral solution. Results from Study MTX003 showed that food affects the rate of absorption of MTX (~28% lower C_{max}) and delayed absorption (T_{max}, 1.25 hour compared to 1 hour) when compared to fasted conditions, however these findings are not considered to be clinically relevant. Similar observations for the effect of food on the absorption of MTX has been reported in the USPI for the reference product, MTX tablet.

For Study MTX003, the effect of food on the BA of MTX oral solution following a 10 mg single-dose under fasted and fed state in healthy male subjects is presented in Table 7. The 90% CI for the fed state/fasted state GMR for AUC_{0-t} and $AUC_{0-\infty}$ were within the bioequivalence limits of 80 to 125%. The geometric mean C_{max} was ~28% lower in the fed state when compared to the fasted state at the same dose of MTX oral solution, and the 90% CI were not within the 80 to 125% criteria. Time to peak concentration of MTX (T_{max}) was delayed under fed state (1.25 hours) compared to the fasted state (1 hour). These food-effect results were confirmed by in-house analysis conducted by the reviewer.

Table 7: Comparison of Geometric Mean Pharmacokinetic Parameters: Fed State vs. Fasted State for Methotrexate Oral Solution 10 mg (Study MTX003, n=26-27)

Parameter (unit)	LS Means		(Test/Reference) Geometric Mean Ratio (%)		Model Intra CV %
	Jylamvo Oral Solution Fasting (Reference) (N=27)	Jylamvo Oral Solution Fed (Test) (N=26)	Estimate	90% Confidence Interval	
C_{max} (ng/mL)	292.8069	212.1480	72.45	64.76 , 81.06	19.48
$AUC_{(0-t)}$ (ng*h/mL/mL)	964.3547	1051.0023	108.99	98.93 , 120.06	16.75
$AUC_{(0-\infty)}$ (ng*h/mL/mL)	986.2363	1077.0282	109.21	99.30 , 120.10	16.45
t_{max} (h) (median)*	1.00	1.25	p-value: 0.0030		

CV = coefficient of variation; LS = least square mean
*Secondary parameter
Jylamvo Fed (Test) vs Jylamvo Fasting (Reference)

Results based on an ANOVA model with treatment, sequence, period as fixed effects and subject(sequence) as a random effect
Note: Jylamvo refers to MTX oral solution
Source: Table 11-6 of CSR for Study MTX003

Of the 27 subjects randomized in the study, all were included in the PK analysis dataset. The Applicant reports that for the food-effect assessment, it was noted that Subject (b) (6) in treatment period 2 under fed conditions showed lower plasma MTX concentrations when compared to his other treatment periods. To determine the cause of this anomaly plasma profile, the Applicant conducted extensive clinical and bioanalytical investigations which confirmed that the study procedures were performed as specified in the study protocol. Upon further investigation, Subject (b) (6) reported that he had vomited after receiving MTX oral solution in the fed state but had not reported this event to the clinical staff at the time. The Applicant reports that further investigations provided sufficient reason to believe that the subject vomited during the first 4 hours after drug administration. The plasma profile for Subject (b) (6) following MTX oral solution administration under fed conditions was determined to be an outlier profile and was excluded from the food effect assessment (Table 7).

For the food-effect assessment, the reviewer considers the exclusion of Subject (b) (6) plasma profile following treatment with MTX oral solution under fed state to be reasonable given that the investigations showed that this observation was due to the subject having vomited following drug administration.

Is the bioanalytical method properly validated to measure methotrexate concentration in plasma samples?

The bioanalytical method used for quantification of MTX in human plasma was a liquid chromatography with tandem mass spectrometry (LC-MS/MS). Method validation (validation

report number: VAL453/01) and sample analysis supporting the phase 1 relative BA and food-effect clinical study (bioanalytical report number: 0154 (b) (4) 18) were in-line with the Agency's recommendations outlined in the Guidance for Industry 'Bioanalytical Method Validation' (May 2018), and all acceptance criteria as specified in the guidance were met. The validation summary of the bioanalytical method used to measure MTX in human plasma is presented in Table 8.

Table 8: Validation Summary of Bioanalytical Method

Validation Report	Validation of an LC-MS/MS Method for the Determination of Methotrexate in Human Plasma (VAL453/01)
Analyte	Methotrexate
Internal standard (IS)	Methotrexate-d3
Matrix (anticoagulant)	Human plasma (lithium heparinate)
Injection volume	3 µL
Method description	Protein precipitation followed by reversed phase high performance liquid chromatography (HPLC) with tandem mass spectrometry using electrospray ionization in the positive mode
Standard curve concentration range	2.30 ng/mL to 600 ng/mL
Regression model	Log-log linear
Response type	Peak area ratio
Limit of quantitation	2.30 ng/mL
QC concentrations	2.30, 6.90, 30, 120, 300, 480 ng/mL and 960 ng/mL (dilution QC; above upper limit of quantification)
QC Interday precision range (%CV)	≤8.6%
QC Interday accuracy range (%Bias)	-1.3% to 2.2%
Absolute recovery of drug	64.5%
Absolute recovery of IS	61.7%
Bench-top stability	12 hours and 50 minutes at room temperature (RT)
Stock stability	Methotrexate (high concentration): 4 days at RT and ~ 5 °C and 5 days and 23 hours at ~ -20 °C in dimethyl sulfoxide in glass containers Methotrexate (low concentration): 4 days at RT and 5 days and 23 hours at ~ 5 °C and ~ -20 °C in dimethyl sulfoxide in glass containers
Processed stability	3 days and 2 hours at 2 – 8 °C
Freeze-thaw stability	3 freeze-thaw cycles at ~ -70 °C
Long-term storage stability	At least 99 days in human lithium heparinate plasma when stored at ~ -70 °C in polypropylene containers
Dilution integrity	960 ng/mL diluted 2-fold Accuracy (%Bias) = 1.7%

	Precision (%CV) = 3.7%
Selectivity	No interfering peaks noted in blank plasma samples
Carry-over effect	No carry-over was detected in the blank samples used to monitor carry-over in each run
Effect of concomitant medication	Methotrexate can be accurately quantified in the presence of commonly used over-the-counter drugs (paracetamol, ibuprofen, cyclizine, cetirizine, pseudoephedrine, codeine, diclofenac) and in the presence of contraceptive drugs (ethinylestradiol, drospirenone, medroxyprogesterone 17-acetate, gestodene, cyproterone acetate, levonorgestrel)
Effect of hemolysis	Methotrexate can be accurately quantified when samples are severely hemolyzed
Effect of lipemia	Methotrexate can be accurately quantified when samples are moderately lipemic
Studies	MTX003

Source: Information collated from Method Validation Report (VAL453/01) and Response to FDA IR dated October 19, 2021

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Three small, open-labeled, single-dose clinical pharmacology studies enrolling healthy male volunteers were conducted to support approval of the proposed MTX oral solution formulation. These studies provide no clinically relevant information regarding the safety or efficacy of the proposed formulation of MTX, and consequently, the studies will not be reviewed here from the clinical perspective.

7.2. Review Strategy

The Applicant has referenced NDA 008085 (MTX tablets, USP, 2.5 mg) of DAVA Pharmaceuticals Inc. to support the clinical efficacy and safety of MTX and did not submit new clinical studies. The listed drug (LD) is approved for treatment of adults with specific neoplastic diseases (including acute lymphoblastic leukemia (ALL)), children with ALL, adults with RA, children with polyarticular juvenile idiopathic arthritis (JIA), and adults with severe psoriasis.

The Applicant is only seeking approval of indications for adults with neoplastic diseases (ALL, cutaneous T-cell lymphoma, and refractory non-Hodgkin lymphomas), adults with RA, and adults with psoriasis since an alternative MTX oral liquid (XATMEP) was approved in 2017 and has exclusivity for use in children with ALL and children with JIA.

The Applicant has submitted a review of the scientific literature to support the efficacy and safety of MTX for use in the proposed indications. Analysis of the data for the proposed indications of adults with neoplastic diseases and psoriasis will be reviewed by the Divisions of Hematologic Malignancies I and II and the Division of Dermatology and Dentistry, respectively. Only the indication for use in adults with RA will be reviewed here.

The Applicant's clinical review of MTX referenced relevant published scientific literature, with emphasis to detailed pharmacological monographs including, the RLD, to provide an assessment of the clinical evaluation of MTX use in the treatment of RA.

Publications included were selected based on the following criteria:

- most recent and relevant publications available
- peer reviewed clinical journals
- specificity to the proposed therapeutic indication of RA

The Applicant's review consisted of a series of databases, to obtain an updated and complete view of the literature on the different safety and clinical studies made in relation to MTX. The pharmacological and clinical databases consulted have been the following:

- Medline (http://www.ncbi.nlm.nih.gov/PubMed/)

The following databases were accessed from the Royal Society of Medicine electronic library:

- Embase 1974 to date
- Biosis
- EBSCO.

MeSH (Medical Subject Headings) and search terms were as follows: *methotrexate, dihydrofolate reductase, purine synthesis, antifolates, polyglutamation, rheumatoid arthritis, autoimmunity, leucovorin, resistance, pharmacology, pharmacodynamics, pharmacokinetics, efficacy, clinical, clinical trials, interactions, and safety*.

All terms were used with Boolean operators. Full articles were obtained from the British Library or the Medical Library of the Royal Society of Medicine, London, UK. The search results yielded approximately 260 validated entries, with articles published during years ranging from 1961 to 2020.

7.2.1. Methotrexate for the Treatment of Rheumatoid Arthritis

Methotrexate has been the cornerstone of treatment for rheumatoid arthritis since the 1980s. In fact, almost 40 years later, the most recent treatment guidelines for rheumatoid arthritis from the American College of Rheumatology (ACR)[3] and the European League Against Rheumatism (EULAR)[4] still recommend MTX as first-line treatment for the disease.

While there are many publications in the scientific literature supporting the use of MTX as monotherapy and/or concomitant therapy for the treatment of rheumatoid arthritis, this review will focus on two placebo-controlled, double-blinded studies conducted in the 1980s that provided the original evidence supporting the use of MTX for treatment for subjects with rheumatoid arthritis. Whereas the ACR20 has been a commonly used composite clinical endpoint for assessment in rheumatoid arthritis studies since the 1990s, the two studies reviewed here predate the development of that endpoint but do use a number of the same clinical outcomes that comprise the components for the ACR20, namely tender joint count, swollen joint count, patient's assessment of disease activity, physician's assessment of disease activity, and measurement of acute phase reactants, i.e., erythrocyte sedimentation rate or c-reactive protein.

[3] Fraenkel L et al., Arthritis Rheumatol. 2020;72(8):1241-1251
[4] Smolen JS et al. Ann Rheum Dis. 2020;79(6):685-699

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Literature Review of MTX for the Treatment of Adults with Rheumatoid Arthritis

In 1985, Weinblatt et al.[5] published a 24-week, double-blinded, crossover trial comparing oral MTX to placebo in subjects with refractory rheumatoid arthritis. Subjects were randomly assigned to receive either MTX 2.5 mg tablets or placebo for 12-weeks (Period 1). Tablets were ingested in equal numbers on three consecutive occasions at 12-hour intervals beginning on the same day of each week. For the first six weeks, three tablets were taken weekly (7.5 mg); at six weeks, the dose could be increased to six tablets (15 mg) weekly if a satisfactory response was not noted by the investigator. At 12-weeks, crossover occurred (Period 2) with subjects initially assigned to MTX receiving placebo for the final 12-weeks of the study and subjects originally assigned placebo receiving MTX in a similar manner as subjects in Period 1.

Each subject was examined by the same investigator every three weeks, and pill counts were performed to assess treatment compliance. The clinical disease variables were determined at each visit and included the following:

- number of swollen joints
- number of tender joints
- joint swelling index
- joint tenderness pain index
- duration of morning stiffness
- physician's assessment of disease activity
- subject assessment of disease activity

In addition to the clinical assessments, laboratory assessments were made every three weeks which included a complete blood count, erythrocyte sedimentation rate, and liver enzyme tests. Serum creatinine was measured every six-weeks.

A total of 35 subjects with rheumatoid arthritis fulfilling the American Rheumatism Association's criteria for definite or classic disease were initially enrolled in the study. All subjects had active disease despite receiving treatment with gold-salt therapy (the previous standard of care), and/or D-penicillamine (n=28), hydroxychloroquine (n=23), and/or azathioprine (n=2). All subjects underwent drug washout prior to starting Period 1 but could maintain stable doses of aspirin or other nonsteroidal anti-inflammatory drugs and prednisone doses of ≤10 mg daily.

[5] Weinblatt ME et al. N Engl J Med 1985; 312:818-822

Additional criteria for entry included the presence of active disease, which was defined by at least three of the following:

- ≥3 swollen joints
- ≥6 tender joints
- ≥45 minutes of morning stiffness
- ESR ≥28 mm/hr

Subjects were also confirmed to have had radiographic evidence of erosive disease.

As shown in Table 9, the baseline demographic and clinical characteristics were similar between treatment arms.

Table 9: Demographic and Baseline Characteristics of Subjects at Study Entry

	Medication Sequence	
	MTX-PBO (N=17)	PBO-MTX (N=18)
Age (year)		
mean (range)	60 (45-70)	59 (44-73)
Female (n)	10	15
White (n)	16	17
Disease Duration (month)		
mean (range)	100 (21-320)	128 (48-352)
RA Functional Class (n)		
II	11	8
III	6	10
RF-positive (n)	16	18
Prednisone ≤10 mg/day (n)	8	12
Previous hip, knee or ankle arthroplasty	6	7

Source: Adapted from Weinblatt ME et al. N Engl J Med 1985; 312:818-822, Table 1. MTX: methotrexate; PBO: placebo; RA: rheumatoid arthritis; RF: rheumatoid factor.

Of the 35 subjects enrolled, 17 were initially assigned to receive MTX and 18 received placebo. All but two MTX-treated subjects had their dose of study drug increased to six tablets. Pill counts suggested a high degree of compliance between subjects in both treatment arms. Four subjects withdrew from the study prior to the crossover visit with the data from these subjects excluded by the authors from the efficacy analyses. Two of the subjects were receiving placebo; one subject was withdrawn because of a cerebrovascular accident and the other because of a protocol violation. One of the subjects receiving MTX was withdrawn at week nine because of diarrhea and the other was withdrawn after one week of treatment with MTX due to an exacerbation of rheumatoid arthritis which required hospitalization. Three placebo-treated subjects did not complete Period 2. One subject withdrew because of a rheumatoid

arthritis flare at Week 18, one subject was withdrawn at Week 21 due to missing a visit appointment, and the third subject died suddenly during an arthritis exacerbation. Another single placebo-treated subject received an intra-articular corticosteroid injection in the knee joint during Period 1 and was excluded from analysis.

At the end of Period 1 (Week 12), MTX-treated subjects demonstrated a significant decrease in the number of swollen and tender joints, duration of morning stiffness and improvement in the physician assessment of disease activity and patient assessment of disease activity (Table 10). A decrease in the erythrocyte sedimentation rate was observed but was not statistically significant.

Table 10: Efficacy Analysis of Subjects completing Period 1.

	Treatment	Value at Entry Visit Mean ± SE	Difference at Crossover Visit Mean ± SE	P Value
Number of Swollen joints	MTX (n=15)	34 ± 3	14 ± 2	<0.05
	PBO (n=16)	28 ± 2	5 ± 2	
Number of Tender joints	MTX (n=15)	37 ± 4	26 ± 4	<0.01
	PBO (n=16)	36 ± 3	4 ± 4	
Duration of morning stiffness (minutes)	MTX (n=15)	182 ± 60	134 ± 58	<0.01
	PBO (n=16)	103 ± 18	-36 ±32	
Physician assessment of disease activity	MTX (n=15)	2.7 ± 0.2	1.5 ± 0.2	<0.01
	PBO (n=16)	2.6 ± 0.2	0 ± 0.2	
Patient assessment of disease activity	MTX (n=15)	2.8 ± 0.2	1.6 ± 0.2	<0.01
	PBO (n=16)	2.7 ± 0.2	0.1 ± 0.2	
ESR (mm/hour)	MTX (n=15)	77 ± 9	17 ± 7	NS
	PBO (n=14)	50 ± 7	-4 ± 5	

Source: Adapted from Weinblatt ME et al. N Engl J Med 1985; 312:818-822, Table 2. MTX: methotrexate; PBO: placebo; NS: nonsignificant; P values determined by analysis of covariance using adjusted means.

Analysis by the authors reported that of the 16 subjects who crossed over to MTX demonstrated a statistically significant improvement in all clinical endpoints (data not shown). In contrast, a statistically significant proportion of the 12 subjects who crossed over to placebo demonstrated a clinically significant flare of their disease (data not shown).

In the same year, Williams et al.[6] published a prospective, multicenter trial comparing MTX and placebo. The study was designed as an 18-week, placebo-controlled, double-blind, parallel trail comparing MTX and placebo in subjects with active rheumatoid arthritis. Subjects were required to be 18 years of age or older with a diagnosis of definite or classic rheumatoid

[6] Williams HJ et al. Arthritis and Rheumatism 1985; 28(7):721-730.

arthritis of more than six months duration. Subjects had active disease despite treatment with conventional doses of salicylates or nonsteroidal anti-inflammatory drugs. Subjects could not have had treatment with antimalarials, chrysotherapy, D-penicillamine, cytotoxic drugs, or pyrazalone derivatives for the preceding two months. All subjects had received previous treatment with either parenteral gold or D-penicillamine. At the time of enrollment, subjects were required to have at least six swollen joints as well as a minimum of two of the following:

- ≥9 tender joints
- ≥45 minutes of morning stiffness
- ESR ≥28 mm/hr

Subjects were randomly assigned in a one-to-one ratio to receive either MTX 2.5 mg tablets or identical placebo tablets. Therapy was initiated at one tablet three times per week at three consecutive 12-hour intervals. MTX dosage could be doubled after six weeks if the investigator judged that the subject had active disease and were experiencing no severe adverse events. All subjects received a stable dose of aspirin or NSAID, which was kept constant during the 18-week trial. Phenylbutazone, oxyphenbutazone and intra-articular steroid injections were not permitted. Prednisone therapy was required to be stable for a minimum of one month prior to study entry and maintained throughout the study at a dose of ≤10 mg per day.

Clinical assessments of disease activity were performed at study entry and at Weeks 6, 12, and 18. Physician and assessment included: joint counts for tenderness and swelling, joint tenderness/pain and joint swelling scores, physician assessment of disease activity, and patient assessment of disease activity including duration of morning stiffness on the day before the visit, and overall assessment of arthritis activity. Regularly scheduled laboratory assessments included complete blood count, liver function testing, and erythrocyte sedimentation rate.

A total of 189 subjects fulfilled entry criteria and were enrolled in the study. There were no clinically meaningful differences between treatment arms regarding baseline demographics and disease activity variables except for a greater number of white subjects in the MTX group (Table 11).

Table 11: Demographic and Baseline Characteristics of Subjects at Study Entry

	PBO (n=94)	MTX (n=95)
Age; mean (years)	55	53
Male/Female (n)	27/67	28/67
Race		
White	60	76
Black	18	11
Other	16	8
Disease duration; mean (months)	156	168
Disease severity; n (%)		
Mild	0	1 (1)
Moderate	35 (43)	49 (52)
Severe	54 (57)	45 (47)
Functional Class; n (%)		
1	1 (1)	0
2	54 (57)	56 (59)
3	39 (41)	39 41)
4	0	0

Source: Adapted from Williams HJ et al. Arthritis and Rheumatism 1985; 28(7):721-730, Table 1. MTX: methotrexate; PBO: placebo

At enrollment, 43 MTX-treated subjects were taking prednisone with an average daily dosage of 6.3 mg compared to 59 placebo-treated subjects who were receiving an average daily dosage of 6.9 mg. As per protocol, all subjects had received either gold therapy (n=172) and/or D-penicillamine (n=119). Additionally, 43 subjects had received therapy with either azathioprine, cyclophosphamide or chlorambucil, and 53 subjects had received anti-malarial medications.

A total of 110/189 (58%) subjects completed the full 18-week study with similar proportions of subjects discontinuing from the MTX (n=57) and placebo (n=53) treatment arms. Reasons for discontinuation are shown in **Table 12**. The majority of subjects in the MTX treatment arm discontinued due to an adverse event, while the majority of placebo-treated subjects discontinued due to lack of efficacy.

Table 12: Subject Discontinuation by Treatment Group

Reason	PBO (n=94)	MTX (n=95)
Subjects discontinued from study; n (%)	41 (44)	39 (41)
Adverse drug reaction	10	30
Elevated liver enzymes	4	18
Mucosal ulcers	3	5
Gastrointestinal upset	0	3
Pancytopenia	0	2
Leukopenia	0	2
Thrombocytopenia	1	0
Rash	1	0
Pulmonary infiltrate	1	0
Lack of efficacy	20	3
Other	11	6

Source: Adapted from Williams HJ et al. Arthritis and Rheumatism 1985; 28(7):721-730, Table 5. MTX: methotrexate; PBO: placebo

Nineteen (33%) subjects in the MTX arm remained on MTX 7.5 mg weekly while the reminder of subjects required an increase of their dose to 15 mg weekly.

Efficacy analysis on the subjects who completed the entire 18-weeks of the study demonstrated a significant decrease in the number of swollen and tender joints, duration of morning stiffness and improvement in the physician assessment of disease activity and patient assessment of disease activity (**Table 13**). Additionally, MTX-treated subjects reported a statistically significant median decrease for erythrocyte sedimentation rates of 14 mm/hr compared to 2 mm/hr for placebo-treated subjects.

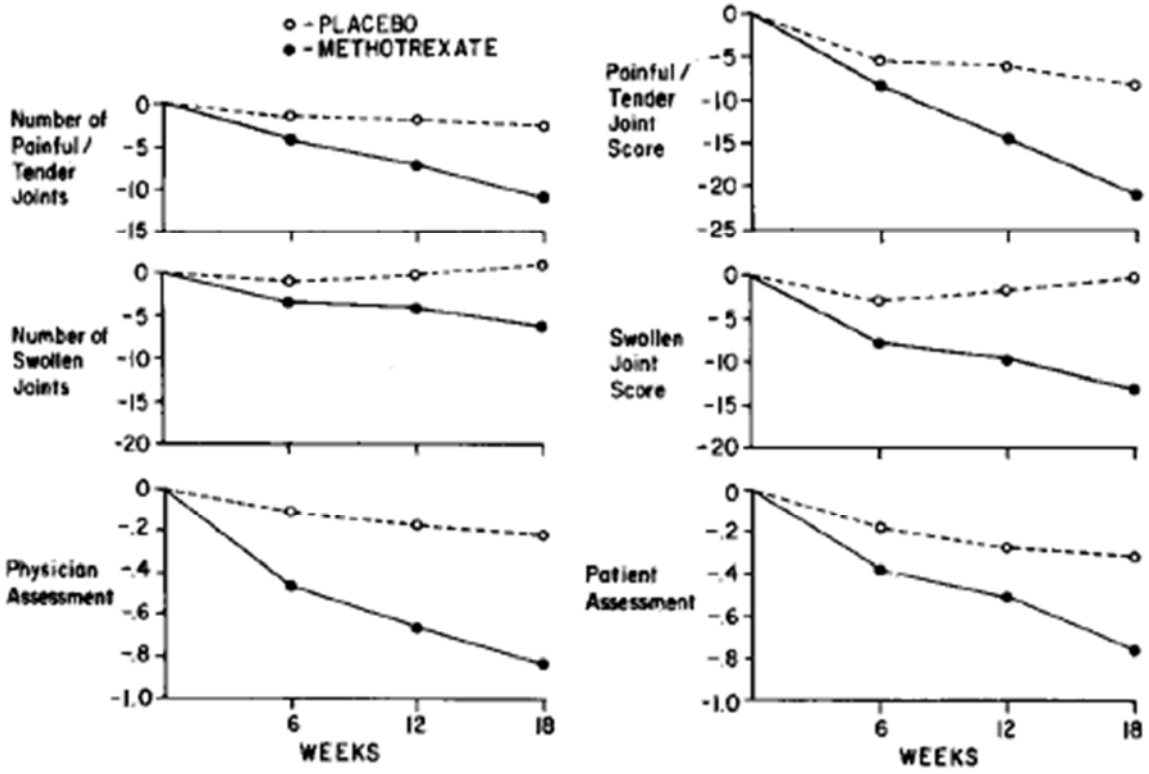
Table 13: Efficacy Analysis of Subjects completing Week 18.

	Treatment	Value at Entry Visit Mean ± SE	Difference at Crossover Visit Mean ± SE	P Value
Number of Swollen joints	MTX (n=56)	24 ± 11	7 ± 9.7	<0.001[a]
	PBO (n=48)	24 ± 12	-1 ± 8.7	
Number of Tender joints	MTX (n=56)	30 ± 12.8	11 ± 12.5	<0.001[a]
	PBO (n=48)	32 ± 13	3 ± 9.5	
Duration of morning stiffness (minutes)	MTX (n=57)	286 ± 308	117 ± 418.3	<0.037[b]
	PBO (n=53)	266 ± 331.9	88 ± 402	
Physician assessment of disease activity (Scale 1-5)	MTX (n=56)	3.3 ± 0.6	0.8 ± 0.9	<0.0002[c]

	PBO (n=48)	3.3 ± 0.8	0.2 ± 0.9	
Patient assessment of disease activity (Scale 1-5)	MTX (n=15)	3.1 ± 0.7	0.8 ± 1	<0.004[c]
	PBO (n=16)	3.2 ± 0.9	0.3 ± 1.1	
Source: Adapted from Williams HJ et al. Arthritis and Rheumatism 1985; 28(7):721-730, Table 3. MTX: methotrexate; PBO: placebo. a: Analysis of covariance; b: Mann-Whitney analysis; c: Mantel-Haenszel chi-square.				

Figure 1 demonstrates the mean change of selected clinical endpoints by study arm at Weeks 6, 12, and 18 weeks of treatment.

Figure 1. Mean Change in Selected Clinical Endpoints at Weeks 6, 12, and 18.



Source: Adapted from Williams HJ et al. Arthritis and Rheumatism 1985; 28(7):721-730, Figure 1.

8.1.1. Integrated Assessment of Effectiveness

Taken together with the plethora of literature published in the previous 40 years, these two clinical studies by Weinblatt et al. and Williams et al. demonstrate the clinically meaningful benefit of MTX therapy in treating subjects with rheumatoid arthritis as evidenced by improvement in the number of swollen and tender joints, duration of morning stiffness, physician's assessment of disease activity, patient's assessment of disease activity, and acute

phase reactants. The clinical endpoints used in these two studies comprise key components of the ACR20 measure which is currently used for approval of drugs used to treat rheumatoid arthritis in the US.

8.2. Review of Safety

The toxicity of MTX is well-characterized given the longevity of its use for a variety of malignant and non-malignant indications. Labeling for JYLAMVO will closely mirror the approved labeling of the RLD, consequently, only an abbreviated overview of MTX-related adverse reactions will be reviewed here based on the data submitted by the Applicant.

8.2.1. Safety Results

The incidence and severity of MTX-related adverse events are typically related to dose, frequency of administration, and the duration of the exposure to significant blood levels of the drug to the target organs. The most frequently reported adverse reactions include ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Indeed, ulcerations of the oral mucosa and gastrointestinal symptoms are usually the earliest signs of toxicity[7]. Other frequently reported adverse effects include malaise, fatigue, chills, fever, dizziness, and decreased resistance to infection.

The most frequently reported dose-related adverse reactions of MTX involve the bone marrow and gastrointestinal tract. Bone-marrow depression can occur abruptly, and leukopenia, thrombocytopenia, and anemia may all occur. The nadir of the platelet and white-blood cell counts is typically five to ten days following a bolus dose, with recovery between approximately 14 to 28 days. Acute and chronic liver damage is also associated with MTX therapy and hepatic fibrosis and cirrhosis may develop without obvious signs of hepatotoxicity. Other adverse effects include renal failure and tubular necrosis after high doses, pulmonary reactions including life-threatening interstitial lung disease, skin reactions, alopecia, and ocular irritation. Other rarer reactions may include megaloblastic anemia, osteoporosis, precipitation of diabetes, arthralgias, necrosis of soft tissue and bone, and anaphylaxis.

Methotrexate may cause defective oogenesis and spermatogenesis, and fertility may be impaired. In most cases, these effects on spermatogenesis/sperm maturation/sexual function are reversible after the discontinuation of the drug[8]. Similar to other folate inhibitors, MTX is a known teratogen, and has been associated with fetal deaths. A possible relationship between

[7] Product Monograph. Methotrexate. 2017; Pfizer Canada Inc.
[8] Semet M and Dayer JM. Andrology. 2017;5(4):640-643.

lymphomas and MTX therapy have also been reported; however, the direct association has been questioned[9].

The following list of adverse reactions by System Organ Class and postmarketing reports were compiled by the Applicant using different sources including the Product Monograph for MTX.

Adverse Reactions by System Organ Class
Hypersensitivity Reactions: Hypersensitivity reactions, including anaphylaxis, can occur with MTX.

Myelosuppression: Methotrexate suppresses hematopoiesis and can cause severe and life-threatening pancytopenia, anemia, leukopenia, neutropenia, and thrombocytopenia.

Gastrointestinal Toxicity: Diarrhea, vomiting, nausea, and stomatitis occurred in up to 10% of patients receiving methotrexate for treatment of non-neoplastic diseases. Hemorrhagic enteritis and fatal intestinal perforation have been reported. Patients with peptic ulcer disease or ulcerative colitis are at a greater risk of developing severe gastrointestinal adverse reactions.

Hepatotoxicity: Methotrexate can cause severe and potentially irreversible hepatotoxicity, including fibrosis, cirrhosis, and fatal liver failure. The safety of methotrexate in patients with hepatic disease is unknown. The risk of hepatotoxicity is increased with heavy alcohol consumption. In patients with psoriasis, fibrosis or cirrhosis may occur in the absence of symptoms or abnormal liver tests; the risk of hepatotoxicity appears to increase with total cumulative dose and generally occurs after receipt of a total cumulative dose of ≥1.5 grams.

Pulmonary Toxicity: Pulmonary toxicity, including acute or chronic interstitial pneumonitis and irreversible or fatal cases, can occur with methotrexate.

Dermatological Reactions: Severe, including fatal dermatologic reactions, such as toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, can occur with methotrexate. Exposure to ultraviolet radiation while taking methotrexate may aggravate psoriasis. Methotrexate can cause radiation recall dermatitis and photodermatitis (sunburn) reactivation.

Renal Toxicity: Methotrexate can cause renal toxicity, including irreversible acute renal failure.

Serious Infections: Patients treated with methotrexate are at increased risk for developing life-threatening or fatal bacterial, fungal, or viral infections, including opportunistic infections such as Pneumocystis jirovecii pneumonia, invasive fungal infections, hepatitis B reactivation,

[9] Martindale. 2020. The Complete Drug Reference: online edition. The Pharmaceutical Press.

tuberculosis primary infection or reactivation, and disseminated Herpes zoster and cytomegalovirus infections.

Neurotoxicity: Methotrexate can cause severe acute and chronic neurotoxicity, which can be progressive, irreversible, and fatal. The risk of leukoencephalopathy is increased in patients who received prior cranial radiation.

Secondary Malignancies: Secondary malignancies can occur with methotrexate. The risk of cutaneous malignancies is further increased when cyclosporine is administered to patients with psoriasis who received prior methotrexate. In some cases, lymphoproliferative disease occurring during therapy with low-dose methotrexate regressed completely following withdrawal of methotrexate.

Tumor Lysis Syndrome: Methotrexate can induce tumor lysis syndrome in patients with rapidly growing tumors.

Increased Risk of Adverse Reactions Due to Third-Space Accumulation: Methotrexate accumulates in third spaces (e.g., pleural effusions or ascites), which results in prolonged elimination and increases the risk of adverse reactions.

8.2.2. Safety in the Postmarket Setting

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of MTX; however, because these adverse events have been reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure:

Cardiovascular: Thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus), pericarditis, pericardial effusion, hypotension, sudden death.

Eye: Optic neuropathy, blurred vision, ocular pain, conjunctivitis, xerophthalmia.

Gastrointestinal: Hemorrhagic enteritis, intestinal perforation, gingivitis, pancreatitis, pharyngitis, hematemesis, melena, gastrointestinal ulceration.

Hematology: Aplastic anemia, lymphadenopathy, hypogammaglobulinemia.

Hepatobiliary: Acute hepatitis, decreased serum albumin, fibrosis, cirrhosis.

Immune system: Anaphylaxis, anaphylactoid reactions, vasculitis

Metabolism: Hyperglycemia

Musculoskeletal: Stress fracture, soft tissue and bone necrosis, arthralgia, myalgia, osteoporosis

Nervous system: Headaches, drowsiness, blurred vision, speech impairment (including dysarthria and aphasia), transient cognitive dysfunction, mood alteration, unusual cranial sensations, paresis, encephalopathy, and convulsions.

Renal: Azotemia, hematuria, proteinuria, cystitis.

Reproductive: Defective oogenesis or spermatogenesis, loss of libido, impotence, gynecomastia, menstrual dysfunction.

Respiratory: Pulmonary fibrosis, respiratory failure, chronic interstitial obstructive pulmonary disease, pleuritic pain and thickening, alveolitis.

Skin: Toxic epidermal necrolysis, Stevens-Johnson syndrome, exfoliative dermatitis, skin necrosis, and erythema multiforme, erythematous rashes, pruritus, alopecia, skin ulceration, accelerated nodulosis, urticaria, pigmentary changes, ecchymosis, telangiectasia, photosensitivity, acne, furunculosis.

8.3. Conclusions and Recommendations

The Applicant has submitted sufficient data based on a thorough review of the published scientific literature and with emphasis to detailed pharmacological monographs including, the RLD, to provide an assessment of the clinical evaluation of MTX use in the treatment of RA.

9 Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was necessary for this application.

10 Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. In consultation with PeRC, DMPH, ORP and OCC, the Agency has determined during pre-submission communications (see Section 3.2 Summary of Presubmission/Submission Regulatory Activity), this proposed NDA application would not trigger PREA.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Proprietary Name
The Applicant's proposed proprietary name, JYLAMVO, was conditionally approved. This name was reviewed by the Division of Medication Error Prevention and Analysis, who concluded that the name is acceptable (DMEPA review dated January 6, 2021).

Other Labeling Recommendations
In view of the recommendation for a Complete Response, the labeling review was deferred until the next review cycle, if applicable.

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable given the Complete Response action.

13 Postmarketing Requirements and Commitment

Not applicable given the Complete Response action.

14 Clinical Division Director/Signatory Comments

The Applicant, Therakind Limited, submitted a 505(b)(2) new drug application (NDA) for methotrexate (MTX) 2 mg/mL oral solution for the following indications.

- 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

The Applicant has referenced Methotrexate 2.5 mg tablets USP (NDA 008085, Dava Pharmaceuticals, Inc.) for this 505(b)(2) NDA. The clinical development program to bridge the proposed MTX oral solution drug product to FDA's finding of clinical efficacy and safety of MTX 2.5 mg tablets includes a phase 1 relative bioavailability (BA) and food-effect study in healthy male subjects (Study MTX003). Based on the data from that study, the Office of Clinical Pharmacology has determined that the Applicant has established adequate scientific bridge to the listed drug and recommended approval of the NDA from a clinical pharmacology perspective. I agree with this assessment and recommendations.

The DRTM team reviewed the data pertinent to the RA indication, the Division of Dermatology and Dentistry team reviewed the data pertinent to the plaque psoriasis indication, and the Division of Hematologic Malignancies I and II teams reviewed the data pertinent to the neoplastic indications. The review teams concluded that the benefit-risk profile of methotrexate for the indications sougth for approval is favorable. The submitted bioavailability data demonstrate bioequivalence between the proposed methotrexate oral solution and the listed drug, methotrexate tablets and support the scientific bridge to the listed drug to rely on the previous findings of safety and effectiveness of methotrexate for the indications sought for approval. Information in the published literature also supports the safety and efficacy of methotrexate in the indications being sought for approval.

However, the CMC review team has identified deficiencies that preclude approval, as detailed in Section 4.2, Product Quality.

Accordingly, the regulatory action for this NDA is Complete Response due to the following deficiencies:

Facility:

(1) 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.

Drug Product:

(2) Include the test for Deliverable Volume per USP <698> "Deliverable Volume" in the drug product specifications.

(3) 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, **and** THE/18/0407) tested at 18 months, failed (THE/17/0331, THE/17/0332). Please provide your course of action to resolve this issue.

(4) 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.

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

(b) (4)

(6) 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.

(7) Revise the post approval stability protocol to include a testing station at 15 months.

(8) 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).

15 Appendices

15.1. References

See footnotes

15.2. Financial Disclosure

The table in this section summarize the financial disclosures from Therakind Ltd for the BE study MTX 003.

Covered Clinical Study (Name and/or Number): MTX003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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/

JIANMENG CHEN
12/17/2021 11:34:55 AM

NIKOLAY P NIKOLOV
12/17/2021 12:41:19 PM

Division of Hematologic Malignancies II Clinical Memo	
NDA	212479
Product	Methotrexate oral solution
Type of application/submission	505(b)(2) NDA
Is proposed labeling in old format?	N
Is labeling being converted to PLR?	N
Is labeling being converted to PLLR?	N
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
Sponsor	Therakind Ltd
Primary Reviewer	Pamela Seam, MD
TL	Nicholas Richardson, MPH, DO
Action Goal Date	12/17/2021

The applicant submitted a 505(b)(2) NDA for Methotrexate oral solution; Methotrexate tablets for oral use (NDA 008085) are the listed drug for this NDA.

The USPI submitted by the applicant was compared to the approved USPI for the listed drug, Methotrexate tablets for oral use, in the context of the proposed indications in mycosis fungoides and relapsed or refractory non-Hodgkin lymphoma, which included highlights, Section 1, Section 2, and Section 5. The proposed labeling sections for the 505b2 are consistent with the listed drug with no differences noted. We have no additional edits or comments for the label in regard to the information relevant to the lymphoma indications.

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/

PAMELA SEAM
12/06/2021 10:55:41 AM
NDA 214121 S-1 MTX consult

NICHOLAS C RICHARDSON
12/06/2021 11:19:35 AM

Medical Officer's Memo-to-File

Division of Dermatology and Dentistry, HFD-540

NDA:	212479
SDN:	5
Stamp date:	3/1/2021
Review date:	12/6/2021
Clinical reviewer:	Hamid Tabatabai, M.D. Division of Dermatology and Dentistry (DDD)
Clinical team leader:	David Kettl, M.D. (DDD)
Project Manager:	Cindy Chee, RPM Division of Rheumatology and Transplant Medicine (DRTM)
Sponsor:	Therakind, Ltd.
Drug:	Jylamvo (Methotrexate)
Dosage Form:	Solution (2 mg/mL)
Route of Administration:	Oral
Pharmacologic Category:	Dihydrofolate Reductase Inhibitor
Indication:	Treatment of certain neoplastic diseases, rheumatoid arthritis, and psoriasis

Summary:
This memorandum of concurrence by the FDA DDD supports the approval of NDA 212479 for the dermatologic indication of treatment of adult patients with severe psoriasis.

NDA 212479 was submitted on 3/1/2021 to the FDA DRTM under the 505(b)(2) regulatory pathway, with reference to the reference listed drug (RLD): NDA 008085 (MTX tablets, USP: Dava Pharmaceuticals). The applicant seeks the indications of treatment of certain neoplastic diseases, rheumatoid arthritis, and severe psoriasis in adult patients.

The application is a 505(b)(2) NDA for JYLAMVO, an oral liquid formulation of Methotrexate (MTX) 2 mg/ml, for the treatment of acute lymphocytic leukemia (ALL), non-Hodgkin's lymphoma, mycosis fungoides rheumatoid arthritis, and psoriasis. The applicant is seeking indication for the liquid form of methotrexate and DDD was asked to comment on the labeling as it relates to the previously approved psoriasis indication.

NDA 212479 includes Clinical Pharmacology study data from bioavailability/bioequivalence (BA/BE) studies (MTX01/02/03). No clinical trial data in subjects with psoriasis was submitted under this NDA for review by the DDD review team, and no dermatologic indications other than "Treatment of adults with severe psoriasis" (consistent with the RLD label) is being sought by the applicant.

Reviewer's Comment:
The Division (DDD) concurs with the approval of this NDA for the indication of "Treatment of adults with severe psoriasis", pending agreement between the applicant and FDA on the final label for Jylamvo (to be appended to the NDA action letter).

The proposed labeling sections for the 505(b)(2) are consistent with the listed drug with respect to the psoriasis indication. We have no additional edits or comments for the label.

Recommended Regulatory Action:
Approval of the NDA, if determined by DRTM to otherwise meet all of the applicable requirements for approval.

Hamid Tabatabai, MD
Medical Officer
CDER/OND/OII/DDD

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/

HAMID N TABATABAI
12/06/2021 03:42:11 PM
DDD Concurrence Memo. for Approval

DAVID L KETTL
12/06/2021 03:44:46 PM

DRTM Consult – DHM1 Clinical Review

From	DRTM
To	DHM1
NDA #	212479
Type of Submission	505(b)(2) NDA
Drug(s)	Methotrexate (JYLAMVO) 2mg/ml oral soln
NDA Sponsor	THERAKIND
Primary Reviewer	Kamar Godder, MD, MPH
Team Leader	Lori Ehrlich, MD, PhD
Division Director	R. Angelo de Claro, MD
Consult Requestor	CHEE, CINDY C.
Requested Completion Date	December 17th, 2021
Labeling Meeting Date	November 17th, 2021

1. Executive Summary:

This is a new 505(b)(2) NDA for JYLAMVO, an oral liquid formulation of Methotrexate (MTX) 2 mg/ml, for the treatment of acute lymphocytic leukemia (ALL), non-Hodgkin's lymphoma, mycosis fungoides rheumatoid arthritis, and psoriasis. The applicant is seeking indication for the liquid form of methotrexate and is submitting a 505(b)(2) application, with reference to the approved Methotrexate tablets (DAVA PHARMACEUTICALS INC, NDA#008085). DHM1 was asked to review the indication for the treatment of adults with ALL as part of a combination chemotherapy maintenance regimen. We concur with the Applicant's plan to include the ALL indication consistent with the reference listed drug. We agree with the Applicant's proposed labeling regarding the ALL indication and have no additional revisions.

2. Regulatory Background

N/A

3. Background and Review of Clinical Data

Study MTX003: The study was designed to determine the bioavailability and evaluate the effect on food on the bioavailability of Jylamvo 2mg/kg oral solution and reference was made to Methotrexate 2.5 mg Tab (NDA 008085) in healthy volunteers. This is single-dose, open-label, laboratory-blind, randomized, three-period, three-sequence crossover study. The study included 27 healthy adults who were given 3 treatments at weekly interval: Study drug (fasting), study drug (fed) and reference drug.

No deaths or IP-related serious adverse events (SAE's) were reported during the study and no AE was of severe intensity. No subjects were withdrawn due to an adverse event (AE). There

was a total of 11 AE's in 7 patients: 4 AE's (4 patients) in MTX tablets, 1 AE (1 patient) in Jylamvo fasting and 5 AE's (2 patients) in Jylamvo fed.

Toxicity of Jylamvo in systems that may be affected by methotrexate:
GI: There were four AEs in 2 patients; two events of nausea and one event of abdominal pain and nausea in each. One patient was fasting, one the other was fed.
Neurology: One patient with headache (mild) Jylamvo fed, unlikely related to the study drug.
Infection: No infections in the Jylamvo groups.
There were not concerning AEs in the renal or hematology systems.

None of the abnormal laboratory findings were reported as AEs and none were considered as clinically significant.

Reviewer's comment:
The clinical data was derived from the CSR and DHM1 did not perform a full review of the clinical data.

4. Labeling review

The following sections in the USPI that are specific to the use of Jylamvo in acute lymphoblastic leukemia were reviewed: Indication and Usage (1.1), Dosage and Administration (2.2), Tumor Lysis Syndrome (5.14), Patient Information.

The proposed label was compared to reference NDA #008085 of Methotrexate Tablets USP, 2.5 mg (DAVA Pharmaceutical Inc.).

1 Indication and Usage

1.1 Neoplastic Diseases

The proposed label reads as follows:

(b) (4)

The reference label reads:

Treatment of adult and pediatric patients with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen (1.1).

Reviewer's comment:

Unlike the indication for Jylamvo, the reference label includes indication for pediatric patients. As per the CSR, a pediatric waiver was submitted to the FDA, however, the FDA informed the sponsor that the product did not trigger PREA. In a Pre-NDA meeting, it was reported that the

sponsor will be seeking their product for adults indication and will exclude from applying for pediatric indications due to the orphan exclusivity granted to Xatmep (methotrexate oral solution, 2.5 mg/mL). The language in the proposed label, including adult patients with acute lymphoblastic leukemia only, is acceptable.

2 Dosage and Administration

2.2 Recommended Dosage for Neoplastic Diseases.

The proposed label reads as follows:

(b) (4)

The reference label reads:

Acute Lymphoblastic Leukemia

The recommended starting dosage of Methotrexate Tablets is 20 mg/m^2 orally once weekly, as part of a combination chemotherapy maintenance regimen. After initiating Methotrexate Tablets, periodically monitor absolute neutrophil count (ANC) and platelet count and adjust the dose to maintain ANC at a desirable level and for excessive myelosuppression.

5.14 Tumor lysis Syndrome:

The proposed label reads as follows:

(b) (4)

The reference label reads:

Methotrexate can induce tumor lysis syndrome in patients with rapidly growing tumors. Institute appropriate prophylactic measures in patients at risk for tumor lysis syndrome prior to initiation of Methotrexate Tablets.

Patient Information.

What is Methotrexate?

The proposed label reads as follows:

(b) (4)

The reference label reads:

Methotrexate is a prescription medicine used: in combination with other chemotherapy medicines in adults and children, for maintenance treatment of acute lymphoblastic leukemia (ALL.)

Reviewer's comment:

All the above proposed sections referencing ALL are identical to the reference label of methotrexate tablets (DAVA), except for the section on indication which includes pediatric patients and discussed above. As such, DHM1 finds all sections of the proposed Jylamvo label that are related to the indication of acute lymphoblastic leukemia acceptable.

5. Recommended Regulatory Action

The clinical review team agrees with the proposed labeling regarding the ALL indication for the 505(b)(2) application for Jylamvo, a methotrexate oral solution, 2 mg/mL, including the indication for the treatment of adults with ALL as part of a combination chemotherapy regimen as summarized in this review.

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/

KAMAR N GODDER
12/01/2021 11:06:45 AM