CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208400Orig1s000
208400Orig2s000

CLINICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Division Of Pulmonary, Allergy, and Rheumatology Products (HFD-570)

APPLICATION:	NDA 208400	**TRADE NAME:**	Xatmep™
APPLICANT/SPONSOR:	Silvergate Pharmaceuticals	**USAN NAME:**	Methotrexate oral solution
MEDICAL OFFICER:	Peter Starke, MD	**CATEGORY:**	Folate analog metabolic inhibitor
TEAM LEADER:	Janet Maynard, MD		
DATE:	March 28, 2017	**ROUTE:**	Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT / OTHER RELEVANT DOCUMENTS

Document Date	CDER Stamp Date	Submission	Comments
June 22, 2016	June 22, 2016	SD-14	Last submitted PI
June 29, 2016			*CR Action letter*
October 25, 2016	October 25, 2016	SD-17	Complete response to CR Action letter
December 6, 2016	December 6, 2016	SD-18	Proprietary Name request
February 6, 2017	February 6, 2017	SD-19	Link to container label (submitted 5/6/2016)
February 27, 2017			*Labeling IR*
March 17, 2017	March 17, 2017	SD-20	Revised labeling

REVIEW SUMMARY:

This is a response to a CR action submitted by Silvergate Pharmaceuticals, Inc., for methotrexate oral solution. From a clinical perspective, the application was approvable in the first cycle; a CR action was taken on June 29, 2016, due to facilities inspection deficiencies. Since the application was not approved, labeling negotiations were not completed in the first cycle. In fact, the applicant had just responded on June 22, 2016, to a late cycle request for additional support for additional data to support PLLR conversion labeling, which represents the first time a methotrexate product has undergone PLLR conversion. However, labeling negotiations will be completed in this cycle.

OUTSTANDING ISSUES:

As of the date of completion of this review, the facilities inspection recommendation is still pending. Therefore, it is unclear whether the application will receive an approval or a CR action in this cycle.

RECOMMENDED REGULATORY ACTION

NDA/SUPPLEMENTS: __X__ **APPROVAL** ____ **COMPLETE RESPONSE**

OTHER ACTION: ____

Introduction and Background

This is a response to a Complete Response (CR) action submitted by Silvergate Pharmaceuticals, Inc., for methotrexate oral solution. The original application, submitted on August 31, 2015, was given a CR action on June 29, 2016, due to facilities inspection deficiencies. Silvergate submitted a complete response on October 25, 2016.

The application is a 505(b)(2) application referencing the agency's previous findings of safety and effectiveness for Methotrexate Sodium Tablets (Dava Pharmaceuticals, Inc., NDA 08085). The development program consisted of 2 studies comparing the bioavailability of the proposed oral solution with Dava's Methotrexate Sodium Tablets; the results showed bioequivalence between the two products.

Although Silvergate could have requested additional indications for this product, they specifically limited themselves to the following two indications: (1) pediatric patients with acute lymphoblastic anemia (ALL), as part of a combination regimen, and (2) the management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full-dose nonsteroidal anti-inflammatory agents (NSAIDs). Both of these are pediatric indications for which the applicant requested and received Orphan Drug designations (ALL: May 28, 2015, 15-4796; pJIA: August 25, 2015, 15-4795) prior to submission of the original application. As a result, Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) was not triggered and a Pediatric Study Plan (PSP) was not required.

The only outstanding issues in this cycle are CMC facilities, labeling, and the Proprietary Name for the product. Since the application was not approved in the first cycle, labeling negotiations were not completed in the first cycle. In fact, the applicant had just responded on June 22, 2016, to a late cycle request for additional support for the proposed PLLR conversion labeling, which represents the first time a methotrexate product has undergone PLLR conversion.

The proposed Proprietary Name for the product is Xatmep™. This name was reviewed and found acceptable by DMEPA in the first review cycle. A request for review of the proprietary name, Xatmep, was resubmitted on December 6, 2016, and was found acceptable by DMEPA on January 18, 2017.

The submission is all electronic and has a standard 6-month review clock with a PDUFA date of April 25, 2017.

CMC

As of the date of completion of this review, the facilities inspection recommendation is still pending. Therefore, it is unclear whether the application will receive an approval or a CR action in this cycle.

Labeling Review

Although labeling negotiations were not completed in the first cycle, the expectation is that they will be completed in this cycle. Labeling was sent to the applicant on February 27, 2017, and the applicant responded on March 17, 2017. Final labeling negotiations are pending as of the date of finalization of this review; as a result, this section summarizes many of the major labeling issues but does not include final labeling.

The proposed PI is in Physician Labeling Rule (PLR) format, whereas the listed product referenced in the application is not. Two recently approved methotrexate auto-injector products are approved in PLR format. As is appropriate, the proposed labeling is also Pregnancy and Lactation Labeling Rule (PLLR) compliant, whereas previously approved products are not. The Pediatric and Maternal Health Team (PMHS) requested additional data to support the proposed PLLR labeling, which was submitted on April 7, 2016, with additional information on June 22, 2016.

During the course of the review, labeling consults were sent to: the Office of Prescription Drug Promotion (OPDP), the Division of Medication Errors and Prevention Analysis (DMEPA), the Division of Pediatric and Maternal Health (DPMH), and to the Office of Regulatory Policy (ORP). ORP helped frame comments to the sponsor regarding changes to the labeling of this product, (b) (5)

This application brought up a number of significant labeling challenges. Please see Virginia Kwitkowski's review from DHP, dated March 20, 2017, for details of labeling issues that were addressed for this product that are not addressed herein.

The major labeling challenges with this application were modification of the language in the PI to be consistent with current labeling practice and to restrict the labeling to that which is appropriate for the dosage form, route of administration, and indications, and having a label in PLR format when the listed reference product is still in non-PLR format. Modifications to the labeling were challenging, as the safety and other information in the current methotrexate labels pertains to all indications, dosages (high-dose treatment regimens and standard dosages), and routes of administration, and it is often difficult to separate out where that information originates and to which indication or dosage it applies. As a result, the clinical and other review teams culled through the proposed PI and removed information not specifically relevant to the limited indications or oral route of administration of this product. For example, information about high-dose methotrexate that can only be achieved with other dosage forms or routes of administration, or information about use in patients with RA or psoriasis, have been deleted. Further, the Dosage and Administration, Warnings, Drug Interactions, and other sections were updated to eliminate scientifically outdated information, thereby providing a more up-to-date and user-friendly label while retaining the critical information needed for safe and effective use.

One of the issues addressed as part of this review was the Indication statement for pJIA. The indication in the Dava tablets reads as follows:

> "Methotrexate is indicated in the management of selected adults with severe, active, rheumatoid arthritis (ACR criteria), or children with active polyarticular-course juvenile rheumatoid arthritis, who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs)."

(b) (5)

(b) (5)

Two small editorial changes were made to the Indication statement. First, since the term 'juvenile rheumatoid arthritis' (JRA) was replaced with the more up-to-date term 'juvenile idiopathic arthritis' (JIA). Second, the term 'children' was replaced with 'pediatric patients', a change that reflects best labeling practice.

With regard to the Dosage and Administration section, DPARP shortened the pJIA subsection to delete extraneous material that does not actually reflect on the safe and effective dosage and administration of methotrexate oral solution for pJIA, while retaining the current dosage recommendations. These changes are primarily editorial and/or decisions about the location and placement of material in the body text of the PI when converting from non-PLR to PLR labeling.

Recommendations

I recommend Approval of this application from a clinical perspective.

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/s/

PETER R STARKE
03/28/2017

JANET W MAYNARD
03/28/2017

CLINICAL REVIEW

Application Type	NDA [505(b)(2)]
Application Number(s)	208400, Original 1
Priority or Standard	Class 2 Resubmission (6 mo)
Submit Date(s)	10/25/2016
Received Date(s)	10/25/2016
PDUFA Goal Date	04/25/2017
Division / Office	DHP & DPARP co-review
Reviewer Name(s)	Virginia Kwitkowski, MS, ACNP-BC
Review Completion Date	03/20/2017
Established Name	Methotrexate Oral Solution
(Proposed) Trade Name	XATMEP
Therapeutic Class	Folate analog metabolic inhibitor
Applicant	Silvergate Pharmaceuticals
Formulation(s)	Oral solution (2.5 mg/mL)
Dosing Regimen	Multiple
Indication(s)	(1) treatment of pediatric patients with acute lymphoblastic leukemia (ALL), as part of a combination regimen, and (2) the management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full-dose nonsteroidal anti-inflammatory agents (NSAIDs).
Intended Population(s)	Pediatric patients

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The initial clinical review of this application was conducted by Dr. Patricia Dinndorf, who concluded in her review dated 05/24/2016 that she recommended approval of the application. No further clinical data was received from the applicant that would change this recommendation. I concur with her initial recommendation.

2 Introduction and Regulatory Background

The text in the asterisked sections is from Dr. Dinndorf's original review.

2.1 Product Information*

Proprietary Name of the Drug Product:	Xatmep Oral Solution
Nonproprietary Name of Drug Product:	Methotrexate Oral Solution
Nonproprietary Name of Drug Substance:	Methotrexate sodium
Dosage Form:	Oral solution
Strength:	2.5 mg/mL (methotrexate)

Each bottle contains 120 mL of the oral solution.

2.2 Tables of Currently Available Treatments for Proposed Indications*

Methotrexate is a component of multi-agent combination chemotherapy regimen for the treatment of acute lymphoblastic leukemia (ALL) and other lymphoid malignancies.

2.3 Availability of Proposed Active Ingredient in the United States

Methotrexate is available in the U.S. in the following formulations:

- Injection (for IV injection) (NDA 040265, Fresenius Kabi and multiple ANDAs)
- Injection (for SQ injection) (NDA 204824, Antares Pharma) & (NDA 205776, MEDAC Pharma
- Tablet (NDA 008085, DAVA Pharms Inc and multiple ANDAs)

2.4 Important Safety Issues With Consideration to Related Drugs*

(copied from DAVA Label 7/15)
Most common adverse reactions reported with oral methotrexate are ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects include malaise, fatigue, chills, fever, dizziness, and decreased resistance to infection.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The original application was submitted in Physicians Labeling Rule (PLR) format as required. Pregnancy and Lactation Labeling Rule (PLLR) labeling was also required by current regulations and the labeling was in the current format but there were limitations in the content. In the original application (received on 08/31/2015), the review team consulted the Divison of Pediatrics and Maternal Health to review the proposed Prescribing Information.

The original prescribing information did not contain all of the available information on the effects of methotrexate exposure during pregnancy, lactation, and reproductive potential in males and females so on 2/25/16, the FDA sent and information request to the Applicant asking them to provide an integrated review of relevant publication on the effects of methotrexate exposure during pregnancy, lactation, and reproductive potential in females and males. We also asked them to update their proposed labeling with these findings.

Several IRs were sent, responses from the Applicant were received, and a teleconference was held with the Applicant to discuss this issue.

During this review clock, DPARP and DHP had met on several occasions to revise the proposed labeling to remove outdated information and include updated and accurate information. The team planned to send labeling to the Applicant upon resubmission.

On 06/22/16, the Applicant submitted the last revised labeling and the requested summary. As the application was moving towards a CR due to facilities deficiencies, no further communications regarding labeling were planned before action.

The original application received a Complete Response letter on 06/29/2016 due to facility deficiencies from an inspection dated (b) (4).

The applicant submitted a response to CR (Class 2 resubmission) on 10/25/2016. The Applicant stated that they believed that the deficiencies identified by FDA have been

resolved because there had been several ANDA products approved that were manufactured in this facility (dates (b) (4)

3 Ethics and Good Clinical Practices

Refer to Dr. Dinndorf's original review dated 5/24/16.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

Refer to Dr. Dinndorf's original review dated 5/24/16.

5 Sources of Clinical Data

Refer to Dr. Dinndorf's original review dated 5/24/16.

6 Review of Efficacy

Efficacy Summary

Refer to Dr. Dinndorf's original review dated 5/24/16.

7 Review of Safety

Safety Summary

In the CR letter, the Applicant was asked to include a safety update as described at 21CFR 314.50(d)(5)(vi)(b).

The Applicant included a safety update in section 1.11.3 of the eCTD.

7.1 Methods

The Applicant conducted a review of published literature between 09/01/15 and 08/31/16 and conducted a search of FAERS for adverse drug experiences involving the use of various MTX formulations from July 2015 through June 2016. (see Section 7.7)

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

No clinical studies were ongoing and no new clinical studies have been initiated with Methotrexate Oral Solution, 2.5 mg/mL, since the initial submission of NDA 208400 on August 31, 2015.

7.7 Additional Submissions / Safety Issues

No nonclinical studies were ongoing and no new nonclinical studies have been initiated with Methotrexate Oral Solution, 2.5 mg/mL, since the initial submission of NDA 208400 on August 31, 2015.

Literature Review:

From the literature search, 8 ALL literature articles were found to be relevant for inclusion in the safety update report discussion. The ALL articles consist of 7 clinical studies, and 1 case report summary.

The Applicant states that "the literature data that were evaluated and summarized as part of this safety update report primarily reflect a potential for adverse events, which have been previously reviewed as part of the NDA 208400 submission and are included in the current draft labeling. However, potential areas for label revision consideration are presented in *Table 1.11.3-1*."

The new adverse reaction relevant to ALL was "mucositis", which is mentioned in Section 10 Overdosage, but not mentioned elsewhere in labeling at this time.

Reviewer Comment: Mucositis is defined as "painful inflammation or ulceration of the mucous membranes anywhere along the gastrointestinal tract". Though this term is not specifically listed in the Adverse Reactions section, it is covered by more specific terms (including 'stomatitis' which is defined as "oral mucositis") that describe various parts of the GI tract affected by mucositis italicized in the list below (currently in the agreed upon labeling):

Gastrointestinal disorders: *Gingivitis*, pharyngitis, *stomatitis,* anorexia, nausea, vomiting, *diarrhea,* hematemesis, melena, *gastrointestinal ulceration* and bleeding, enteritis, pancreatitis

Reviewer Recommendation: I recommend that the term "mucositis" as a broader term of GI ulceration does not need to be added to the XATMEP labeling at this time, because it is already addressed by more specific terms.

FAERS Search:
Per the Applicant, as an additional source of safety data, FAERS was searched for adverse drug experiences involving the use of various MTX formulations. Drug search terms included methotrexate,Otrexup, Rasuvo, Trexall, and Rheumatrex in patients less than 17 years of age. The period searched in the FAERS database was July 2015 through June 2016, which is the latest update available on FDA's website.

In addition to medication and age, search terms included cancer- or chemotherapy-related indications for MTX use. During this 12-month period, 171 cases, which may include more than 1 individual safety report per case, were found with MTX listed as the primary suspect medication for causing the AE.

Eighty-nine of the patients reporting AEs where MTX was the primary suspect were receiving the IT MTX formulation, 47 patients received an unspecified MTX formulation, 31 patients received IV MTX, 2 patients received MTX via PO administration, and 2 patients received MTX via intrathoracic administration. The patient outcome for the majority of cases was "other," followed by hospitalization. Death was reported as the outcome for 21 cases. The outcome was life-threatening for 16 cases and was reported as disability for 2 cases. The age range for the majority of patients was 0 to 9 years (89 patients) with the remainder being 10 to 19 years (82 patients). The 25 most frequently reported adverse reactions reported to FAERS for patients less than 17 years of age are displayed in Figure 1.11.3-2.

The most common AEs reported to FAERS were posterior reversible encephalopathy syndrome, followed by leukoencephalopathy, seizure, and neurotoxicity. Encephalopathy and leukoencephalopathy are expected adverse events in patients taking MTX (Methotrexate package insert, DAVA Pharmaceuticals, 2016). Seizures and neurotoxicity have been reported in patients treated with IV MTX (Methotrexate Injection package insert, Hospira Inc., 2015). Of the 25 most frequently reported AEs in cancer patients less than 17 years of age, 11 of the events are included as (or closely related to) expected events in the RLD Methotrexate Tablets, USP label (Methotrexate package insert, DAVA Pharmaceuticals, 2016) and an additional 2 are included as (or closely related to) expected events in the Methotrexate Injection, USP label (Methotrexate Injection package insert, Hospira Inc., 2015). The remaining 12 events not specified in either of the MTX labels include eyelid ptosis (8 cases), hypertension (7 cases), loss of consciousness, asthenia, treatment failure, and muscular weakness (6 cases each), and abasia, cerebrovascular disorder, electrolyte imbalance, lethargy, inappropriate antidiuretic hormone secretion, and colitis (5 cases each). Therefore, these remaining events occurred in 3% (5 out of 171) to 5% (8 out of 171) of the total cases reported.

Thus, a definitive relationship between the events and MTX cannot be determined.

Furthermore, although both of the MTX labels include a small paragraph on the dosing of MTX for ALL, it does not include any information specific to adverse reaction in ALL studies.

Applicant's Conclusion: "Following a comprehensive review and evaluation of this information, there was no suggestion of any new safety findings and the safety profile of Methotrexate Oral Solution, 2.5 mg/mL, is in concordance with that observed and reported in the MTX clinical program and summarized in the draft label."

Reviewer Conclusion: No new adverse reactions specific to ALL have been identified during this safety review that require inclusion into the revised labeling. The XATMEP labeling (as agreed upon with FDA and Applicant) provides adequate information for the safe and effective use of methotrexate oral solution.

8 Postmarket Experience

Refer to Dr. Dinndorf's original review dated 5/24/16.

9 Appendices

9.1 Literature Review/References

No new literature was identified beyond the review conducted by the Applicant.

9.2 Labeling Recommendations

Multi-disciplinary labeling meetings were held with attendees from DHP and DPARP. This labeling also received input from DPMH, OSE, ORP, and the OND Labeling Development Team. For detailed labeling recommendations and comments, see the review that I archived on 03/07/17.

9.3 Advisory Committee Meeting

No AC was recommended as this is a 505B2 application which has no new clinical data.

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/s/

VIRGINIA E KWITKOWSKI
03/20/2017

ANN T FARRELL
03/20/2017

Clinical Investigator Financial Disclosure
Review Template

Application Number:	NDA 208400
Submission Date(s):	August 31, 2015
Applicant:	Silvergate Pharmaceuticals, Inc.
Product:	Xatmep (methotrexate) Oral Solution, 2.5 mg/mL
Reviewer:	Peter Starke, MD
Date of Review:	July 1, 2016

Covered Clinical Study (Name and/or Number): The clinical pharmacology of this product was assessed in 2 open-label, randomized, single dose, 2-way crossover relative bioavailability studies in healthy adult males, Study SG02-3 and Study SG02-4.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: One principal investigator and eight sub-investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
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 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) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

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/s/

PETER R STARKE
07/01/2016
Clinical Investigator Financial Disclosure form

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208400 original 1
Applicant Name	Silvergate Pharmaceuticals
Date of Submission	August 31, 2015
PDUFA Goal Date	June 30, 2016
Proprietary Name / **Established (USAN) Name**	Xatmep/methotrexate
Dosage Forms / Strength	Oral solution/2.5 mg/mL
Proposed Indication(s)	Treatment of pediatric patients with ALL as a component of a combination chemotherapy maintenance therapy regimen
Action/Recommended Action for NME:	**Complete Response**

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Patricia Dinndorf, MD
Regulatory Health Project Manager	Jessica Boehmer, BA, MBA
Statistical Review	N/A
Pharmacology Toxicology Review	Pedro Del Valle, PhD, Christopher M Sheth, PhD, and John Leighton, PhD
CMC Review/OBP Review	Product Quality Tracy Rogers, PhD, and Donna Christner, PhD, Anamitro Banerjee, PhD
Microbiology Review	N/A
Clinical Pharmacology Review	Salaheldin Hamed, PhD, Bahru Habtemariam, PhD and NAM Atiqur Rahman, PhD
DDMAC	N/A
OSI	N/A
CDTL Review (same as primary review)	Albert Deisseroth, MD, PhD
OSE/DMEPA	N/A

Signatory Authority Review Template

1. Introduction

This application is a 505(b)(2) NDA submitted by Silvergate Pharmaceuticals, Inc. requesting the approval of Xatmep (methotrexate oral solution, 2.5 mg/mL) for the treatment of pediatric patients with acute lymphoblastic leukemia (ALL), as part of a combination regimen (original 1 indication and subject of this review), and the management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy, including full-dose nonsteroidal anti-inflammatory agents (original 2 indication).

2. Background

This is a 505 (b) (2) application. The RLD is NDA 008085.

3. CMC/Device

The facilities inspection uncovered a number of deficiencies precluding approval. The Withhold recommendation is dated 6/17/2016.

4. Nonclinical Pharmacology/Toxicology

The applicant referenced the RLD (NDA 008085). No new information was submitted.

5. Clinical Pharmacology/Biopharmaceutics

From the Clin Pharm review for the submission:

To support this NDA, the applicant submitted results of a relative bioavailability study where the oral solution formulation was compared to the immediate release tablet formulation, the reference listed drug (RLD). The applicant also conducted a food effect study where the proposed oral solution was administered with or without food. Results from the two studies showed that the proposed oral solution formulation and the immediate release tablets, at a 2.5 mg dose, have similar area under the curve (AUC) and maximum plasma concentration (CMAX) and that administration with tablets, at a 2.5 mg dose, have similar area under the curve (AUC) and maximum

plasma concentration (CMAX) and that administration with food reduces the CMAX of the oral solution formulation by 50%.

No issues that would preclude approval were identified. The Clinical Pharmacology Review recommended approval.

6. Microbiology

No issues were identified that would preclude approval except for the issues identified during the facilities' inspection.

7. Clinical/Statistical-Efficacy

The clinical team reviewed the application concentrating on the oral bioavailability study and published literature and recommend approval.

8. Safety

No new safety issues were identified during the review of this portion of the application.

9. Advisory Committee Meeting

N/A

10. Pediatrics

This product when approved will have two pediatric indications.

11. Other Relevant Regulatory Issues

None

12. Labeling

N/A

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action

Complete Response based on the facilities assessment

- Risk Benefit Assessment

N/A

- Recommendation for Post marketing Risk Management Activities

N/A

- Recommendation for other Post marketing Study Requirements/ Commitments

N/A

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/s/

JESSICA L BOEHMER
06/29/2016

ANN T FARRELL
06/29/2016

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sarah Yim, M.D. Supervisory Associate Director Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Subject	Division Summary Review
NDA/BLA # **Supplement #**	NDA 204800 Original 1 (reviewed by Division of Hematology Products, DHP) Original 2 (reviewed by DPARP)
Applicant Name	Silvergate Pharmaceuticals, Inc.
Date of Submission	August 31, 2015
PDUFA Goal Date	June 30, 2016
Proprietary Name / Established (USAN) Name	Xatmep/Methotrexate oral solution
Dosage Forms / Strength	2.5 mg/mL oral solution
Proposed Indication(s)	Original 1 Indication: Treatment of pediatric patients with acute lymphoblastic leukemia (ALL), as part of a combination regimen Original 2 Indication: Management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full-dose non-steroidal anti-inflammatory agents (NSAIDs)
Action:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
CDTL Review	Janet Maynard, M.D., M.H.S.
Medical Officer Review	DPARP: Peter Starke, M.D.; DHP: Patricia Dinndorf M.D.
Statistical Review	Gregory Levin, Ph.D.
Pharmacology Toxicology Review	For DHP: Pedro Del Valle, PhD, Christopher Sheth, PhD; For DPARP: Andrew Goodwin, PhD, Timothy Robison, PhD
CMC Reviews	DS/DP/EA: Sam Bain; Process: Yetao Jin; Microbiology: Wendy Tan; Facility: Ebern Dobbin; ORA: Paul Perdue; Biopharmaceutics: Banu Zolnik; Regulatory Business Process Manager: Rabiya Laiq; Application Technical Lead: Anamitro Banerjee; Laboratory (OTR): Lucinda Buhse

Clinical Pharmacology Review	For DHP: Salaheldin Hamed, PhD, Bahru Habtemariam Ph.D.; For DPARP: Manuela Grimstein, PhD, Anshu Marathe, PhD
OSE/DMEPA	Rhiannon Leutner, PharmD, MPH, MBA; Yelena Maslov, PharmD

OND=Office of New Drugs CMC=Chemistry, Manufacturing, Controls CDTL=Cross-Discipline Team Leader
OSE=Office of Surveillance and Epidemiology DMEPA=Division of Medication Error Prevention and Analysis

1. Introduction

This is a 505(b)(2) new drug application (NDA) for an oral methotrexate (MTX) solution. The oral solution contains 2.5 mg of methotrexate per milliliter and is packaged in a 120 mL bottle.

Methotrexate tablets have been marketed since December of 1953 (NDA 08085, DAVA) when the product was approved for the treatment of acute leukemia in adults. In addition to tablets, methotrexate is approved as an injection (NDA 11719; approved 1959; Hospira) for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intra-thecal (IT) administration. Two methotrexate autoinjector products (NDA 204824; approved 2013; Antares Pharma, Inc. and NDA 205776; approved 2014; Medac Pharma, Inc.) are approved for SC administration. Methotrexate is currently available in 2.5 mg tablets (multiple companies), and 5, 7.5, 10, and 15 mg tablets (Barr). Injectable methotrexate is available from multiple companies in varying quantities of 25 mg/mL solution. Methotrexate autoinjectors are available in a variety of fixed doses.

At the time of submission of this NDA, approved indications and routes of administration for methotrexate included neoplastic diseases (oral, intramuscular, intravenous, intra-articular, and intra-thecal routes), rheumatoid arthritis (oral and subcutaneous routes), polyarticular juvenile idiopathic arthritis (oral, intramuscular, and subcutaneous routes), and severe psoriasis (oral, intramuscular, subcutaneous, and intravenous routes). Of note, polyarticular juvenile idiopathic arthritis (pJIA) was previously called polyarticular juvenile rheumatoid arthritis (JRA). In this review, it will be referred to as pJIA, recognizing that some methotrexate products still have labeling that uses the previous terminology, which is JRA.

In this NDA, the Applicant is seeking approval of their product for treatment of pediatric patients with acute lymphoblastic leukemia (ALL), as part of a combination regimen and management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full-dose non-steroidal anti-inflammatory agents (NSAIDs). This application was administratively split into Original 1 for the ALL indication and Original 2 for the pJIA indication. This review will focus on the data relevant to Original 2 and the Division of Hematology Products (DHP) will separately review Original 1.

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

- The Agency's previous findings of safety and effectiveness of methotrexate in children with JRA/JIA for the listed drug, Methotrexate Sodium Tablets (NDA 008085, DAVA Pharmaceuticals, Inc.)

- One comparative bioavailability (BA) study comparing the proposed oral solution with Dava's methotrexate sodium tablets and one food-effect study to evaluate methotrexate oral solution in the fasted and fed state
- Information in the published literature supporting the safety and efficacy of methotrexate for pJIA

The primary data to support this NDA submission and approval for pJIA is from the BA study comparing the proposed methotrexate oral solution to oral methotrexate (SG02-03). The applicant also performed and submitted a relative BA study to evaluate the effect of food on the absorption of the proposed methotrexate oral solution formulation (SG02-04).

2. Background

Regulatory History

The Applicant had two meetings with the Division of Hematology Products (DHP) prior to submission of their application. A pre-IND meeting (IND 117387) was held on May 21, 2013 (meeting minutes dated May 21, 2013) to discuss the clinical development plan for methotrexate oral solution. The Applicant proposed a 505(b)(2) application with reference to the Agency's previous finding of safety and effectiveness of the DAVA Methotrexate Tablets. In addition, the Applicant proposed a randomized, parallel, single-dose pivotal comparative bioavailability (BA) study of its methotrexate product to DAVA's Methotrexate Sodium 2.5 mg tablet in 60 healthy adult male subjects. In general, the Applicant's proposal was felt to be reasonable, but the Applicant was given recommendations regarding the timing and type of assessments needed in the BA study.

A Type C (CMC) meeting was held on April 7, 2105 (meeting minutes dated April 14, 2015). The purpose was to discuss the requirements for a methotrexate oral solution regarding the active pharmaceutical ingredient and drug product specifications, as well as the stability requirements for submission.

On May 28, 2015, the Applicant was granted orphan designation for methotrexate oral solution for treatment of acute lymphoblastic leukemia in pediatric patients (0 through 16 years of age).

On August 27, 2015, the Applicant was granted orphan designation for methotrexate oral solution for treatment of oligoarticular juvenile idiopathic arthritis (persistent oligoarthritis, psoriatic juvenile idiopathic arthritis, enthesitis-related arthritis, or undifferentiated arthritis) and polyarticular juvenile idiopathic arthritis in children 0 through 16 years of age.

3. CMC/Device

Drug substance

Methotrexate Sodium is a yellow to orange crystalline powder. It is freely soluble in water, slightly soluble in ethanol, and practically insoluble in chloroform. The pH of an aqueous solution (1%w/v) is 7.0 to 9.0. It is hygroscopic and shows no polymorphism. The structure of Methotrexate Sodium contains one asymmetric carbon atom, located in the glutamic acid side chain. (b) (4) The applicant has referred to the DMF (b) (4) for the drug substance. The DMF was reviewed on February 09, 2016 and was found to be adequate.

Drug product

The drug product is a clear, yellow to orange colored, oral solution. The strength is 2.5 mg/mL of methotrexate (120 mL total volume). (b) (4) (b) (4) (b) (4) (b) (4) (b) (4). The HDPE bottles were chosen (b) (4). The product contains 2.74 mg/mL of methotrexate sodium, equivalent to 2.5 mg/mL (b) (4). The excipients include citric acid (b) (4) USP, sodium citrate (b) (4) USP, methylparaben sodium USP, propylparaben sodium USP, sucralose NF, sodium hydroxide (b) (4) NF, hydrochloric acid (b) (4) NF, and purified water. All excipients are compendial. No excipient is of human or animal origin. No novel excipients are used.

The container closure is a 150 cc (b) (4), white HDPE bottle capped with a (b) (4) white cap with a (b) (4) induction seal.

The applicant has proposed a 24 months expiration dating period when stored at 5±3ºC.

Facilities Inspection

The drug substance manufacturing facility was inspected in (b) (4) and had multiple inspections dating back through (b) (4) that were acceptable. Therefore no prior approval inspection was determined to be necessary for this application. However, based on inspection of the drug product manufacturing and packaging facility in (b) (4), the facility status is Official Action Indicated, and satisfactory resolution of deficiencies is required before the application may be approved. Therefore the Office of Pharmaceutical Quality's overall recommendation is withhold approval on this NDA.

4. Nonclinical Pharmacology/Toxicology

No nonclinical studies were submitted or required for this application. There are no nonclinical issues precluding approval.

5. Clinical Pharmacology/Biopharmaceutics

Study SG02-03 evaluated the PK of the proposed oral solution product in comparison to 2.5 mg immediate release oral tablets. The study was a randomized, open-label, single-dose, two-period, two-treatment, two-way crossover study in 31 healthy adults. The reported results indicate that methotrexate C_{MAX} and AUC of the proposed oral solution are similar to those of the immediate release tablet. The geometric mean ratio test (oral solution) to reference (tablets) along with the 90% confidence interval fell within 80% to 125%.

This study was conducted at the lower dose of 2.5 mg. Although this is lower than the typical therapeutic doses of methotrexate, and methotrexate exhibits saturable absorption when given orally at higher doses (i.e., >30 mg/m^2), the applicant provided a literature reference[1] demonstrating that intravenous methotrexate prepared as an oral solution has comparable exposure to that of methotrexate tablets up to doses of 25 mg/m^2. Therefore, the relative BA findings at 2.5 mg dose were considered to be likely representative of the relative BA of methotrexate at recommended doses for ALL (20 mg/m^2) and JIA (up to 30 mg/m^2/wk).

Study SG02-04 evaluated the effect of food on the relative BA of the proposed methotrexate oral solution formulation. The study was a randomized, open-label, single-dose, two-period, two-treatment, two-way, crossover study in healthy adults. The reported results also indicate that food intake reduces C_{MAX} and delays median T_{MAX} (range) from 0.83 h (0.5-1) in the fasted state to 2 h (0.66-4) in the fed state. The food effect finding, where food is shown to reduce the C_{MAX} of the oral solution formulation, is consistent with the effect of food on the tablet formulation, as per listed product labeling and the published literature[2].

The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection at (b) (4). The inspection was conducted in support of review of this application in addition to other applications. The analytical portions of the bioequivalence study (Methotrexate Pediatric Oral Solution 4002745; Protocol #SG02-04) were audited during the inspection. No deficiencies were observed and the data from the bioequivalence study were considered acceptable for review.

6. Clinical Microbiology

No clinical microbiology data were submitted or required for this application.

7. Clinical/Statistical-Efficacy

Oral methotrexate tablets are already approved for the indication of polyarticular-course juvenile rheumatoid arthritis (now known as polyarticular juvenile idiopathic arthritis or pJIA). Given that Silvergate's oral methotrexate solution has been demonstrated to have similar exposure to oral methotrexate tablets, efficacy data are not needed to support approval of the oral methotrexate solution for pJIA. Nonetheless, the existing efficacy data in the literature for

[1] Harvey VJ, et al. Cancer Chemother Pharmacol 1984;13:91-4.
[2] Cronstein BN. Pharmacol Rev 2005;57(2):163-72.

methotrexate in pJIA were submitted and were reviewed. No concerns about the efficacy of methotrexate in pJIA were identified.

8. Safety

The toxicity of methotrexate is well characterized given its long history of use for a variety of malignant and non-malignant indications. The most common toxicities are gastrointestinal toxicities, such as nausea, stomatitis, and gastrointestinal upset. Other potential serious toxicities with methotrexate include myelosuppression, pulmonary toxicities, and hepatotoxicity. Based on these concerns, it is standard practice to get baseline liver enzymes, creatinine, and complete blood count. In addition, folic acid is given to reduce the incidence of GI toxicity and bone marrow suppression. Regular monitoring of liver enzymes, creatinine, and blood count is performed for the duration of therapy.[3]

The safety experience specific to the methotrexate oral solution is limited to two single-dose bioavailability studies, Study SG02-3 and Study SG02-4. The total dose of methotrexate administered in these studies was 5 mg (2.5 mg in each study period). There were no serious adverse events or deaths. Based on these limited data, no new safety signals were identified.

9. Advisory Committee Meeting

Methotrexate is not a new molecular entity and no issues were identified that would warrant discussion at an Advisory Committee (AC) meeting; therefore no AC meeting was convened.

10. Pediatrics

This application is exempt from the requirements of the Pediatric Research Equity Act (PREA), because the applicant received orphan drug designation for "the treatment of acute lymphoblastic leukemia in pediatric patients (0 through 16 years of age)," and "treatment of oligoarticular juvenile idiopathic arthritis (persistent oligoarthritis, psoriatic juvenile idiopathic arthritis, enthesitis-related arthritis, or undifferentiated arthritis) and polyarticular juvenile idiopathic arthritis in children 0 through 16 years of age."

11. Other Relevant Regulatory Issues

As noted in Section 3 above, there are unresolved issues pertaining to the facilities inspection that preclude approval of this application. There are no other unresolved relevant regulatory issues.

[3] Visser K, et al. Ann Rheum Dis 2009;68:1086-93.

12. Labeling

- **Proprietary name:** "Xatmep" conditionally found to be acceptable.
- **Physician labeling:** Labeling for methotrexate oral solution will be Physician's Labeling Rule (PLR) format, and would also be required to comply with new Pregnancy and Lactation Labeling Rule (PLLR) format requirements, but will not be completed this cycle.
- **Carton and immediate container labels:** Revisions were recommended, but final carton and container labeling will not be completed this cycle.
- **Patient labeling/Medication guide:** A medication guide was not proposed or required. Final patient labeling will not be completed this cycle.

13. Decision/Action/Risk Benefit Assessment

- **Regulatory Action**

The action on this application will be Complete Response

- **Risk Benefit Assessment**

The risk-benefit profile of methotrexate, which is already approved for pJIA, remains favorable. However, Silvergate's oral methotrexate solution cannot be approved until deficiencies in the manufacturing facilities have been determined to be resolved.

- **Postmarketing Risk Evaluation and Mitigation Strategies**

Not applicable.

- **Other Postmarketing Requirements and Commitments**

Not applicable.

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/s/

SARAH K YIM
06/29/2016

Cross Disciplinary Team Lead Review

Date	June 9, 2016
From	Albert Deisseroth, MD, PhD
Subject	Cross Disciplinary Team Lead Review (CDTL)
NDA Number	208400
Applicant	Silvergate Pharmaceuticals, Inc
Date of Submission	August 31, 2015
PDUFA Goal Date	June 30, 2016
Proprietary Name/Trade Name	Methotrexate/Xatmep
Dosage Regimen	20 mg/m^2/week po
Approved Indications	Treatment of pediatric patients with ALL as a component of a combination chemotherapy maintenance therapy regimen
Recommendation:	Complete Response (Non-Approval)

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Patricia Dinndorf, MD
Clinical Pharmacology	Salaheldin Hamed, PhD, Bahru Habtemariam, PhD and NAM Atiqur Rahman, PhD
Pharmacology/Toxicology (DHOT, OHOP, OND)	Pedro Del Valle, PhD, Christopher M Sheth, PhD, and John Leighton, PhD
Product Quality	Tracy Rogers, PhD, and Donna Christner, PhD, Anamitro Banerjee, PhD
Project Manager	Jessica Boehmer

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1. EXECUTIVE SUMMARY: (This section was derived in part from the review of Dr. Patricia Dinndorf. For details, please see her review).

Methotrexate (tablets) was originally approved by the FDA on December 7, 1953 for the indication: Treatment of pediatric patients with ALL as a component of a combination chemotherapy maintenance therapy regimen. On August 31, 2015, Silvergate Pharmaceuticals, Inc. submitted NDA 208400 in which approval of an oral solution of methotrexate (Xatmep) as a 505(b)(2) was requested for the same indication on the basis of two bioavailability clinical trials: one for fasted individuals (SG02-03) and one for fed individuals (SG02-04).
Risk Benefit Assessment: The Risk Benefit assessment is presented below in Table 1.

Table 1: Risk Benefit Assessment

Decision Factor	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood with a peak incidence at the age of 3 years.	**Summary of evidence:** Oral methotrexate has been an integral component of ALL therapy since it was approved in 1953. Successive clinical trials have demonstrated its contribution to successful maintenance therapy and improved survival of patients with ALL.	**Conclusions (implications for decision):** 1. A formulation that provides more accurate dosing is a significant contribution to ALL therapy, especially in younger patients unable to swallow pills. 2. An alternative formulation also ensures better drug availability in the event of a drug shortage.
Unmet Medical Need Oral methotrexate is a component of maintenance chemotherapy for ALL. The 2.5 mg tablet or oral administration of methotrexate for injection are not ideal formulations for younger children or children who have difficulty swallowing pills.	**Summary of evidence**: • The solution is an appropriate formulation for young children or children who have difficulty swallowing pills. • The formulation of an oral solution of 2.5 mg/ml is an appropriate presentation of a medicine for children who are receiving doses of 20 to 40 mg/m^2 weekly. • The dose of methotrexate is modified to maintain an absolute neutrophil count (ANC) between 500 to 1500/µL and platelet count > 75,000/	**Conclusions (implications for decision):** The methotrexate solution is an appropriate formulation which is superior to the 2.5 mg tablet or use of methotrexate for injection orally, especially for children less than 5 years of age. The solution is a superior presentation to pills to allow dose adjustments.

	µL. The oral solution is a formulation that facilitates dose adjustments.	
Clinical Benefit See Unmet Medical Need		
Risk No risk in excess of the available tablet formulation	**Summary of evidence**: The solution is a superior presentation for children it allows straightforward provision of the appropriate dose.	**Conclusions (implications for decision):** This is a superior presentation compared to tablets for children who have difficulty swallowing pills.
Risk Management Ensure caregivers have adequate instructions to accurately measure and administer the correct dose	**Summary of evidence**:	**Conclusions (implications for decision):** 1. Label information and a Med Guide to provide instructions for correct administration
Benefit-Risk Summary and Assessment Xatmep is a superior presentation of methotrexate for children unable to swallow tablets. This formulation provides a superior presentation to tablets that are broken, crushed or extemporaneously formulated.		

Regulatory Recommendation: While the above discussion in Table 1 might lead to a recommendation for approval, the observations made at the manufacturing site by the FDA (see Section 3 below) leads this Cross Disciplinary Team Lead Reviewer to recommend non-approval (Complete Response).

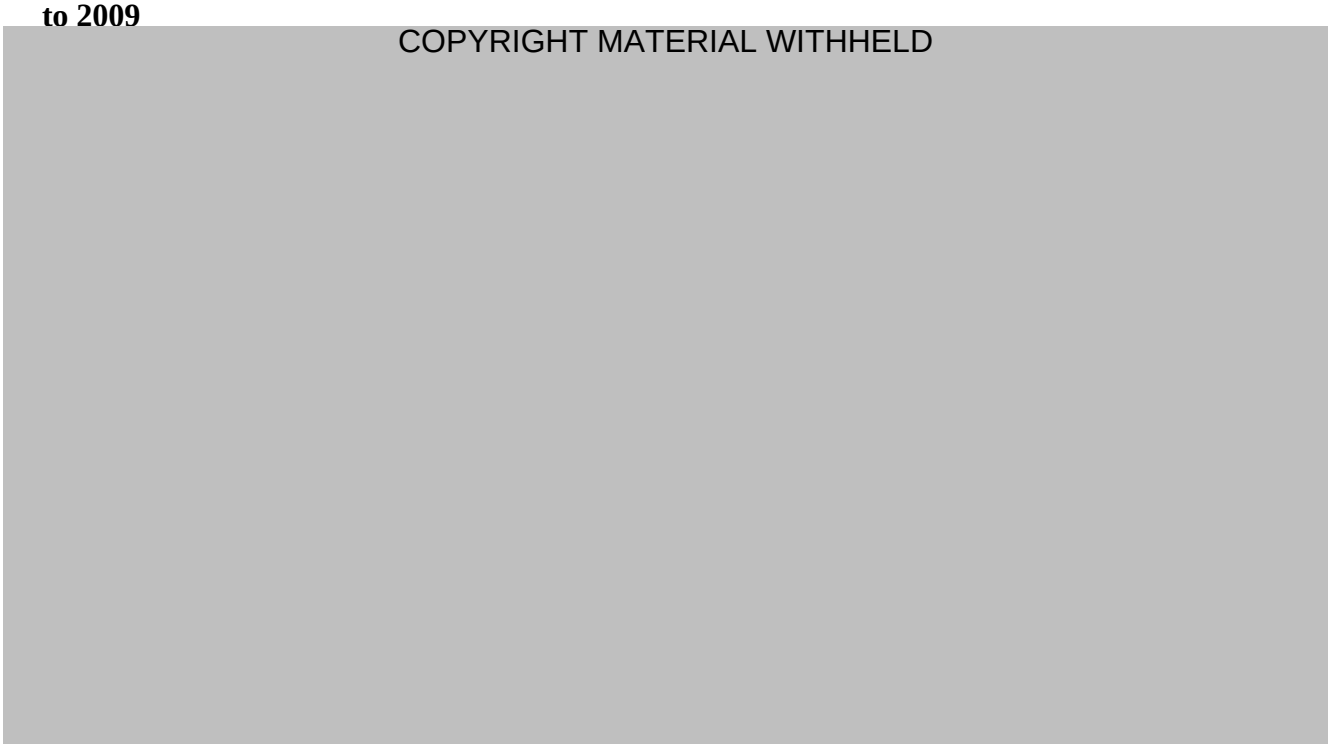
2. BACKGROUND: (This section was derived in part from the review of Dr. Patricia Dinndorf. For details, please see her review).

2A. Acute Lymphocytic Leukemia (ALL): ALL is the most common form of cancer in children and young adults. With current therapies the overall survival rate is over 85%. Successful treatment of children and young adults with ALL involves administration of a multi-drug regimen that that that are administered in several distinct phases, including induction, consolidation, delayed intensification and maintenance.

The first description of temporary remissions reported in children with ALL were induced by aminopterin, an anti-folate closely related to methotrexate (Farber 1948). Methotrexate, an antifolate related to aminopterin, began to replace aminopterin in the 1950s because of a more favorable toxicity profile. Continued improvement in survival in patients with ALL was achieved by the introduction of multi-agent chemotherapy regimens evaluated in cooperative group randomized trials. As prognostic factors were identified trials subsequent trials included stratification of treatment intensity according to the clinical features of the patient, the biologic

features of the leukemia cells, and the early response to treatment. Collectively, these advances have increased the survival rate from less than 10% in the 1960s to greater than 90% with current therapies. See **Figure 1**. (Hunger 2015).

Figure 1: Survival of Successive Cohorts of Patients with ALL in COG Clinical Trials 1968 to 2009



Current therapy (derived from Hunger 2015)

The basic components of contemporary therapies for children and young adults with ALL include induction therapy which lasts 4 to 6 weeks and includes a glucocorticoid (prednisone or dexamethasone), vincristine, an asparaginase preparation, optional use of an anthracycline, and intrathecal chemotherapy. Almost all patients attain remission, but this is not a cure, since relapse will occur universally without additional therapy.

After induction of remission, treatment includes 6 to 8 months of intensive combination chemotherapy that is designed to consolidate remission and prevent development of overt CNS leukemia. Treatment in an 8 week delayed intensification phase, based on the 8 week Berlin–Frankfurt–Münster protocol (Riehm 1980), is then administered. Repeated courses of intravenous methotrexate, administered either through short intravenous infusion or at high doses over 24 hours followed by administration of folinic acid to "rescue" normal tissues from toxic effects, are a critical component of this intensification therapy utilized in contemporary ALL regimens.

Patients then begin maintenance therapy low intensity "anti-metabolite" based therapy for 18 to 30 months. This therapy consists of daily oral mercaptopurine or thioguanine and weekly oral methotrexate. Some regimens also include periodic 5 to 7 day "pulses" of glucocorticoids and

vincristine. The exact reasons why maintenance therapy is required and the most effective composition and duration of chemotherapy are unknown.

The current open protocol in the Children's Oncology Group (COG) for the treatment of B-lineage ALL is comparing 2 doses of oral methotrexate during maintenance, 20 mg/m²/week (standard) and 40 mg/m²/week (experimental). During the course of maintenance therapy, the dose of oral methotrexate is adjusted to maintain an absolute neutrophil count (ANC) ≥ 500 /μL and < 1500/μL and a platelet count ≥ 50,000/μL.

2B. Regulatory History: The regulatory history of methotrexate is summarized in Table 2.

Table 2: Regulatory History

Regulatory History		
Date	**Item**	**Discussion**
5/21/13	Pre-IND Meeting	• Sponsor plans to reference nonclinical section of DAVA methotrexate to support 505(b)(2) • FDA response - in general acceptable
		• Sponsor plans to conduct a randomized, parallel, single-dose pivotal comparative bioavailability study of its methotrexate product to DAVA's Methotrexate Sodium 2.5-mg Tablet in 60 healthy adult male subjects under fasted condition to assess bioequivalence. • FDA response – o In general acceptable o PK sampling inadequate o Must assess food effect
		• Sponsor plans to use the 80-125% bounds for the bioavailability study. • FDA – noted no objection
		• Sponsor plans to restrict label indication to the pediatric population • FDA response – no objection
11/7/14	IND 117387	Methotrexate Pediatric Oral Solution Original protocol submitted to IND on 10/9/14 as discussed at Pre IND meeting was the parallel trial in 60 subjects. On 10/17/14 the sponsor queried the agency concerning revising the protocol to a crossover design in 30 subjects. FDA informed sponsor a second protocol could be submitted after the 30 day letter had been issued for the current submission.
11/21/14	New protocol IND 117387 submitted	SG02-03 with cross-over design (n=34) with the same dose and PK time points as SG02-01 was submitted. The clinical pharmacology reviewer determined the protocol was acceptable.
4/4/15	Type C CMC Meeting	To discuss CMC requirements for a methotrexate pediatric oral solution regarding the active pharmaceutical ingredient and drug product specifications, as well as the stability requirements for submission of the 505(b)(2) NDA.
5/28/15	Orphan Designation (15-4796)	Treatment of ALL in pediatric patients The oral solution is an improved presentation making it superior to the currently available methotrexate tablets and injectable formulations approved for use in pediatric patients with ALL.
8/28/15	Orphan Designation (15-4795)	Treatment of oligoarticular JIA (which includes persistent oligoarthritis, psoriatic JIA, enthesitis-related arthritis, or undifferentiated arthritis) and polyarticular JIA pediatric patients The oral solution is an improved presentation making it superior to the currently available methotrexate tablets and injectable formulations approved for use in pediatric

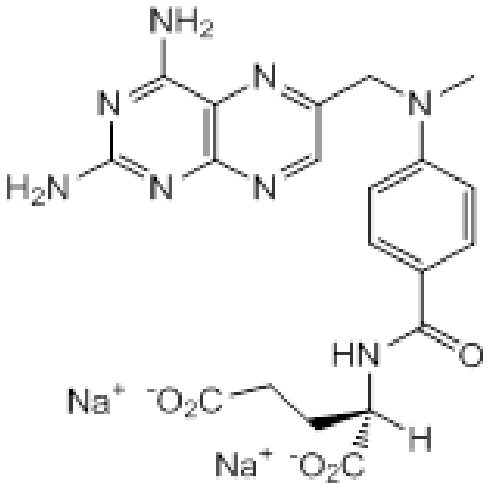
		patients with ALL.
8/31/15	NDA 208400 submitted	

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC):

Drug Substance:

- DMF (b) (4) is referenced, adequate
- Methotrexate Sodium is a yellow to orange crystalline powder.
- It is freely soluble in water.

Figure 2: Methothrexate Structure



Drug Product:

- Methotrexate Oral Solution, 2.5 mg/mL, is a ready-to-use aqueous solution, which is a clear, yellow to orange colored.
- In addition to the API, methotrexate sodium, the drug product contains citric acid, sodium citrate, methylparaben sodium, propylparaben sodium and sucralose, (b) (4) water.
- The pH of the product is adjusted (b) (4) with NaOH and HCl

Clinical Microbiology: (copied from midcycle meeting slides)

The following issues were identified at the midcycle meeting:

- The applicant needs to provide data from Antimicrobial Effectiveness studies using the drug product formulated with the (b) (4) content (i.e. (b) (4) %) established in the release or stability specifications

- Non-sterile aqueous drug products may potentially be contaminated with organisms in the Burkholderia cepacia complex (BCC). In order to control for the presence of BCC in the product, the applicant should:
    - identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product.
    - Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC.

Observations During Inspection of the Manufacturing Facility of the (b) (4) (b) (4). On the following dates (b) (4), (b) (4) the (b) (4) manufacturing facility in (b) (4) was inspected by the FDA and the following observations (see Observations 1-7 listed below) were made:

OBSERVATION 1:

(b) (4)

OBSERVATION 2:
Equipment and utensils are not cleaned and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

OBSERVATION 3:
Buildings used in the manufacturing, processing and packing of a drug product are not maintained in a good state of repair.

OBSERVATION 4:
Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

OBSERVATION 5:
The responsibilities and procedures applicable to the quality control unit are not fully followed.

OBSERVATION 6:
There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

OBSERVATION 7:
Written production and process control procedures are not documented at the time of performance.

Regulatory Recommendation: On the basis of these deficiencies uncovered at the manufacturing site, the recommendation of the CMC group is Complete Response.

4. CLINICAL PHARMACOLOGY: (This section was excerpted from the reviews of Dr. Salaheldin Hamed, and Dr. Bahru Habtemariam. For details, please see their review)

A. Mechanism of Action: Methotrexate is a folic acid analogue. Methotrexate inhibits purine and pyrimidine synthesis.

B. Pharmacodynamics: Rely on reference product.

C. Pharmacokinetics: (copied from midcycle meeting slides). The Applicant submitted two trials: SG02-03 and SG02-04. The pivotal trial SG02-03 was a bioequivalence study and SG02-04 was a food effect study.

Summary of Results of SG02-03:

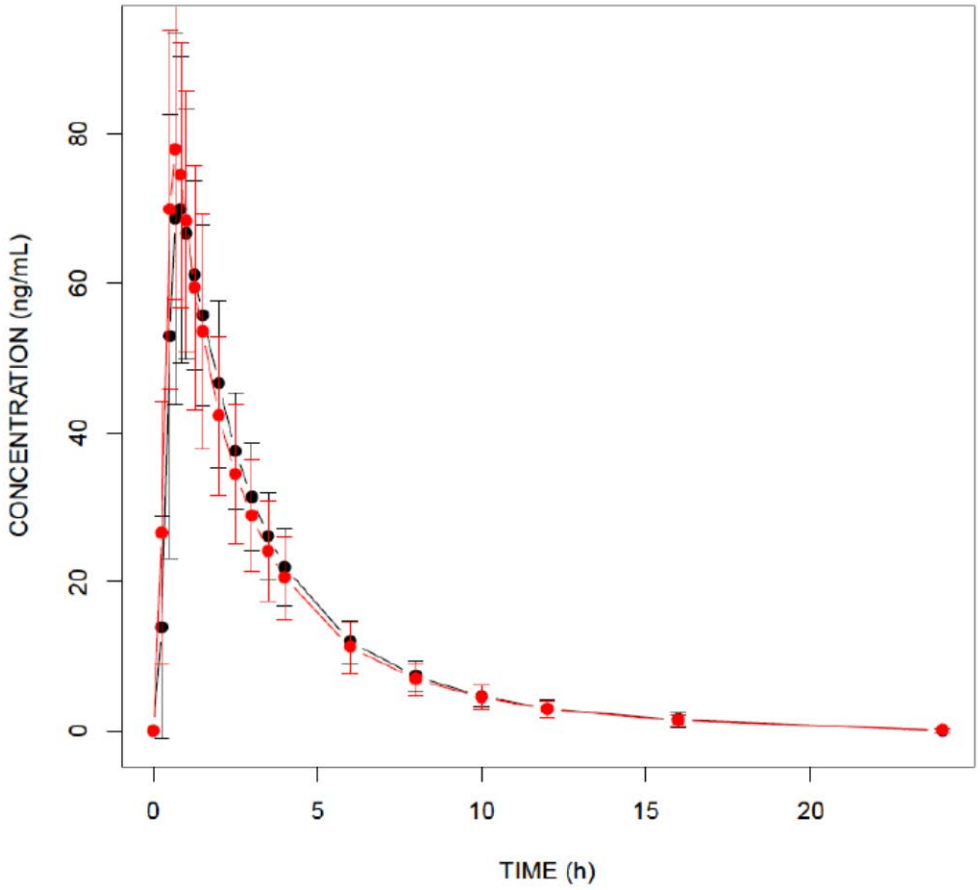
SG02-03 was a 2 x 2 crossover design comparing the pharmacokinetics associated with 2.5 mg tablets with pharmacokinetics associated with 1 ml of 2.5 mg/ml solution.

Results: The results of the SG02-03 trial are summarized below in Table 3 and Figure 3.

Table 3: SG02-03 PK Results - Bioequivalence Trial

Parameter	Ratio (% of Reference)	90% CI
AUC_{inf}	98	[95, 105]
C_{max}	107	[100, 115]

Figure 3: SG02-03 Comparison of Mean PK Profiles – Bioequivalence Trial



Conclusion: On the basis of the analysis of this data (see Figure 3 and Table 3), the clinical pharmacology reviewer concluded that the tablet and the oral solution formulations of methotrexate were bioequivalent.

Summary of Results of SG02-04:

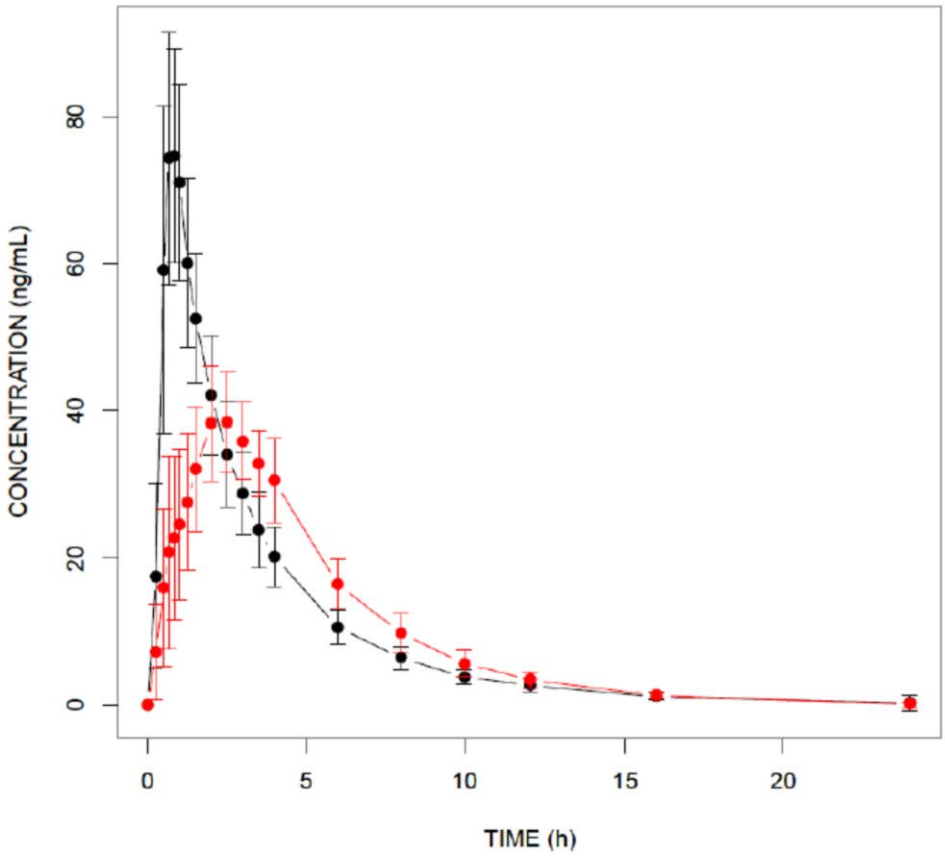
The sponsor also conducted a food effect study, SG02-04. The rationale for this trial was that the drug label indicates there is a food effect, specifically a decreased C_{max} and T_{max} when the oral solution is given with food. The SG 02-04 was a 2 x 2 crossover design of 21 patients comparing administration after a 10 hour fast (solid black circles) and after a standard high fat meal (solid red circles).

Results: The results of the SG02-04 trial are summarized below in Figure 4 and Table 4.

Table 4: SG02-04 PK Results - Food Effect Trial

Parameter	Ratio (% of Reference)	90% CI
AUC_{inf}	96	[91, 102]
C_{max}	50	[47, 54]

Figure 4: SG02-04 Comparison of Mean PK Profiles – Food Effect Trial



Conclusion: The clinical pharmacology reviewer concluded that administration with high fat meal resulted in an approximately 50% decrease in the C_{max}, and prolonged the T_{max} from 0.83 hours fasted to 2 hours fed. However, the AUC_{inf} was comparable.

Regulatory Recommendation: Approval from a clinical pharmacology perspective. However, observations made at the manufacturing site by the FDA will lead to a recommendation of Complete Response.

5. SAFETY: (This section is excerpted from the review of Dr. Patricia Dinndorf. For details, please see her review).

The Applicant submitted the results of the trials presented below in Table 5 to support NDA 208400. The clinical pharmacology results from these two trials were presented in the previous section. The safety results from these two trials will now be presented (see below).

Table 5: Trials supporting NDA 208400

Table 5.2-1. Listing of All Clinical Studies						
Type of Study	**Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Dosage Regimen Route of Administration Duration; Test Product(s)**	**Healthy Subjects or Diagnosis of Patients Number of Subjects**	**Study Status Type of Report**
BA	*SG02-03*	To assess the bioavailability of Methotrexate Oral Solution versus Methotrexate Tablets (DAVA) under fasted conditions	Single-dose, open-label, randomized, 2-period, 2-treatment, 2-way crossover	A: Single dose; oral; Methotrexate Oral Solution 2.5 mg (fasted) B: Single dose; oral; Methotrexate Tablets 2.5 mg (fasted)	Healthy adult male subjects 34 enrolled (31 completed)	Complete eCTD
BA	*SG02-04*	To assess the bioavailability of Methotrexate Oral Solution under fasted and fed conditions	Single-dose, open-label, randomized, 2-period, 2-treatment, 2-way crossover	A: Single dose; oral; Methotrexate Oral Solution 2.5 mg (fasted) B: Single dose; oral; Methotrexate Oral Solution 2.5 mg (fed)	Healthy adult male subjects 24 enrolled (21 completed)	Complete eCTD
BA = bioavailability; DAVA = DAVA Pharmaceuticals, Inc.; eCTD = electronic Common Technical Document.						

The SG02-03 Trial:
STUDY INFORMATION:

- Title: "A Randomized, Open-Label, Two-Period, Two-Treatment, Two-Way, Crossover Study to Determine the Relative Bioavailability of Methotrexate Pediatric Oral Solution vs Methotrexate Tablets USP, (DAVA) 2.5 mg under Fasted Conditions in Healthy Adult Male Volunteers"
- Phase: I
- Design: Open Label, single-dose, randomized, two-period two-treatment, two-way crossover
- Study Sites: Worldwide Clinical Trials Early Phase Services, San Antonio, Texas
- Proposed Sample Size: 34
- Gender: Male
- Age Range: 18 to 55 years

Dose: 2.5 mg/mL (Silvergate); Methotrexate Tablet, 2.5 mg (DAVA)
Route: oral
Planned enrollment: 34

Actual enrollment: 34, 31 analyzed

Primary Objective:

The objective of this study was to assess the relative bioavailability of a test formulation of methotrexate pediatric oral solution, 2.5 mg/mL (Silvergate) compared to an equivalent oral dose of the commercially available reference listed drug methotrexate tablet, 2.5 mg (DAVA), when administered under fasted conditions in healthy adult male subjects.

Treatment Plan: (copied from eCTD submission section 5.3.1.2 SG02-03 page 21 of 136)

Adult male subjects were to receive a single dose of methotrexate pediatric oral solution, 2.5 mg/mL (Treatment A) in one period, and a separate single dose of methotrexate tablet, 2.5 mg (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours. Treatment A was administered via a 1 mL glass dosing syringe and followed with 240 mL of room temperature tap water. Treatment B was administered with 240 mL of room temperature tap water. The subjects fasted for 4 hours after dosing. Except for the 240 mL of room temperature water provided with the dose, no water was consumed for 1 hour prior to dose through 1 hour post dose. Each drug administration was separated by a washout period of at least 7 days. During each study period, meals were the same and scheduled at approximately the same times relative to dose.

Results: (copied from eCTD submission section 5.3.1.2 SG02-03 page 38 of 136)

A total of 34 subjects were randomized into the study; 31 of these subjects completed both periods of the study. Two subjects were withdrawn at Period 2 check-in due to protocol non-compliance. One subject was withdrawn at Period 2 check-in due to an AE of fungal skin infection. The demographics of the study subjects are presented below in Table 6.

Table 6: Demographics: (copied from eCTD submission section 5.3.1.2 SG02-03 page 40 of 136)

			Sequence	
Characteristic		**All (N= 34)**	**AB (N= 17)**	**BA (N= 17)**
Sex	Male	34 (100.0%)	17 (100.0%)	17 (100.0%)
Age (years)	N	34	17	17
	Mean (SEM)	34.41 (1.80)	37.24 (2.16)	31.59 (2.79)
	Std Dev	10.52	8.89	11.50
	Median	32.00	34.00	27.00
	Min, Max	19.00, 54.00	26.00, 53.00	19.00, 54.00
Ethnicity	Hispanic or Latino	13 (38.2%)	5 (29.4%)	8 (47.1%)
	Not Hispanic or Latino	21 (61.8%)	12 (70.6%)	9 (52.9%)
Race	American Indian or Alaska Native	2 (5.9%)	1 (5.9%)	1 (5.9%)
	Asian	1 (2.9%)	0 (0.0%)	1 (5.9%)
	Black or African American	14 (41.2%)	9 (52.9%)	5 (29.4%)
	White	17 (50.0%)	7 (41.2%)	10 (58.8%)
Height (cm)	N	34	17	17
	Mean (SEM)	173.81 (1.54)	172.21 (1.78)	175.41 (2.51)
	Std Dev	8.97	7.34	10.33
	Median	172.50	172.00	174.00
	Min, Max	159.00, 203.00	159.50, 183.00	159.00, 203.00
Weight (kg)	N	34	17	17
	Mean (SEM)	79.28 (1.74)	80.45 (2.54)	78.11 (2.43)
	Std Dev	10.16	10.48	10.00
	Median	80.20	80.80	79.60
	Min, Max	60.80, 99.60	61.30, 99.60	60.80, 93.30
BMI (kg/m^2)	N	34	17	17
	Mean (SEM)	26.20 (0.41)	27.05 (0.56)	25.35 (0.54)
	Std Dev	2.39	2.29	2.23
	Median	26.40	27.60	25.80
	Min, Max	21.90, 30.00	21.90, 30.00	22.20, 29.90

Safety Results: (copied from eCTD submission section 5.3.1.2 SG02-03 page 48 of 136)

The TEAEs from SG02-03 are presented below in Table 7 and in Table 8.

Table 7: SG02-03 Treatment-emergent Adverse Events

Number of Subjects:	Treatment A (N=33)	Treatment B (N=32)
Treatment-emergent AE	2 (6.1%)	2 (6.3%)
Treatment-related Treatment-emergent AE	1 (3.0%)	1 (3.1%)
Serious Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Serious Treatment-related Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Treatment-emergent AE Leading to Study Discontinuation	1 (3.0%)	0 (0.0%)

(copied from eCTD submission section 5.3.1.2 SG02-03 page 49 of 136)

Table 8: SG02-03 Treatment-emergent Adverse Events by SOC and PT

System Organ Class	Preferred Term	Treatment A (N=33)	Treatment B (N=32)
Gastrointestinal disorders	Paraesthesia oral	0 (0.0%)	1 (3.1%)
Immune system disorders	Hypersensitivity	0 (0.0%)	1 (3.1%)
Infections and infestations	Fungal skin infection	1 (3.0%)	0 (0.0%)
Nervous system disorders	Headache	1 (3.0%)	1 (3.1%)
Respiratory, thoracic and mediastinal disorders	Nasal congestion	1 (3.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Seborrhoeic dermatitis	1 (3.0%)	0 (0.0%)

(copied from eCTD submission section 5.3.1.2 SG02-03 page 48 of 136)

Conclusions:

Overall, both the methotrexate pediatric oral solution, 2.5 mg/mL and the methotrexate tablets, 2.5 mg, were well-tolerated in this study and the AE profiles were consistent with the known effects of both drugs. The incidence of treatment-emergent AEs was 6.3% or less for both treatment groups; 4 subjects overall experienced treatment-emergent AEs.

Treatment-emergent AEs were reported by 2 (6.1%) subjects following administration of Treatment A, and by 2 (6.3%) subjects following Treatment B. Of these, 1 (3.0%) subject reported a treatment-related AE following Treatment A, and 1 (3.1%) subject reported a treatment-related AE following Treatment B. There were no serious AEs

The SG02-04 Trial

- **Title: "A Randomized, Open-Label, Single-Dose, Two-Period, Two-Treatment, Two-Way Crossover Relative Bioavailability Study of Methotrexate Pediatric Oral Solution under Fasted and Fed Conditions in Healthy Adult Male Volunteers"**
- Phase: I
- Design: Open Label, single-dose, randomized, two-period two-treatment, two-way crossover
- Study Sites: Worldwide Clinical Trials Early Phase Services, San Antonio, Texas
- Proposed Sample Size: 24
- Gender: Male
- Age Range: 18 to 55 years

Dose: 2.5 mg/mL (Silvergate); Methotrexate Tablet, 2.5 mg (DAVA)
Route: oral
Planned enrollment: 24
Actual enrollment: 24 enrolled, 21 analyzed

Primary Objective: The objective of this study was to assess the effect of food on the relative bioavailability of a test formulation of methotrexate pediatric oral solution, 2.5 mg/mL.

Treatment Plan: (copied from eCTD submission section 5.3.1.2 SG02-04 page 21 of 144)

Healthy adult male subjects were to receive a single dose of the study treatment, methotrexate pediatric oral solution, 2.5 mg/mL, after a 10-hour overnight fast in one period and a single dose of the study treatment after consuming a Food and Drug Administration (FDA) standard high-calorie, high-fat breakfast meal in another period.

During the study period in which a subject was given the fed treatment, the subject fasted overnight for at least 10 hours, then began consuming the high-calorie, high-fat breakfast meal 30 minutes prior to administration of the study drug. With the exception of the high-calorie, high-fat breakfast served in the fed treatment period, meals were the same and scheduled at approximately the same times relative to dose.

Each dose was administered via a 1 mL glass dosing syringe and followed with 240 mL of room temperature water. The subjects fasted for 4 hours after dosing. Except for the 240 mL of room temperature water provided with the dose, no water was consumed for 1 hour prior to dose through 1 hour postdose. Each drug administration was separated by a washout period of 7 days.

Results: (copied from eCTD submission section 5.3.1.2 SG02-04 page 38 of 144)

A total of 24 subjects participated in the study and 21 of these subjects completed both study periods. Three subjects discontinued from the study early, one due to a mouth injury, one due to vomiting 1 hour after treatment B, one due to non-compliance.

Demographics: (copied from eCTD submission section 5.3.1.2 SG02-04 page 40 of 144)
The baseline demographics for the subjects entered onto SG02-04 are summarized below in Table 9.

Table 9: SG02-04 Demographics

			Sequence	
Characteristic		**All (N= 24)**	**AB (N= 12)**	**BA (N= 12)**
Sex	Male	24 (100.0%)	12 (100.0%)	12 (100.0%)
Age (years)	Mean (SEM)	36.92 (2.43)	39.00 (3.48)	34.83 (3.45)
	Std Dev	11.93	12.05	11.95
	Median	34.00	34.00	35.00
	Min, Max	18.00, 55.00	20.00, 55.00	18.00, 54.00
Ethnicity	Hispanic or Latino	15 (62.5%)	7 (58.3%)	8 (66.7%)
	Not Hispanic or Latino	9 (37.5%)	5 (41.7%)	4 (33.3%)
Race	American Indian or Alaska Native	1 (4.2%)	0 (0.0%)	1 (8.3%)
	Asian	1 (4.2%)	0 (0.0%)	1 (8.3%)
	Black or African American	7 (29.2%)	3 (25.0%)	4 (33.3%)
	White	15 (62.5%)	9 (75.0%)	6 (50.0%)
Height (cm)	Mean (SEM)	174.73 (1.61)	175.29 (2.83)	174.17 (1.66)
	Std Dev	7.87	9.79	5.73
	Median	174.75	177.75	174.00
	Min, Max	153.00, 187.50	153.00, 187.50	167.50, 185.00
Weight (kg)	Mean (SEM)	80.29 (1.88)	80.28 (2.80)	80.30 (2.64)
	Std Dev	9.21	9.69	9.13
	Median	80.75	79.95	82.60
	Min, Max	60.70, 98.50	60.70, 98.50	64.20, 93.30
BMI (kg/m^2)	Mean (SEM)	26.35 (0.61)	26.23 (0.94)	26.48 (0.82)
	Std Dev	2.99	3.25	2.84
	Median	27.30	27.15	27.30
	Min, Max	18.80, 29.70	18.80, 29.60	22.40, 29.70

Safety: (copied from eCTD submission section 5.3.1.2 SG02-04 page 48 of 144)

The safety results from SG02-04 are summarized below in Tables 10-11.

Table 10: SG02-04 Treatment-emergent Adverse Events

Number of Subjects:	Treatment A (N=22)	Treatment B (N=23)
Treatment-emergent AE	0 (0.0%)	3 (13.0%)
Treatment-related Treatment-emergent AE	0 (0.0%)	1 (4.3%)
Serious Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Serious Treatment-related Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Treatment-emergent AE Leading to Study Discontinuation	0 (0.0%)	1 (4.3%)

(copied from eCTD submission section 5.3.1.2 SG02-04 page 49 of 144)

Table 11: SG02-04 Treatment-emergent Adverse Events by SOC and PT

System Organ Class	Preferred Term	Treatment A (N=22)	Treatment B (N=23)
Gastrointestinal disorders	Vomiting	0 (0.0%)	1 (4.3%)
Injury, poisoning and procedural complications	Mouth injury	0 (0.0%)	1 (4.3%)
Nervous system disorders	Dizziness	0 (0.0%)	1 (4.3%)
	Hypoaesthesia	0 (0.0%)	1 (4.3%)
	Presyncope	0 (0.0%)	1 (4.3%)

(copied from eCTD submission section 5.3.1.2 SG02-04 page 48 of 144)

Conclusions: Overall, methotrexate pediatric oral solution, 2.5 mg/mL was well-tolerated in this study under both fasted and fed conditions, and the AE profiles were consistent with the known effects of methotrexate. There were no AEs reported after administration of Treatment A. Three (13%) subjects reported AEs after administration of Treatment B. Of the 3 subjects who reported treatment-emergent AEs after Treatment B, only 1 reported a treatment-related event. There were no serious AEs. One AE led to a subject discontinuation from the study.

Regulatory Recommendation: On the basis of the data summarized from Trials SG02-03 and SG02-04, this secondary reviewer is recommending approval of NDA 208400. However, the impact of the observations made at the manufacturing site by the FDA will lead to a non-approval recommendation.

6. ADVISORY COMMITTEE MEETING: None.

7. DRAFT POST MARKETING COMMITMENTS AND REQUIREMENTS: Non applicable

8. LABELING: Non applicable

9. REGULATORY RECOMMENDATION: This Cross Disciplinary Team Lead Reviewer recommends non-approval based on the observations made by the FDA at the manufacturing site (see Section 3 above).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALBERT B DEISSEROTH
06/09/2016

Cross-Discipline Team Leader Review

Date	June 2, 2016
From	Janet Maynard, MD, MHS
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 208400, Original 2
Applicant	Silvergate Pharmaceuticals, Inc. (Silvergate)
Date of Submission	August 31, 2015
PDUFA Goal Date	June 30, 2016
Proprietary Name / Established (USAN) names	Xatmep/Methotrexate oral solution
Dosage forms / Strength	2.5 mg/mL (equivalent to 2.74 mg of methotrexate sodium/mL)
Proposed Indication(s)	**Original 1 Indication**: Treatment of pediatric patients with acute lymphoblastic leukemia (ALL), as part of a combination regimen **Original 2 Indication**: Management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full-dose non-steroidal anti-inflammatory agents (NSAIDs)
Recommended:	*Complete response based on deficiencies noted at manufacturing site*

1. Introduction

This is a 505(b)(2) new drug application (NDA) for an oral methotrexate (MTX) solution. The oral solution contains 2.5 mg of methotrexate per milliliter and is packaged in a 120 mL bottle.

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, methotrexate is approved as an injection (NDA 11719; approved 1959; Hospira) for intramuscular (IM), intravenous (IV), subcutaneous (SC), intra-arterial (IA), and intra-thecal (IT) administration. Two methotrexate autoinjector products (NDA 204824; approved 2013; Antares Pharma, Inc. and NDA 205776; approved 2014; Medac Pharma, Inc.) are approved for SC administration. Methotrexate is currently available in 2.5 mg tablets (multiple companies), and 5, 7.5, 10, and 15 mg tablets (Barr). Injectable methotrexate is available from multiple companies in varying quantities of 25 mg/mL solution. Methotrexate autoinjectors are available in a variety of fixed doses. At the time of submission

of this NDA, approved indications and routes of administration for methotrexate included neoplastic diseases (oral, intramuscular, intravenous, intra-articular, and intra-thecal routes), rheumatoid arthritis (oral and subcutaneous routes), polyarticular juvenile idiopathic arthritis (oral, intramuscular, and subcutaneous routes), and severe psoriasis (oral, intramuscular, subcutaneous, and intravenous routes). Of note, polyarticular juvenile idiopathic arthritis (pJIA) was previously called polyarticular juvenile rheumatoid arthritis (JRA). In this review, it will be referred to as pJIA, recognizing that some methotrexate products still have labeling that uses the previous terminology, which is JRA.

In this NDA, the Applicant is seeking approval of their product for treatment of pediatric patients with acute lymphoblastic leukemia (ALL), as part of a combination regimen and management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full-dose non-steroidal anti-inflammatory agents (NSAIDs). This application was administratively split into Original 1 for the ALL indication and Original 2 for the pJIA indication. This review will focus on the data relevant to Original 2 and the Division of Hematology Products (DHP) will separately review Original 1.

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

- The Agency's previous findings of safety and effectiveness of methotrexate in children with JRA/JIA 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 one food-effect study to evaluate methotrexate oral solution in the fasted and fed state
- Information in the published literature supporting the safety and efficacy of methotrexate for pJIA

The primary data to support this NDA submission and approval for pJIA is from the BA study comparing the proposed methotrexate oral solution to oral methotrexate (SG02-03).

2. Background

Polyarticular Juvenile Idiopathic Arthritis (pJIA)

JIA is a group of autoimmune diseases that comprises the most common rheumatic diseases in children with an estimated incidence of 15 per 100,000. The classification system historically used to characterize arthritis in children and adolescents utilized the nomenclature Juvenile Rheumatoid Arthritis (JRA), as defined by the American College of Rheumatology (ACR). However, pediatric rheumatologists now favor the more detailed classification system proposed by the International League of Associations for Rheumatology (ILAR). Further, this classification system is now used by the rheumatology academic community. According to the ILAR classification system, JIA includes 7 mutually exclusive categories: systemic arthritis, oligoarthritis, polyarthritis (rheumatoid factor negative or positive), psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis (Table 1).

Juvenile idiopathic arthritis is the umbrella term used to encompass all the subtypes listed in Table 1. Broadly, JIA is defined as arthritis of one or more joints occurring for at least 6 weeks in a child younger than 16 years of age, where other diagnoses that cause arthritis have been excluded. JIA affects an estimated 294,000 children between the ages of 0 and 17 in the United States.[1]

Table 1: International League of Associations for Rheumatology (ILAR) Juvenile Idiopathic Arthritis (JIA) Classification

Category	Definition	Frequency (% of all JIA)	Age of Onset	Sex Ratio
Systemic onset JIA	Arthritis in one or more joints with or preceded by fever of at least 2 weeks' duration that is documented as daily ("quotidian") for at least 3 days and accompanied by one or more of the following: rash (evanescent), lymphadenopathy, hepatomegaly, splenomegaly, serositis	4-17%	Throughout childhood	F=M
Oligo JIA Persistent Extended	Arthritis affecting one to four joints during the first 6 months of disease Affects no more than 4 joints throughout the disease course Affects more than 4 joints after the first 6 months of disease	27-56%	Early childhood; peak at 2-4 years	F>>>M
Polyarthritis (RF negative)	Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are negative.	11-28%	Biphasic distribution; early peak at 2-4 years and later peak at 6-12 years	F>>M
Polyarthritis (RF positive)	Arthritis affects five or more joints in the first 6 months of disease. Tests for RF are positive on at least two occasions that are 3 months apart.	2-7%	Late childhood or adolescence	F>>M
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least two of the following: dactylitis, nail pitting, family history of psoriasis in a first-degree relative.	2-11%	Biphasic distribution; early peak at 2-4 years and later peak at 9-11 years	F>M
Enthesitis-related arthritis	Arthritis or enthesitis with at least two of the following: sacroiliac tenderness or lumbosacral pain, presence of HLA-B27 antigen, onset of arthritis in male >6 years old, acute anterior uveitis, family history in a first-degree relative of HLA-B27 associated disease	3-11%	Late childhood or adolescence	M>>F
Undifferentiated arthritis	Arthritis that fulfills criteria in no category or in two or more of the above categories.	11-21%	--	--

Adapted from Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369:767-768.

In addition to corticosteroids, sulfasalazine, and methotrexate, four biologic disease-modifying anti-rheumatic drugs (DMARDs) have been approved for pJIA: etanercept (Enbrel®), approved for patients 2 years of age and older; adalimumab (Humira®), approved for patients 2 years of age and older; abatacept (Orencia®), approved for patients 6 years of age and older;

[1] Espinosa M, Gottlieb BS. Pediatrics in Review, 2012;33:303-313.

and tocilizumab (Actemra®), approved for patients 2 years of age and older. Currently, there is no methotrexate oral solution available for administration to children or adults who are unable to take tablets or the parenteral formulation. Interestingly, published data suggest that oral administration of the injectable form of methotrexate may be an alternative method of administration[2].

Methotrexate history

In the 1940's, folic acid antagonists were first postulated as potential treatment for leukemias, with the first successful drug being the folate analog aminopterin, demonstrated by Sidney Farber in 1947 to induce remission in children with acute lymphocytic leukemia. Other folate analogs, such as methotrexate, soon followed in the 1950's. Due to methotrexate's improved tolerability and easier production, it became the preferred treatment for a number of malignancies and neoplasms.

Although aminopterin was investigated as a treatment for RA as early as 1951, and methotrexate as early as 1962, use of methotrexate for RA languished until the 1970's and 1980's. The reason for this disinterest is not known, but is postulated by some to be due to a greater enthusiasm for corticosteroids during that time frame. Throughout the 1980's interest in methotrexate blossomed, prompting an increasing number of clinical studies and controlled trials of methotrexate, and culminating in the FDA approval of methotrexate for RA in 1988[3]. Although the pivotal trials for the approval of methotrexate evaluated oral methotrexate, the gastrointestinal tolerability issues, relatively poor oral absorption of methotrexate at higher doses, and ready availability of parenteral methotrexate quickly led practitioners to use parenteral methotrexate as an alternative for patients who were not tolerating oral methotrexate[4]. Methotrexate is now approved, via both subcutaneous route and oral routes, for RA and pJIA.

Regulatory history

The Applicant had two meetings with the Division of Hematology Products (DHP) prior to submission of their application. A pre-IND meeting (IND 117387) was held on May 21, 2013 (meeting minutes dated May 21, 2013) to discuss the clinical development plan for methotrexate oral solution. The Applicant proposed a 5050(b)(2) application with reference to the Agency's previous finding of safety and effectiveness of the DAVA Methotrexate Tablets. In addition, the Applicant proposed a randomized, parallel, single-dose pivotal comparative bioavailability (BA) study of its methotrexate product to DAVA's Methotrexate Sodium 2.5 mg tablet in 60 healthy adult male subjects. In general, the Applicant's proposal was felt to be reasonable, but the Applicant was given recommendations regarding the timing and type of assessments needed in the BA study.

A Type C (CMC) meeting was held on April 7, 2105 (meeting minutes dated April 14, 2015). The purpose was to discuss the requirements for a methotrexate oral solution regarding the

[2] Marshal S. J Rheum 1996;23(3):455-8.
[3] Coury FF and Weinblatt ME, Clin Exp Rheumatol 2010;28(Suppl 61):S9-S12.
[4] Visser et al, Ann Rheum Dis 2009 Jul;68(7)1086-93.

active pharmaceutical ingredient and drug product specifications, as well as the stability requirements for submission.

On May 28, 2015, the Applicant was granted orphan designation for methotrexate oral solution for treatment of acute lymphoblastic leukemia in pediatric patients (0 through 16 years of age).

On August 27, 2015, the Applicant was granted orphan designation for methotrexate oral solution for treatment of oligoarticular juvenile idiopathic arthritis (persistent oligoarthritis, psoriatic juvenile idiopathic arthritis, enthesitis-related arthritis, or undifferentiated arthritis) and polyarticular juvenile idiopathic arthritis in children 0 through 16 years of age.

3. CMC/Device

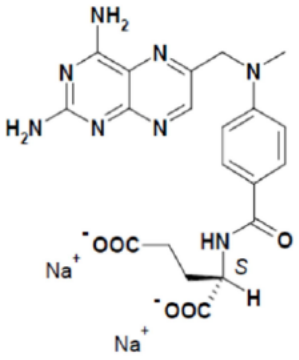
Discipline	***Reviewer***
Drug Substance	*Sam Bain*
Drug Product	*Sam Bain*
Process	*Yetao Jin*
Microbiology	*Wendy Tan*
Facility	*Ebern Dobbin*
Biopharmaceutics	*Banu Zolnik*
Regulatory Business Process Manager	*Rabiya Laiq*
Application Technical Lead	*Anamitro Banerjee*
Laboratory (OTR)	*Lucinda Buhse*
ORA Lead	*Paul Perdue Jr.*
Environmental Assessment (EA)	*Sam Bain*

- **General product quality considerations**

Drug substance

Methotrexate Sodium is a yellow to orange crystalline powder. It is freely soluble in water, slightly soluble in ethanol, and practically insoluble in chloroform. The pH of an aqueous solution (1%w/v) is 7.0 to 9.0. It is hygroscopic and shows no polymorphism. The structure of Methotrexate Sodium contains one asymmetric carbon atom, located in the glutamic acid side chain. (b) (4) The applicant has referred to the DMF (b) (4) for the drug substance. The DMF was reviewed on February 09, 2016 and was found to be adequate. See Figure 1 for Methotrexate Sodium's Structure.

Figure 1: Methotrexate Sodium Structure



Molecular structure: $C_{20}H_{20}N_8Na_2O_5$

Molecular mass: 498.41

Source: Module 3.2.S.1.2

Drug product

The drug product is a clear, yellow to orange colored, oral solution. The strength is 2.5 mg/mL of methotrexate (120 mL total volume). [redacted] The HDPE bottles were chosen [redacted]. The product contains 2.74 mg/mL of methotrexate sodium, equivalent to 2.5 mg/mL [redacted]. The excipients include citric acid [redacted] USP, sodium citrate [redacted] USP, methylparaben sodium USP, propylparaben sodium USP, sucralose NF, sodium hydroxide [redacted] NF, hydrochloric acid [redacted] NF, and purified water. All excipients are compendial. No excipient is of human or animal origin. No novel excipients are used.

The container closure is a 150 cc [redacted], white HDPE bottle capped with a [redacted] white cap with a [redacted] induction seal.

The applicant has proposed a 24 months expiration dating period when stored at 5±3°C.

- **Facilities review/inspection**

The site for drug manufacture is the [redacted] facility. This site was inspected on multiple occasions over a period from [redacted]. Seven observations were noted:

1. [redacted]

2. Equipment and utensils are not cleaned and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.
3. Buildings used in the manufacturing, processing and packaging of a drug product are not maintained in a good state of repair.
4. Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.
5. The responsibilities and procedures applicable to the quality control unit are not fully followed.
6. There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has already been distributed.
7. Written production and process control procedures are not documented at the time of performance.

Additional details of these definiciences are listed in the Form 483. Final designation and recommendations from CMC are pending at this time. It is anticipated that CMC will recommend withholding approval based on these facilities issues.

- **Product Quality Microbiology**

The Applicant provided adequate information to support product quality microbiologic concerns.

- **Other notable issues (resolved or outstanding)**

A final recommendation from the CMC is pending at the time of this review. A final CMC recommendation could not be made yet as the facility review is pending for this submission.

4. Nonclinical Pharmacology/Toxicology

For DHP: Pharmacology-Toxicology reviewer: Pedro L. Del Valle, PhD; Pharmacology-Toxicology Supervisor: Christopher Sheth, PhD
For DPARP: Pharmacology-Toxicology reviewer: Andrew Goodwin, PhD; Pharmacology-Toxicology Team Leader: Tim Robison, PhD

- **General nonclinical pharmacology/toxicology considerations**

No nonclinical studies were submitted to or required for this application. Relevant pharmacology/toxicology information is contained in the listed drug (NDA 208400, methotrexate oral tablets, Dava).

- **Other notable issues (resolved or outstanding)**

There are no other notable issues. From a nonclinical pharmacology/toxicology perspective, the application is recommended for approval.

5. Clinical Pharmacology/Biopharmaceutics

For DHP: Clinical pharmacology reviewer: Salaheldin Hamed, PhD; Clinical pharmacology team leader: Bahru Habtemariam, PhD
For DPARP: Clinical pharmacology reviewer: Manuela Grimstein, PhD; Clinical pharmacology team leader: Anshu Marathe, PhD

- **General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc**

This NDA references one previously approved methotrexate product: NDA 8085 (Dava's oral methotrexate tablets).

Study SG02-03 evaluated the PK of the proposed oral solution product in comparison to 2.5 mg immediate release oral tablets (Figure 2). The study was a randomized, open-label, single-dose, two-period, two-treatment, two-way crossover study in 31 healthy adults. The reported results indicate that methotrexate C_{MAX} and AUC of the proposed oral solution are similar to those of the immediate release tablet (Table 2). The geometric mean ratio test (oral solution) to reference (tablets) along with the 90% confidence interval fell within 80% to 125%.

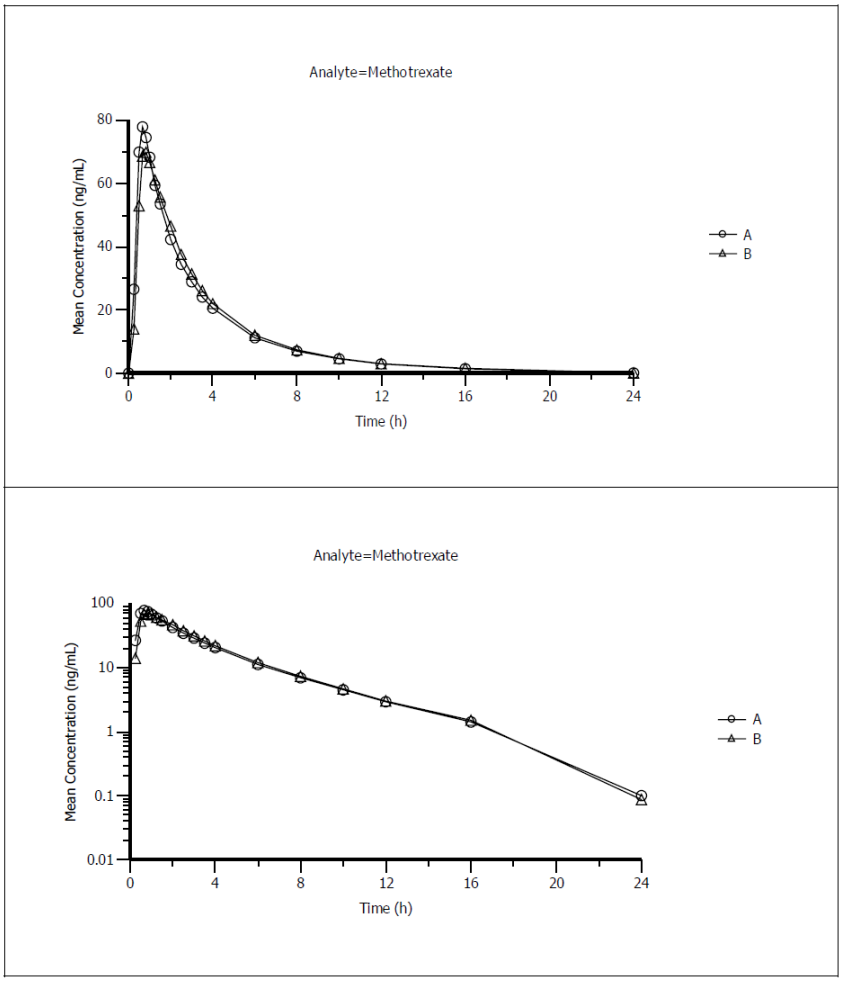
Study SG02-04 evaluated the effect of food on the relative BA of the proposed methotrexate oral solution formulation (Figure 3). The study was a randomized, open-label, single-dose, two-period, two-treatment, two-way, crossover study in healthy adults. The reported results also indicate that food intake reduces C_{MAX} (Table 2) and delays median T_{MAX} (range) from 0.83 h (0.5-1) in the fasted state to 2 h (0.66-4) in the fed state.

Table 2: Summary of Relative BA and Food Effect Findings

Study	Parameter	Geometric Mean Ratio (90% CI)
BA study	AUC_{inf}	98 (95,102)
	C_{MAX}	107 (100, 115)
Food effect	AUC_{inf}	96 (91, 102)
	C_{MAX}	50 (47,54)

Source: Clinical pharmacology review dated April 14, 2016, page 3

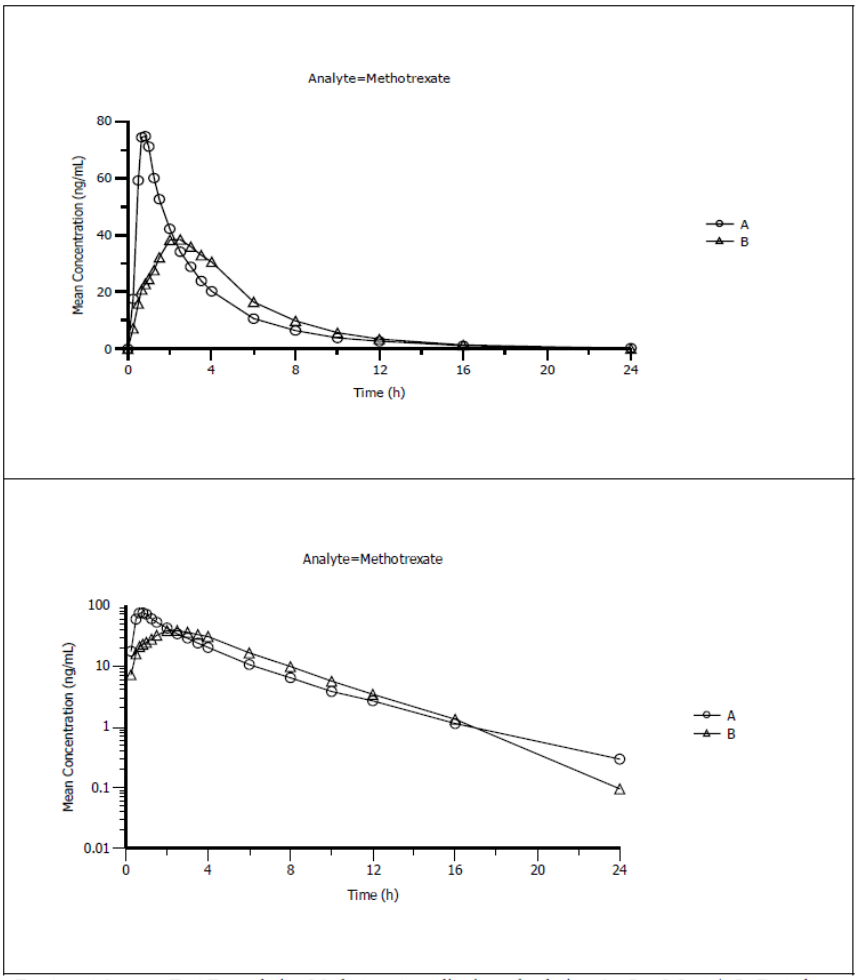
Figure 2: Mean Methotrexate Concentration-Time Profiles after Administration of the Test Formulation (Treatment A) and the Reference Product (Treatment B) in Study SG02-03



Treatment A = Test Formulation methotrexate pediatric oral solution, 1 mL x 2.5 mg/mL
Treatment B = Reference Product methotrexate tablet, 1 x 2.5 mg
Source data: Tables 14.2.1 and 14.2.2

Source: Module 5.3.1, Study Report (SG02-03), Figure 11.4.3.1, page 44

Figure 3: Mean Methotrexate Concentration-Time Profiles after Administration of the Test Formulation under Fasted Conditions (Treatment A) and the Test Formulation under Fed Conditions (Treatment B) in Study SG02-04



Treatment A = Test Formulation Methotrexate pediatric oral solution, 1 mL x 2.5 mg/mL, Fasted
Treatment B = Test Formulation Methotrexate pediatric oral solution, 1 mL x 2.5 mg/mL, Fed
Source data: Tables 14.2.1 and 14.2.2
Source: Module 5.3.1, Study Report (SG02-04), Figure 11.4.3.1, page 44

The relative BA/BE study was conducted at a lower dose of 2.5 mg whereas the recommended starting dose for the JIA indication is 10 mg/m^2 once weekly and the dose is titrated to achieve an optimal response. The label mentions doses up to 30 mg/m^2/wk, but also mentions that children receiving 20 to 30 mg/m^2/wk may have better absorption and fewer gastrointestinal side effects if methotrexate is administered (b) (4). For the ALL indication, the recommended dose is 20 mg/m^2. According to the methotrexate package insert, methotrexate exhibits saturable absorption at higher doses (>30 mg/m^2). The Applicant provided a literature reference[5] demonstrating that intravenous methotrexate prepared as an oral solution has comparable exposure to that of methotrexate tablets up to doses of 25 mg/m^2. Therefore, the relative BA findings at 2.5 mg dose were deemed representative of the relative BA of methotrexate at the recommended doses for the ALL indication, which would also

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

apply to the JIA indication. Furthermore, any potential lack of bioequivalence at higher doses is not expected to have a meaningful therapeutic consequence since methotrexate treatment is titrated to achieve a therapeutic target in JIA patients.

The food effect finding, where food is shown to reduce the C_{MAX} of the oral solution formulation, is consistent with the effect of food on the tablet formulation, as per listed product labeling and the published literature[6]. Given that methotrexate is titrated to optimal clinical response and there is no known exposure-response relationship for efficacy for any exposure parameter, there was not a significant clinical concern.

- **Other notable issues (resolved or outstanding)**

As discussed in Section 11 of this review, the Office of Study Integrity and Surveillance (OSIS) recommended that the results from the bioanalytical portions of the study be accepted for Agency review.

The Clinical Pharmacology team recommends the proposed product for approval from a clinical pharmacology perspective.

6. Clinical Microbiology

No new clinical microbiology data were included in the supplement.

7. Clinical/Statistical- Efficacy

Primary clinical reviewer: Peter Starke, MD; Statistical team leader: Gregory Levin, PhD

- **Efficacy review**

As discussed in Section 5, compared to oral methotrexate tablets, the exposure of the proposed methotrexate oral solution is similar. Therefore, the efficacy of methotrexate oral solution could be presumed based on the Agency's previous findings of efficacy of methotrexate for JIA.

In addition to this pharmacokinetic (PK) bridge, the Applicant summarized the clinical efficacy and safety data on methotrexate from the literature. In addition, Dr. Starke and I conducted a review of the available literature for methotrexate treatment. This literature includes randomized controlled trials (Giannini 1992) and multiple studies and clinical reports. Some highlights of the literature review are summarized here:

Giannini et al. 1992.[7] This randomized, controlled, double-blind trial evaluated the efficacy and safety of orally administered methotrexate in patients with resistant JRA. A total of 127

[6] Cronstein BN. Pharmacol Rev 2005;57(2):163-72.
[7] Giannaini EH, et al. N Engl J Med 1992:326:1043-9.

patients were randomized to 10 mg/m^2 methotrexate, 5mg/m^2 methotrexate, or placebo weekly for six months. The trial enrolled children with various JIA subtypes, but more than two-thirds of the patients had polyarticular JRA. The primary outcome variables were the physician's global assessment of the patient's response, the articular-severity score (the sum of all the articular severity ratings), and the composite index (reduction of ≥25% from baseline in the articular-severity score and classified as improved according to the physician's and the parent's final global assessments).

Both methotrexate groups had consistently higher proportions of patients with improvements in physician's global assessment than the placebo group. Similar results were obtained for the articular severity score and the composite index (Table 3).

Table 3: Oral Methotrexate Response in JIA

	Low-dose methotrexate (10 mg/m^2) (N=38)	**Very-low dose methotrexate (5 mg/m^2) (N=37)**	**Placebo**	**P value**
Articular severity score, mean±SE	-63±15	-28±9	-36.4±8.8	0.077
Composite index responders, n (%)	24 (63)	12 (32)	14 (36)	0.013

Hinks et al 2011.[8] This publication was part of the Sparks CHARMS (CHildhood Arthritis Response to Medication Study), which recruits children who fulfil ILAR criteria for JIA of all subtypes and who are about to start new disease-modifying medication for active arthritis. Children who were starting weekly methotrexate by either oral or subcutaneous route at 10-15mg/m^2 were included. Response to methotrexate was defined using the American College of Rheumatology (ACR) pediatric response criteria. An ACR-Ped30 is when there is at least 30% improvement from baseline in three of any the six variables, with no more than one of the remaining variables worsening by >30%. The six variables include physician's global assessment of disease activity, parent/patient global assessment of disease activity, functional ability, number of joints with active arthritis, number of joints with restricted range of movement, and the erythrocyte sedimentation rate. ACR-Ped50 and ACR-Ped70 for JIA require improvements of 50% or 70% in at least three of the variables, respectively, again with no more than one of the remaining variables worsening by >30%. The majority of patients had ACR-Ped30 or ACR-Ped50 responses.

The Applicant submitted many articles describing the efficacy of methotrexate in JIA. Similar data are also available to support the efficacy of methotrexate in JIA patients with extended oligoarthritis[9]. Further, the Applicant relies on the listed drug which is approved for JRA.

- **Efficacy conclusions**

[8] Hinks A, et al. Ann Rhuem Dis 2011;70:1395-1400.
[9] Woo P, et al. Arthritis Rheum 2000;43(8):1849-57.

Methotrexate is already approved for polyarticular juvenile idiopathic arthritis, including via oral administration. Dr. Starke and I are in agreement that the available evidence would also support the efficacy of methotrexate oral solution for the proposed indication.

8. Safety

- **Discuss the adequacy of the database, major findings/signals, special studies, etc.**

The toxicity of methotrexate is well characterized given its use for a variety of malignant and non-malignant indications. The most common toxicities are gastrointestinal toxicities, such as nausea, stomatitis, and gastrointestinal upset. Other potential serious toxicities with methotrexate include myelosuppression, pulmonary toxicities, and hepatotoxicity. Based on these concerns, it is standard practice to get baseline liver enzymes, creatinine, and complete blood count. In addition, folic acid is given to reduce the incidence of GI toxicity and bone marrow suppression. Regular monitoring of liver enzymes, creatinine, and blood count is performed for the duration of therapy.[10]

- **General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.**

The safety experience specific to the methotrexate oral solution is limited to two bioavailability studies.

Study SG02-3 was a single dose BA study that compared the systemic methotrexate exposure of 2.5 mg of the oral solution with 2.5 mg of methotrexate tablets in adults. In study SG02-03, 31 of 34 subjects enrolled were administered all scheduled doses of methotrexate oral solution, 2.5 mg/mL and methotrexate tablet, 2.5 mg. Dosing in the 2 study periods was separated by a 7-day washout period. The total dose administered to each subject who completed both study periods was 5 mg of methotrexate. There were no serious adverse events or deaths. The proportion of treatment emergent adverse events was similar in the two treatment arms (approximately 6% in each treatment arm). There was one adverse event (fungal skin infection) that led to a subject discontinuation from the study. The most frequently experienced treatment-emergent AE, reported by MedDRA preferred term, was headache, which was reported by 1 (3.0%) subject after methotrexate oral solution and by 1 (3.1%) subject after methotrexate tablet.

Study SG02-4 was a single dose BA study that compared the systemic methotrexate exposure after dosing with the proposed oral solution in the fasted and fed states in adults. In study SG02-04, 21 of 24 subjects enrolled were administered all scheduled doses of methotrexate oral solution 2.5 mg/mL. Dosing in the 2 study periods was separated by a 7-day washout period. The total dose administered to each subject who completed both study periods was 5 mg (2 mLs) of methotrexate. There were no serious adverse events or deaths. After

[10] Visser K, et al. Ann Rheum Dis 2009;68:1086-93.

administration of methotrexate oral solution in the fasted condition, there were no adverse events reported. After administration of methotrexate oral solution in the fed condition, 3 subjects reported adverse events. The treatment-emergent adverse events, reported by MedDRA preferred term, were vomiting, mouth injury, dizziness, hypoesthesia, and presyncope. Each event was reported in 1 (4.3%) subject. All the events were mild, except for presyncope which was moderate in severity. One adverse event (mouth injury) led to subject discontinuation from the study.

Based on these limited data, no new safety signals were identified.

- **Immunogenicity**

Immunogenicity was not assessed. As a small molecule chemical, methotrexate has not been, nor would it be expected to be, associated with significant immunogenicity.

- **Special safety concerns**

None

- **Safety conclusions**

Dr. Starke has concluded that there is adequate evidence to support the proposed methotrexate oral solution given the relative bioavailability data and based on the Agency's previous findings of safety and effectiveness of methotrexate for pJIA, and I concur.

- **Discussion of notable safety issues (resolved or outstanding)**

See above.

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

- **Peds exclusivity board review** – PPSR/WR – Not applicable
- **PeRC Review Outcome—**PMCs, deferrals, waivers, pediatric plan, peds assessment

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. For this application, PREA does not apply because the Applicant

received orphan drug designation for the treatment of ALL in pediatric patients and the management of oligoarticular JIA (which includes persistent oligoarthritis, psoriatic arthritis, enthesitis-related arthritis, or undifferentiated arthritis) and polyarticular JIA pediatric patients.

11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP)—**Not applicable.
- **Exclusivity or patent issues or concern**

The Applicant submitted the required patent certification with respect to the listed drug.

The Applicant also submitted a request for 7 years of exclusivity for Methotrexate Oral Solution for the treatment of pediatric patient with ALL as part of a combination regimen and for the management of children with pJIA who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full dose NSAIDs. The Agency granted the Applicant's Orphan Drug Designation Request of methotrexate oral solution for the treatment of ALL in pediatric patients on May 28, 2015. Similarly, the Agency granted the Applicant's Orphan Drug Designation Request for methotrexate oral solution for the management of oligoarticular JIA (which includes persistent oligoarthritis, psoriatic JIA, enthesitis-related arthritis, or undifferentiated arthritis) and polyarticular JIA pediatric patients (0 to 16 years of age) on August 28, 2015.

- **Financial disclosures—**No issues.
- **Other GCP issues—**No issues.
- **Office of Scientific Investigation (OSI) audits—**

The Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection at (b) (4). The inspection was conducted in support of review of this application in addition to other applications. The analytical portions of the bioequivalence study (Methotrexate Pediatric Oral Solution 4002745; Protocol #SG02-04) were audited during the inspection. The audit included a thorough review of the method validation and the study reports, examination of facilities and equipment, and interviews and discussions with the firm's management and staff. At the conclusion of the inspection, no deficiencies were observed, and no Form FDA-483 was issued. Thus, the reviewers recommended that results from the bioanalytical portions of the study be accepted for further Agency review.

- **Other outstanding regulatory issues—**None

12. Labeling

- **Proprietary name**

On October 2, 2015, the Applicant requested review of the proposed proprietary name, (b) (4). On November 27, 2105, DMEPA found the proposed proprietary name unacceptable. On December 23, 2015, the Applicant requested the proposed proprietary name, Xatmep, which was found to be conditionally acceptable.

- **Physician labeling**

The labeling for the methotrexate oral solution is the third instance of Prescribing Information (PI) in Physicians Labeling Rule (PLR) format for a methotrexate product. Two methotrexate injection autoinjectors are approved in PLR format: Otrexup (NDA 204824, approved October 11, 2013) and Rasuvo (NDA 205776, approved July 10, 2014). Both products are approved for the management of patients with severe, active rheumatoid arthritis (RA) and polyarticular juvenile idiopathic arthritis (pJIA), and for symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy. (b) (5) the Agency's approach to the Otrexup and Rasuvo labels was to keep the current content of the parenteral MTX product labels as applicable, but modified to conform to the PLR format.

In the current application, the Applicant submitted proposed labeling with similar content to the listed drug (NDA 08085, Dava), but limited to the proposed indications (ALL and pJIA) and in PLR format. At this time, neither the listed drug label (NDA 08085, Dava) nor the parenteral methotrexate label is in PLR format. The Agency decided to utilize publically available information in the medical literature to update the scientific information in the proposed label. Of note, labeling modifications are ongoing at the time of the review. Given the facilities issues, it is not anticipated that the Agency will engage in labeling negotiations with the Applicant. However, the review team did assess the proposed labeling and considered the proposed changes reviewed below:

1) Boxed Warning: The Boxed Warning was revised to provide information related to the proposed indications.

2) Indications and usage: The proposed indication was "management of children with active polyarticualr juvenile idiopathic arthritis (pJIA) who have had an insufficient response to, or are intolerant of, an adequate trial of first-line therapy including full dose non-steroidal anti-inflammatory agents (NSAIDs)." (b) (5) .

[11] Hinks A, et al. Ann Rheum Dis 2011;70:1395-1400.
[12] Giannaini EH, et al. N Engl J Med 1992:326:1043-9.
[13] Woo P, et al. Arthritis Rheum 2000;43(8):1849-57.

3) Dosage and Administration: Information that was not directly related to dosage and administration, such as information about side effects, was removed from the Dosage and Administration section.

4) Contraindications: The contraindications for immunodeficiency, liver disease, and blood dyscrasias were removed because methotrexate could be administered in patients with less severe forms of with these conditions (i.e., contraindicating use would preclude an appropriate subset of patients from receiving treatment). Instead, these risks were discussed in Warnings and Precautions. The contraindication for use in nursing mothers was also removed. Instead, the information is discussed in 8.2 since nursing mothers are advised to discontinue nursing while taking methotrexate. The contraindication concerning hypersensitivity was revised to contraindicate for "severe hypersensitivity to methotrexate" because based on literature, desensitization to methotrexate can be effective.

5) Warnings and Precautions: The Warnings and Precautions were revised significantly to be consistent with the Guidance on labeling for this section[14]. Per the guidance, each adverse reaction, syndrome, or group of reactions with a common pathogenesis included in Warnings and Precautions section should have its own numbered subsection. The subsection title should accurately characterize the risk. Warnings were deleted if they were not relevant to the proposed dosage form and dosing.

6) Adverse Reactions section: This section was updated to be consistent with the updated Warning and Precautions section. In addition, information was deleted for indications the Applicant did not seek approval for, such as psoriasis and rheumatoid arthritis.

7) Use in Specific Populations: This is the first methotrexate label to undergo Pregnancy and Lactation Labeling Rule (PLLR) formatting. The section was revised based on PLLR regulations and guidance and input from Division of Pediatric and Maternal Health. For example, based on regulations, the Risk Summary must contain risk statement(s) based on data from all relevant sources (human, animal, and/or pharmacologic) that describe, for the drug. The Applicant was asked to provide an integrated review of published literature relevant to methotrexate use during pregnancy, lactation, and in females and males of reproductive potential. Modifications to this section are ongoing at the time of this review.

8) Pharmacokinetics: (b) (4) were removed from the labeling. Pharmacokinetic information not directly related to the proposed product, such as information regarding intrathecal administration, were removed.

9) Clinical Studies: Information related to indications that were not proposed, such as rheumatoid arthritis, were removed.

- **Highlight major issues that were discussed, resolved, or not resolved at the time of completion of the CDTL review**

[14] http://www fda.gov/downloads/Drugs/.../Guidances/ucm075096.pdf

As discussed above.

Labeling negotiations are not anticipated given the facilities issues identified at the time of this review.

- **Carton and immediate container labels (if problems are noted)**

The labeling was reviewed by DMEPA and changes were recommended.

- **Patient labeling/Medication guide (if considered or required)**

A medication guide is not proposed.

10) Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

I recommend a complete response for this application given the CMC deficiencies related to observations at the manufacturing site.

- **Risk Benefit Assessment**

The risk-benefit profile of methotrexate for pJIA is favorable. This is based on the Agency's previous findings of safety and effectiveness of methotrexate for children with pJIA. 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 JIA. However, the CMC deficiencies may preclude approval.

- **Recommendations for Postmarketing Risk Evaluation and Management Strategies**

Not applicable given anticipated complete response action.

- **Recommendation for other Postmarketing Requirements and Commitments**

Not applicable given anticipated complete response action.

- **Recommended comments to applicant**

Pending final disposition of the CMC deficiencies identified at the drug manufacturing site inspection.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JANET W MAYNARD
06/04/2016

Secondary Clinical Review

Date	May 27, 2015
From	Albert Deisseroth, MD, PhD
Subject	Secondary Clinical Review
NDA Number	208400
Applicant	Silvergate Pharmaceuticals, Inc
Date of Submission	August 31, 2015
PDUFA Goal Date	June 30, 2016
Proprietary Name/Trade Name	Methotrexate/Xatmep
Dosage Regimen	20 mg/m^2/week po
Approved Indications	Treatment of pediatric patients with ALL as a component of a combination chemotherapy maintenance therapy regimen
Recommendation:	Approval

Material Reviewed/Consulted	Reviewer/Author
Medical Officer Review	Patricia Dinndorf, MD
Clinical Pharmacology	Salaheldin Hamed, PhD, Bahru Habtemariam, PhD and NAM Atiqur Rahman, PhD
Pharmacology/Toxicology (DHOT, OHOP, OND)	Pedro Del Valle, PhD, Christopher M Sheth, PhD, and John Leighton, PhD
Product Quality	Tracy Rogers, PhD, and Donna Christner, PhD, Anamitro Banerjee, PhD
Project Manager	Jessica Boehmer

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1. EXECUTIVE SUMMARY: (This section was derived in part from the review of Dr. Patricia Dinndorf. For details, please see her review).

Methotrexate (tablets) was originally approved by the FDA on December 7, 1953 for the indication: Treatment of pediatric patients with ALL as a component of a combination chemotherapy maintenance therapy regimen. On August 31, 2015, Silvergate Pharmaceuticals, Inc. submitted NDA 208400 in which approval of an oral solution of methotrexate (Xatmep) as a 505(b)(2) was requested for the same indication on the basis of two bioavailability clinical trials: one for fasted individuals (SG02-03) and one for fed individuals (SG02-04).
Risk Benefit Assessment: The Risk Benefit assessment is presented below in Table 1.

Table 1: Risk Benefit Assessment

Decision Factor	**Evidence and Uncertainties**	**Conclusions and Reasons**
Analysis of Condition Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood with a peak incidence at the age of 3 years.	**Summary of evidence:** Oral methotrexate has been an integral component of ALL therapy since it was approved in 1953. Successive clinical trials have demonstrated its contribution to successful maintenance therapy and improved survival of patients with ALL.	**Conclusions (implications for decision):** 1. A formulation that provides more accurate dosing is a significant contribution to ALL therapy, especially in younger patients unable to swallow pills. 2. An alternative formulation also ensures better drug availability in the event of a drug shortage.
Unmet Medical Need Oral methotrexate is a component of maintenance chemotherapy for ALL. The 2.5 mg tablet or oral administration of methotrexate for injection are not ideal formulations for younger children or children who have difficulty swallowing pills.	**Summary of evidence**: • The solution is an appropriate formulation for young children or children who have difficulty swallowing pills. • The formulation of an oral solution of 2.5 mg/ml is an appropriate presentation of a medicine for children who are receiving doses of 20 to 40 mg/m^2 weekly. • The dose of methotrexate is modified to maintain an absolute neutrophil count (ANC) between 500 to 1500/µL and platelet count > 75,000/	**Conclusions (implications for decision):** The methotrexate solution is an appropriate formulation which is superior to the 2.5 mg tablet or use of methotrexate for injection orally, especially for children less than 5 years of age. The solution is a superior presentation to pills to allow dose adjustments.

	µL. The oral solution is a formulation that facilitates dose adjustments.	
Clinical Benefit See Unmet Medical Need		
Risk No risk in excess of the available tablet formulation	**Summary of evidence**: The solution is a superior presentation for children it allows straightforward provision of the appropriate dose.	**Conclusions (implications for decision):** This is a superior presentation compared to tablets for children who have difficulty swallowing pills.
Risk Management Ensure caregivers have adequate instructions to accurately measure and administer the correct dose	**Summary of evidence**:	**Conclusions (implications for decision):** 1. Label information and a Med Guide to provide instructions for correct administration
Benefit-Risk Summary and Assessment Xatmep is a superior presentation of methotrexate for children unable to swallow tablets. This formulation provides a superior presentation to tablets that are broken, crushed or extemporaneously formulated.		

Regulatory Recommendation: On the basis of the information presented in Table 1, this Secondary Clinical Reviewer agrees with Dr. Patricia Dinndorf, the primary clinical reviewer and recommends approval of Xatmep as a 505(b)(2). However, the impact of the observations made at the manufacturing site by the FDA (see Section 3 below) on the approvability of this protocol are unknown at this time.

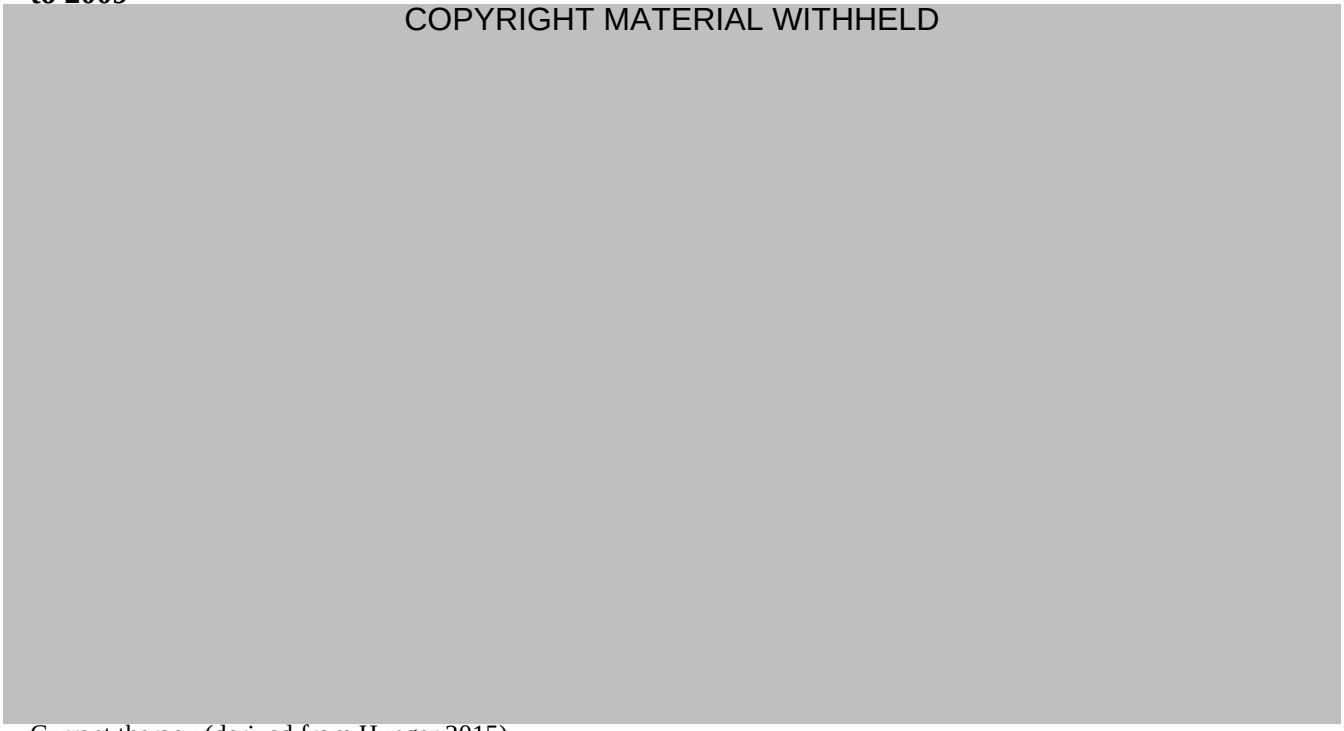
2. BACKGROUND: (This section was derived in part from the review of Dr. Patricia Dinndorf. For details, please see her review).

2A. Acute Lymphocytic Leukemia (ALL): ALL is the most common form of cancer in children and young adults. With current therapies the overall survival rate is over 85%. Successful treatment of children and young adults with ALL involves administration of a multi-drug regimen that that that are administered in several distinct phases, including induction, consolidation, delayed intensification and maintenance.

The first description of temporary remissions reported in children with ALL were induced by aminopterin, an anti-folate closely related to methotrexate (Farber 1948). Methotrexate, an antifolate related to aminopterin, began to replace aminopterin in the 1950s because of a more favorable toxicity profile. Continued improvement in survival in patients with ALL was achieved by the introduction of multi-agent chemotherapy regimens evaluated in cooperative group randomized trials. As prognostic factors were identified trials subsequent trials included

stratification of treatment intensity according to the clinical features of the patient, the biologic features of the leukemia cells, and the early response to treatment. Collectively, these advances have increased the survival rate from less than 10% in the 1960s to greater than 90% with current therapies. See **Figure 1**. (Hunger 2015).

Figure 1: Survival of Successive Cohorts of Patients with ALL in COG Clinical Trials 1968 to 2009



Current therapy (derived from Hunger 2015)

The basic components of contemporary therapies for children and young adults with ALL include induction therapy which lasts 4 to 6 weeks and includes a glucocorticoid (prednisone or dexamethasone), vincristine, an asparaginase preparation, optional use of an anthracycline, and intrathecal chemotherapy. Almost all patients attain remission, but this is not a cure, since relapse will occur universally without additional therapy.

After induction of remission, treatment includes 6 to 8 months of intensive combination chemotherapy that is designed to consolidate remission and prevent development of overt CNS leukemia. Treatment in an 8 week delayed intensification phase, based on the 8 week Berlin–Frankfurt–Münster protocol (Riehm 1980), is then administered. Repeated courses of intravenous methotrexate, administered either through short intravenous infusion or at high doses over 24 hours followed by administration of folinic acid to "rescue" normal tissues from toxic effects, are a critical component of this intensification therapy utilized in contemporary ALL regimens.

Patients then begin maintenance therapy low intensity "anti-metabolite" based therapy for 18 to 30 months. This therapy consists of daily oral mercaptopurine or thioguanine and weekly oral methotrexate. Some regimens also include periodic 5 to 7 day "pulses" of glucocorticoids and

vincristine. The exact reasons why maintenance therapy is required and the most effective composition and duration of chemotherapy are unknown.

The current open protocol in the Children's Oncology Group (COG) for the treatment of B-lineage ALL is comparing 2 doses of oral methotrexate during maintenance, 20 mg/m²/week (standard) and 40 mg/m²/week (experimental). During the course of maintenance therapy, the dose of oral methotrexate is adjusted to maintain an absolute neutrophil count (ANC) ≥ 500 /μL and < 1500/μL and a platelet count ≥ 50,000/μL.

2B. Regulatory History: The regulatory history of methotrexate is summarized in Table 2.

Table 2: Regulatory History

Regulatory History		
Date	**Item**	**Discussion**
5/21/13	Pre-IND Meeting	• Sponsor plans to reference nonclinical section of DAVA methotrexate to support 505(b)(2) • FDA response - in general acceptable
		• Sponsor plans to conduct a randomized, parallel, single-dose pivotal comparative bioavailability study of its methotrexate product to DAVA's Methotrexate Sodium 2.5-mg Tablet in 60 healthy adult male subjects under fasted condition to assess bioequivalence. • FDA response – o In general acceptable o PK sampling inadequate o Must assess food effect
		• Sponsor plans to use the 80-125% bounds for the bioavailability study. • FDA – noted no objection
		• Sponsor plans to restrict label indication to the pediatric population • FDA response – no objection
11/7/14	IND 117387	Methotrexate Pediatric Oral Solution Original protocol submitted to IND on 10/9/14 as discussed at Pre IND meeting was the parallel trial in 60 subjects. On 10/17/14 the sponsor queried the agency concerning revising the protocol to a crossover design in 30 subjects. FDA informed sponsor a second protocol could be submitted after the 30 day letter had been issued for the current submission.
11/21/14	New protocol IND 117387 submitted	SG02-03 with cross-over design (n=34) with the same dose and PK time points as SG02-01 was submitted. The clinical pharmacology reviewer determined the protocol was acceptable.
4/4/15	Type C CMC Meeting	To discuss CMC requirements for a methotrexate pediatric oral solution regarding the active pharmaceutical ingredient and drug product specifications, as well as the stability requirements for submission of the 505(b)(2) NDA.
5/28/15	Orphan Designation (15-4796)	Treatment of ALL in pediatric patients The oral solution is an improved presentation making it superior to the currently available methotrexate tablets and injectable formulations approved for use in pediatric patients with ALL.
8/28/15	Orphan Designation (15-4795)	Treatment of oligoarticular JIA (which includes persistent oligoarthritis, psoriatic JIA, enthesitis-related arthritis, or undifferentiated arthritis) and polyarticular JIA pediatric patients The oral solution is an improved presentation making it superior to the currently available methotrexate tablets and injectable formulations approved for use in pediatric

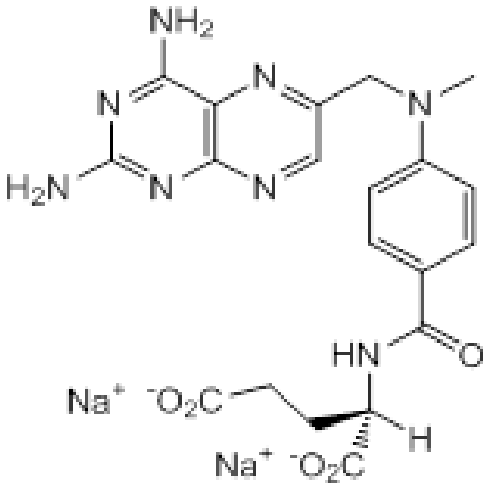
		patients with ALL.
8/31/15	NDA 208400 submitted	

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC):

Drug Substance:

- DMF (b) (4) is referenced, adequate
- Methotrexate Sodium is a yellow to orange crystalline powder.
- It is freely soluble in water.

Figure 2: Methothrexate Structure



Drug Product:

- Methotrexate Oral Solution, 2.5 mg/mL, is a ready-to-use aqueous solution, which is a clear, yellow to orange colored.
- In addition to the API, methotrexate sodium, the drug product contains citric acid, sodium citrate, methylparaben sodium, propylparaben sodium and sucralose, (b) (4) water.
- The pH of the product is adjusted (b) (4) with NaOH and HCl

Clinical Microbiology: (copied from midcycle meeting slides)

The following issues were identified at the midcycle meeting:

- The applicant needs to provide data from Antimicrobial Effectiveness studies using the drug product formulated with the (b) (4) content (i.e. (b) (4) %) established in the release or stability specifications

- Non-sterile aqueous drug products may potentially be contaminated with organisms in the Burkholderia cepacia complex (BCC). In order to control for the presence of BCC in the product, the applicant should:
    - identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product.
    - Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC.

Observations During Inspection of the Manufacturing Facility of the (b) (4) (b) (4). On the following dates (b) (4) (b) (4), the (b) (4) manufacturing facility in (b) (4) was inspected by the FDA and the following observations (see Observations 1-7 listed below) were made:

OBSERVATION 1:

(b) (4)

OBSERVATION 2:
Equipment and utensils are not cleaned and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product.

OBSERVATION 3:
Buildings used in the manufacturing, processing and packing of a drug product are not maintained in a good state of repair.

OBSERVATION 4:
Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other records are instituted only by authorized personnel.

OBSERVATION 5:
The responsibilities and procedures applicable to the quality control unit are not fully followed.

OBSERVATION 6:
There is a failure to thoroughly review any unexplained discrepancy and the failure of a batch or any of its components to meet any of its specifications whether or not the batch has been already distributed.

OBSERVATION 7:
Written production and process control procedures are not documented at the time of performance.

At the time of the submission of this review, these findings are still being reviewed and therefore the impact that they would have on the regulatory recommendation for NDA 208400 is unclear.

4. CLINICAL PHARMACOLOGY: (This section was excerpted from the reviews of Dr. Salaheldin Hamed, and Dr. Bahru Habtemariam. For details, please see their review)

A. Mechanism of Action: Methotrexate is a folic acid analogue. Methotrexate inhibits purine and pyrimidine synthesis.

B. Pharmacodynamics: Rely on reference product.

C. Pharmacokinetics: (copied from midcycle meeting slides). The Applicant submitted two trials: SG02-03 and SG02-04. The pivotal trial SG02-03 was a bioequivalence study and SG02-04 was a food effect study.

Summary of Results of SG02-03:

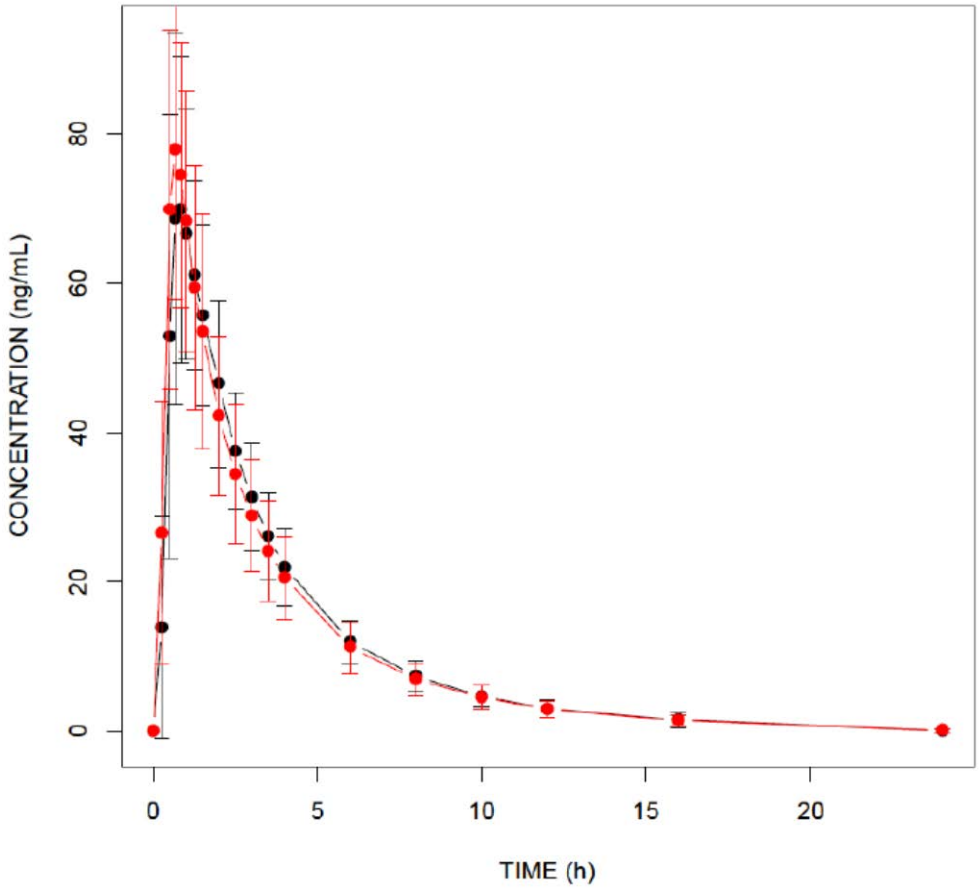
SG02-03 was a 2 x 2 crossover design comparing the pharmacokinetics associated with 2.5 mg tablets with pharmacokinetics associated with 1 ml of 2.5 mg/ml solution.

Results: The results of the SG02-03 trial are summarized below in Table 3 and Figure 3.

Table 3: SG02-03 PK Results - Bioequivalence Trial

Parameter	Ratio (% of Reference)	90% CI
AUC_{inf}	98	[95, 105]
C_{max}	107	[100, 115]

Figure 3: SG02-03 Comparison of Mean PK Profiles – Bioequivalence Trial



Conclusion: On the basis of the analysis of this data (see Figure 3 and Table 3), the clinical pharmacology reviewer concluded that the tablet and the oral solution formulations of methotrexate were bioequivalent.

Summary of Results of SG02-04:

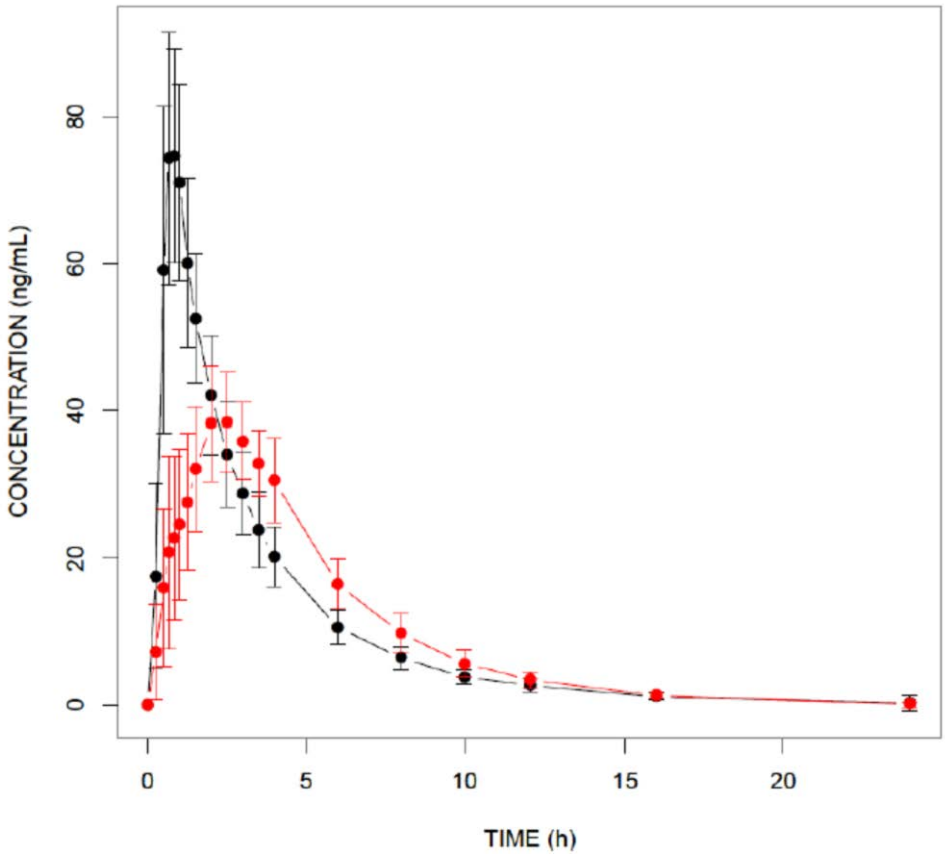
The sponsor also conducted a food effect study, SG02-04. The rationale for this trial was that the drug label indicates there is a food effect, specifically a decreased C_{max} and T_{max} when the oral solution is given with food. The SG 02-04 was a 2 x 2 crossover design of 21 patients comparing administration after a 10 hour fast (solid black circles) and after a standard high fat meal (solid red circles).

Results: The results of the SG02-04 trial are summarized below in Figure 4 and Table 4.

Table 4: SG02-04 PK Results - Food Effect Trial

Parameter	Ratio (% of Reference)	90% CI
AUC_{inf}	96	[91, 102]
C_{max}	50	[47, 54]

Figure 4: SG02-04 Comparison of Mean PK Profiles – Food Effect Trial



Conclusion: The clinical pharmacology reviewer concluded that administration with high fat meal resulted in an approximately 50% decrease in the C_{max}, and prolonged the T_{max} from 0.83 hours fasted to 2 hours fed. However, the AUC_{inf} was comparable.

5. SAFETY: (This section is excerpted from the review of Dr. Patricia Dinndorf. For details, please see her review).

The Applicant submitted the results of the trials presented below in Table 5 to support NDA 208400. The clinical pharmacology results from these two trials were presented in the previous section. The safety results from these two trials will now be presented (see below).

Table 5: Trials supporting NDA 208400

Table 5.2-1. Listing of All Clinical Studies						
Type of Study	**Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Dosage Regimen Route of Administration Duration; Test Product(s)**	**Healthy Subjects or Diagnosis of Patients Number of Subjects**	**Study Status Type of Report**
BA	*SG02-03*	To assess the bioavailability of Methotrexate Oral Solution versus Methotrexate Tablets (DAVA) under fasted conditions	Single-dose, open-label, randomized, 2-period, 2-treatment, 2-way crossover	A: Single dose; oral; Methotrexate Oral Solution 2.5 mg (fasted) B: Single dose; oral; Methotrexate Tablets 2.5 mg (fasted)	Healthy adult male subjects 34 enrolled (31 completed)	Complete eCTD
BA	*SG02-04*	To assess the bioavailability of Methotrexate Oral Solution under fasted and fed conditions	Single-dose, open-label, randomized, 2-period, 2-treatment, 2-way crossover	A: Single dose; oral; Methotrexate Oral Solution 2.5 mg (fasted) B: Single dose; oral; Methotrexate Oral Solution 2.5 mg (fed)	Healthy adult male subjects 24 enrolled (21 completed)	Complete eCTD
BA = bioavailability; DAVA = DAVA Pharmaceuticals, Inc.; eCTD = electronic Common Technical Document.						

The SG02-03 Trial:
STUDY INFORMATION:

- Title: "A Randomized, Open-Label, Two-Period, Two-Treatment, Two-Way, Crossover Study to Determine the Relative Bioavailability of Methotrexate Pediatric Oral Solution vs Methotrexate Tablets USP, (DAVA) 2.5 mg under Fasted Conditions in Healthy Adult Male Volunteers"
- Phase: I
- Design: Open Label, single-dose, randomized, two-period two-treatment, two-way crossover
- Study Sites: Worldwide Clinical Trials Early Phase Services, San Antonio, Texas
- Proposed Sample Size: 34
- Gender: Male
- Age Range: 18 to 55 years

Dose: 2.5 mg/mL (Silvergate); Methotrexate Tablet, 2.5 mg (DAVA)
Route: oral
Planned enrollment: 34
Actual enrollment: 34, 31 analyzed

Primary Objective:

The objective of this study was to assess the relative bioavailability of a test formulation of methotrexate pediatric oral solution, 2.5 mg/mL (Silvergate) compared to an equivalent oral dose of the commercially available reference listed drug methotrexate tablet, 2.5 mg (DAVA), when administered under fasted conditions in healthy adult male subjects.

Treatment Plan: (copied from eCTD submission section 5.3.1.2 SG02-03 page 21 of 136)

Adult male subjects were to receive a single dose of methotrexate pediatric oral solution, 2.5 mg/mL (Treatment A) in one period, and a separate single dose of methotrexate tablet, 2.5 mg (Treatment B) in another period. Each treatment was administered after an overnight fast of at least 10 hours. Treatment A was administered via a 1 mL glass dosing syringe and followed with 240 mL of room temperature tap water. Treatment B was administered with 240 mL of room temperature tap water. The subjects fasted for 4 hours after dosing. Except for the 240 mL of room temperature water provided with the dose, no water was consumed for 1 hour prior to dose through 1 hour post dose. Each drug administration was separated by a washout period of at least 7 days. During each study period, meals were the same and scheduled at approximately the same times relative to dose.

Results: (copied from eCTD submission section 5.3.1.2 SG02-03 page 38 of 136)

A total of 34 subjects were randomized into the study; 31 of these subjects completed both periods of the study. Two subjects were withdrawn at Period 2 check-in due to protocol non-compliance. One subject was withdrawn at Period 2 check-in due to an AE of fungal skin infection. The demographics of the study subjects are presented below in Table 6.

Table 6: Demographics: (copied from eCTD submission section 5.3.1.2 SG02-03 page 40 of 136)

			Sequence	
Characteristic		**All (N= 34)**	**AB (N= 17)**	**BA (N= 17)**
Sex	Male	34 (100.0%)	17 (100.0%)	17 (100.0%)
Age (years)	N	34	17	17
	Mean (SEM)	34.41 (1.80)	37.24 (2.16)	31.59 (2.79)
	Std Dev	10.52	8.89	11.50
	Median	32.00	34.00	27.00
	Min, Max	19.00, 54.00	26.00, 53.00	19.00, 54.00
Ethnicity	Hispanic or Latino	13 (38.2%)	5 (29.4%)	8 (47.1%)
	Not Hispanic or Latino	21 (61.8%)	12 (70.6%)	9 (52.9%)
Race	American Indian or Alaska Native	2 (5.9%)	1 (5.9%)	1 (5.9%)
	Asian	1 (2.9%)	0 (0.0%)	1 (5.9%)
	Black or African American	14 (41.2%)	9 (52.9%)	5 (29.4%)
	White	17 (50.0%)	7 (41.2%)	10 (58.8%)
Height (cm)	N	34	17	17
	Mean (SEM)	173.81 (1.54)	172.21 (1.78)	175.41 (2.51)
	Std Dev	8.97	7.34	10.33
	Median	172.50	172.00	174.00
	Min, Max	159.00, 203.00	159.50, 183.00	159.00, 203.00
Weight (kg)	N	34	17	17
	Mean (SEM)	79.28 (1.74)	80.45 (2.54)	78.11 (2.43)
	Std Dev	10.16	10.48	10.00
	Median	80.20	80.80	79.60
	Min, Max	60.80, 99.60	61.30, 99.60	60.80, 93.30
BMI (kg/m^2)	N	34	17	17
	Mean (SEM)	26.20 (0.41)	27.05 (0.56)	25.35 (0.54)
	Std Dev	2.39	2.29	2.23
	Median	26.40	27.60	25.80
	Min, Max	21.90, 30.00	21.90, 30.00	22.20, 29.90

Safety Results: (copied from eCTD submission section 5.3.1.2 SG02-03 page 48 of 136)

The TEAEs from SG02-03 are presented below in Table 7 and in Table 8.

Table 7: SG02-03 Treatment-emergent Adverse Events

Number of Subjects:	Treatment A (N=33)	Treatment B (N=32)
Treatment-emergent AE	2 (6.1%)	2 (6.3%)
Treatment-related Treatment-emergent AE	1 (3.0%)	1 (3.1%)
Serious Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Serious Treatment-related Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Treatment-emergent AE Leading to Study Discontinuation	1 (3.0%)	0 (0.0%)

(copied from eCTD submission section 5.3.1.2 SG02-03 page 49 of 136)

Table 8: SG02-03 Treatment-emergent Adverse Events by SOC and PT

System Organ Class	Preferred Term	Treatment A (N=33)	Treatment B (N=32)
Gastrointestinal disorders	Paraesthesia oral	0 (0.0%)	1 (3.1%)
Immune system disorders	Hypersensitivity	0 (0.0%)	1 (3.1%)
Infections and infestations	Fungal skin infection	1 (3.0%)	0 (0.0%)
Nervous system disorders	Headache	1 (3.0%)	1 (3.1%)
Respiratory, thoracic and mediastinal disorders	Nasal congestion	1 (3.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Seborrhoeic dermatitis	1 (3.0%)	0 (0.0%)

(copied from eCTD submission section 5.3.1.2 SG02-03 page 48 of 136)

Conclusions:

Overall, both the methotrexate pediatric oral solution, 2.5 mg/mL and the methotrexate tablets, 2.5 mg, were well-tolerated in this study and the AE profiles were consistent with the known effects of both drugs. The incidence of treatment-emergent AEs was 6.3% or less for both treatment groups; 4 subjects overall experienced treatment-emergent AEs.

Treatment-emergent AEs were reported by 2 (6.1%) subjects following administration

of Treatment A, and by 2 (6.3%) subjects following Treatment B. Of these, 1 (3.0%) subject reported a treatment-related AE following Treatment A, and 1 (3.1%) subject reported a treatment-related AE following Treatment B. There were no serious AEs

The SG02-04 Trial

- **Title: "A Randomized, Open-Label, Single-Dose, Two-Period, Two-Treatment, Two-Way Crossover Relative Bioavailability Study of Methotrexate Pediatric Oral Solution under Fasted and Fed Conditions in Healthy Adult Male Volunteers"**
- Phase: I
- Design: Open Label, single-dose, randomized, two-period two-treatment, two-way crossover
- Study Sites: Worldwide Clinical Trials Early Phase Services, San Antonio, Texas
- Proposed Sample Size: 24
- Gender: Male
- Age Range: 18 to 55 years

Dose: 2.5 mg/mL (Silvergate); Methotrexate Tablet, 2.5 mg (DAVA)
Route: oral
Planned enrollment: 24
Actual enrollment: 24 enrolled, 21 analyzed

Primary Objective: The objective of this study was to assess the effect of food on the relative bioavailability of a test formulation of methotrexate pediatric oral solution, 2.5 mg/mL.

Treatment Plan: (copied from eCTD submission section 5.3.1.2 SG02-04 page 21 of 144)

Healthy adult male subjects were to receive a single dose of the study treatment, methotrexate pediatric oral solution, 2.5 mg/mL, after a 10-hour overnight fast in one period and a single dose of the study treatment after consuming a Food and Drug Administration (FDA) standard high-calorie, high-fat breakfast meal in another period.

During the study period in which a subject was given the fed treatment, the subject fasted overnight for at least 10 hours, then began consuming the high-calorie, high-fat breakfast meal 30 minutes prior to administration of the study drug. With the exception of the high-calorie, high-fat breakfast served in the fed treatment period, meals were the same and scheduled at approximately the same times relative to dose.

Each dose was administered via a 1 mL glass dosing syringe and followed with 240 mL of room temperature water. The subjects fasted for 4 hours after dosing. Except for the 240 mL of room temperature water provided with the dose, no water was consumed for 1 hour prior to dose through 1 hour postdose. Each drug administration was separated by a washout period of 7 days.

Results: (copied from eCTD submission section 5.3.1.2 SG02-04 page 38 of 144)

A total of 24 subjects participated in the study and 21 of these subjects completed both study periods. Three subjects discontinued from the study early, one due to a mouth injury, one due to vomiting 1 hour after treatment B, one due to non-compliance.

Demographics: (copied from eCTD submission section 5.3.1.2 SG02-04 page 40 of 144)
The baseline demographics for the subjects entered onto SG02-04 are summarized below in Table 9.

Table 9: SG02-04 Demographics

			Sequence	
Characteristic		**All (N= 24)**	**AB (N= 12)**	**BA (N= 12)**
Sex	Male	24 (100.0%)	12 (100.0%)	12 (100.0%)
Age (years)	Mean (SEM)	36.92 (2.43)	39.00 (3.48)	34.83 (3.45)
	Std Dev	11.93	12.05	11.95
	Median	34.00	34.00	35.00
	Min, Max	18.00, 55.00	20.00, 55.00	18.00, 54.00
Ethnicity	Hispanic or Latino	15 (62.5%)	7 (58.3%)	8 (66.7%)
	Not Hispanic or Latino	9 (37.5%)	5 (41.7%)	4 (33.3%)
Race	American Indian or Alaska Native	1 (4.2%)	0 (0.0%)	1 (8.3%)
	Asian	1 (4.2%)	0 (0.0%)	1 (8.3%)
	Black or African American	7 (29.2%)	3 (25.0%)	4 (33.3%)
	White	15 (62.5%)	9 (75.0%)	6 (50.0%)
Height (cm)	Mean (SEM)	174.73 (1.61)	175.29 (2.83)	174.17 (1.66)
	Std Dev	7.87	9.79	5.73
	Median	174.75	177.75	174.00
	Min, Max	153.00, 187.50	153.00, 187.50	167.50, 185.00
Weight (kg)	Mean (SEM)	80.29 (1.88)	80.28 (2.80)	80.30 (2.64)
	Std Dev	9.21	9.69	9.13
	Median	80.75	79.95	82.60
	Min, Max	60.70, 98.50	60.70, 98.50	64.20, 93.30
BMI (kg/m^2)	Mean (SEM)	26.35 (0.61)	26.23 (0.94)	26.48 (0.82)
	Std Dev	2.99	3.25	2.84
	Median	27.30	27.15	27.30
	Min, Max	18.80, 29.70	18.80, 29.60	22.40, 29.70

Safety: (copied from eCTD submission section 5.3.1.2 SG02-04 page 48 of 144)

The safety results from SG02-04 are summarized below in Tables 10-11.

Table 10: SG02-04 Treatment-emergent Adverse Events

Number of Subjects:	Treatment A (N=22)	Treatment B (N=23)
Treatment-emergent AE	0 (0.0%)	3 (13.0%)
Treatment-related Treatment-emergent AE	0 (0.0%)	1 (4.3%)
Serious Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Serious Treatment-related Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Treatment-emergent AE Leading to Study Discontinuation	0 (0.0%)	1 (4.3%)

(copied from eCTD submission section 5.3.1.2 SG02-04 page 49 of 144)

Table 11: SG02-04 Treatment-emergent Adverse Events by SOC and PT

System Organ Class	Preferred Term	Treatment A (N=22)	Treatment B (N=23)
Gastrointestinal disorders	Vomiting	0 (0.0%)	1 (4.3%)
Injury, poisoning and procedural complications	Mouth injury	0 (0.0%)	1 (4.3%)
Nervous system disorders	Dizziness	0 (0.0%)	1 (4.3%)
	Hypoaesthesia	0 (0.0%)	1 (4.3%)
	Presyncope	0 (0.0%)	1 (4.3%)

(copied from eCTD submission section 5.3.1.2 SG02-04 page 48 of 144)

Conclusions: Overall, methotrexate pediatric oral solution, 2.5 mg/mL was well-tolerated in this study under both fasted and fed conditions, and the AE profiles were consistent with the known effects of methotrexate. There were no AEs reported after administration of Treatment A. Three (13%) subjects reported AEs after administration of Treatment B. Of the 3 subjects who reported treatment-emergent AEs after Treatment B, only 1 reported a treatment-related event. There were no serious AEs. One AE led to a subject discontinuation from the study.

Regulatory Recommendation: On the basis of the data summarized from Trials SG02-03 and SG02-04, this secondary reviewer is recommending approval of NDA 208400. However, the impact of the observations made at the manufacturing site by the FDA on the approvability of this protocol are unknown at this time.

6. ADVISORY COMMITTEE MEETING: None.

7. DRAFT POST MARKETING COMMITMENTS AND REQUIREMENTS: Under negotiation.

8. LABELING: Under negotiation.

9. REGULATORY RECOMMENDATION: This Secondary Clinical Reviewer recommends approval. However, the impact of the observations (see Section 3) made at the manufacturing site by the FDA on the approvability of this NDA is unknown at this time.

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/s/

ALBERT B DEISSEROTH
05/27/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208-400, Original 2
Priority or Standard	Standard
Submit Date(s)	August 31, 2015
Received Date(s)	August 31, 2015
PDUFA Goal Date	June 30, 2016
Division / Office	DPARP / OND
Reviewer Name(s)	Peter Starke, MD
Review Completion Date	May 26, 2016
Established Name	Methotrexate Oral Solution
Trade Name	Xatmep™
Therapeutic Class	Folate analog metabolic inhibitor
Applicant	Silvergate Pharmaceuticals, Inc.
Formulation(s)	Oral Solution, 2.5 mg/mL
Dosing Regimen	Oral
Proposed Indication(s)	Polyarticular Juvenile Idiopathic Arthritis (pJIA); [Original 1: Acute Lymphocytic Leukemia – see separate review]
Intended Population(s)	pJIA: 2 years of age and older

MEDICAL OFFICER REVIEW

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
August 31, 2015	August 31, 2015	SD-1	Original application
October 2, 2015	October 2, 2015	SD-2	Proprietary Name request #1
December 4, 2015	December 4, 2015	SD-3	Draft labeling
December 17, 2015	December 17, 2015	SD-4	Response to Clinical Pharmacology 74-day comment
December 18, 2015	December 18, 2015	SD-5	120-day Safety Update report
December 23, 2015	December 23, 2015	SD-6	Proprietary Name request #2
February 25, 2016			*Information request for publications on the effects of MTX on pregnancy, lactation, and reproductive potential (per PLLR labeling requirements)*
February 29, 2016			*Proprietary Name granted letter*
March 15, 2016			*DMEPA container labeling comments #1*
April 5, 2016	April 5, 2016	SD-10	Response to March 15 labeling comments
April 7, 2016	April 7, 2016	SD-11	Response to February 25 IR with revised labeling
April 15, 2016			*DMEPA container labeling comments #2*
May 6, 2016	May 6, 2016	SD-13	Container labeling

RECOMMENDED REGULATORY ACTION

NDA/Supplements: X Approval

____ Complete Response

Other Action: ____

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Glossary

AC	advisory committee
AE	adverse event
API	active pharmaceutical ingredient
BA	bioavailability
BAN	British approved name
BE	bioequivalence
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	benefit risk framework
CBER	Center for Biologics Evaluation and Research
CCABA	Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic monograph (21 CFR 341.16)
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
DMC	data monitoring committee

DMPP	Division of Medical Policy Programs
DPARP	Division of Pulmonary, Allergy, and Rheumatology Products
ECG	electrocardiogram
EP	European Pharmacopoeia
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 Harmonization
IFU	instructions for use
IM	intramuscular
IND	Investigational New Drug
INN	international nonproprietary name
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
JIA	juvenile idiopathic arthritis (formerly known as JRA)
JRA	juvenile rheumatoid arthritis (now known as JIA)
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
NDC	National Drug Code
NME	new molecular entity
NSAIDs	nonsteroidal anti-inflammatory agents
OCS	Office of Computational Science
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
OTC	over-the-counter
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
pJIA	polyarticular juvenile idiopathic arthritis (formerly known as polyarticular JRA)

PK	pharmacokinetics
PLR	Physician Labeling Rule
PLLR	Pregnancy and Lactation Labeling Rule
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act (21 U.S.C. 355c)
PRO	patient reported outcome
PSP	Pediatric Study Plan
PSUR	Periodic Safety Update report
RA	rheumatoid arthritis
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
USAN	United States approved name

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, I recommend approval of this application.

1.2 Risk Benefit Assessment

Summary

This is a 505(b)(2) application from Silvergate Pharmaceuticals, Inc. ('Silvergate') for Methotrexate Oral Solution. The application references the Agency's previous findings of safety and effectiveness for the listed drug, Methotrexate Sodium Tablets, manufactured by Dava Pharmaceuticals, Inc., NDA 08085. The development program consisted of 2 comparative bioavailability studies comparing the proposed oral solution with Dava's Methotrexate Sodium Tablets, and the results show bioequivalence between the systemic exposure with the proposed oral solution and the marketed oral tablets. Therefore, the results support approval of this product.

Background and Assessment

There are two listed originator products, both approved in the 1950s, Dava's tablets (approved 1953) and an injection solution (NDA 11719, Hospira, approved 1959). Generics are available for both the oral tablets and parenteral formulations. There are also several auto-injectors approved for subcutaneous use by patients. No methotrexate oral solution products are approved; as a result, healthcare providers often prepare an ad hoc oral formulation based on the parenteral injection solution.

Methotrexate (MTX) is a folate analog metabolic inhibitor currently indicated for the treatment of various neoplastic diseases, adults with severe recalcitrant psoriasis, severe active rheumatoid arthritis (RA), and active polyarticular-course juvenile rheumatoid arthritis (JRA, now called polyarticular juvenile idiopathic arthritis or pJIA). With this application, Silvergate is requesting to limit the indications for their product to two pediatric indications: (1) pediatric patients with acute lymphoblastic anemia (ALL), as part of a combination regimen, and (2) the management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full-dose nonsteroidal anti-inflammatory agents (NSAIDs). Both are pediatric indications for which the applicant has received Orphan Drug designations (ALL: May 28, 2015, 15-4796; pJIA: August 25, 2015, 15-4795). As a result, Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) is not triggered by this application and a Pediatric Study Plan (PSP) was not required.

As noted above, the development program consisted of 2 comparative bioavailability (BA) studies that compared Silvergate's proposed oral solution with Dava's Methotrexate Sodium Tablets. These consisted of 2 open-label, randomized, single dose, 2-way crossover relative bioavailability studies in healthy adult males, Study SG02-3 and Study SG02-4 (Table 2). Study SG02-3 was a single dose BA study that compared the systemic methotrexate exposure of 2.5 mg of the oral solution with 2.5 mg of the Dava tablets in the fasted state. Study SG02-4 was a single dose BA study that compared the systemic methotrexate exposure of 2.5 mg of the oral solution in the fasted and fed states. The results show bioequivalence between the systemic exposure with the proposed product and that from marketed approved oral tablets.

During the review, it was noted that the BA studies used a very low dose (2.5 mg) to establish a link between systemic exposure after dosing with the proposed oral solution and the approved tablet formulation. However, the clinical pharmacology team feels that the studies are acceptable and are applicable across all oral doses, and therefore, their recommendation is Approval of this application. The clinical team agrees. The studies are discussed within Section 4.4, and the results are presented within Section 5.3.1, of this review.

How to label this product was the single largest issue with this application, since the indications for this product are limited to two pediatric indications, whereas the labeling for the listed product referenced in this application (Dava's tablets) includes multiple indications, dosages, and routes of administration. Further, the labeling of the listed product is not in Physician Labeling Rule (PLR) format, includes safety information that pertains to all indications, dosages, and routes of administration, and has dosing information for indications and dosing regimens that cannot be achieved with oral administration. Additionally, it is difficult to separate out where the safety information originates and to which indication it applies. Finally, this label is required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, whereas the listed product is not [in PLLR format]. While the labeling of this product has not been finalized at the time of completion of this review, the focus will be retaining safety information that is relevant to the use of methotrexate for the proposed indications.

Reviewer's Comments

Disclaimer: These comments reflect the personal views of this reviewer, and do not necessarily reflect the views of the Agency.

This product will potentially provide benefit to many children who cannot swallow a tablet formulation of methotrexate and for whom an injection is either unnecessary or undesirable. In current clinical practice, when a liquid formulation of methotrexate is needed for pediatric or adult patients, a relatively inexpensive but palatable ad hoc oral formulation is typically made based on the parenteral methotrexate injection product. In fact there are a number of highly reputable web sites that explain how do this; the drawback being that stability is limited and not assured for such formulations.

In the current application, Silvergate has intentionally limited this product to two pediatric indications for which they have obtained Orphan status. By doing so, Silvergate has avoided user fees, which will allow them to get this product to market with less expense. At the same time they will obtain Orphan exclusivity that will block similar oral solution products from entering the market for these pediatric indications in the near future. Further, by focusing on only pediatric indications, the labeling will not include dosing for any of the adult indications for which an oral solution might be appropriate.

The FDA does not have the authority to regulate drug prices, so I await pricing information for this product. If Silvergate prices this product reasonably and competitively with currently available alternatives, then they have used their savvy to create a marketing niche for their product while fulfilling a major part of the public health need for a marketed low-cost oral solution of methotrexate. If, however, Silvergate uses this as an opportunity to market this product at a price that is markedly higher than the tablet and injectable products, while perfectly legal and understandable from a business perspective, such pricing will not be in the best interest of the public health.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

This is a 505(b)(2) application from Silvergate Pharmaceuticals, Inc. (Silvergate) for Methotrexate Oral Solution. The application references the Agency's previous findings of safety and effectiveness for the listed drug, Methotrexate Sodium Tablets, manufactured by Dava Pharmaceuticals, Inc., NDA 08-085. The development program consisted of 2 comparative bioavailability studies, conducted by Silvergate, comparing their proposed oral solution with Dava's Methotrexate Sodium Tablets.

Methotrexate (MTX) is a folate analog metabolic inhibitor that was first approved in 1953. MTX is approved as tablets (NDA 08-085, Dava Pharmaceuticals Inc., approved 1953) and as an injection solution (NDA 11-719, Hospira, approved 1959). Generics are available for both formulations, and two auto-injectors (Otrexup, NDA 204824, Antares, approved on October 11, 2103; and Rasuvo, NDA 205776, Medac, approved on July 10, 2014) are approved specifically for SC self-administration by patients with RA, pJIA and psoriasis. There are no approved oral solution formulations.

MTX tablets are currently indicated for the treatment of various neoplastic diseases, adults with severe recalcitrant psoriasis, severe active rheumatoid arthritis (RA), and active polyarticular-course juvenile rheumatoid arthritis (pJRA, now called polyarticular juvenile idiopathic arthritis or pJIA). When originally approved, the indications for methotrexate only included oncology indications, which were later the subject of DESI review (DESI 08085).[1] The other approved indications were added subsequent to that time.

With this application, Silvergate is requesting to limit the indications for their product to two pediatric indications: (1) pediatric patients with acute lymphoblastic anemia (ALL), as part of a combination regimen, and (2) the management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full-dose nonsteroidal anti-inflammatory agents (NSAIDs). Both are pediatric indications for which the applicant has received Orphan Drug designations (ALL: May 28, 2015, 15-4796; pJIA: August 25, 2015, 15-4795). As a result, the applicant states that PREA was not triggered by the application and a PSP was not submitted.

The application was submitted on August 31, 2015, and is in electronic Common Technical Document (eCTD) format. Since two review divisions are involved in the

1 In 1962, Congress amended the Food, Drug and Cosmetic Act to require that new drugs also be proven effective for their labeled indications, as well as safe. This amendment also required FDA to conduct a retrospective evaluation of the effectiveness of the drug products that FDA had approved as safe between 1938 and 1962. FDA contracted with the National Academy of Science/National Research Council (NAS/NRC) to make an initial evaluation of the effectiveness of over 3,400 products that were approved only for safety. The NAS/NRC reports for these drug products were submitted to FDA in the late 1960s and early 1970s. The agency reviewed and re-evaluated the reports and published its findings in Federal Register notices. FDA's administrative implementation of the NAS/NRC reports was called the Drug Efficacy Study Implementation (DESI).

review, the application has been administratively split into Original 1 for the hematololgy/oncology indication and Original 2 for the rheumatology indication. This review focuses on the Original 2 indication for pJIA.

2.1 Product Information

The proposed product is an oral solution containing methotrexate sodium equivalent to 2.5 mg/mL of methotrexate.

2.2 Tables of Currently Available Treatments for Proposed Indications

Methotrexate is a folic acid analogue that inhibits production of DNA, RNA, and proteins. Because it is structurally similarity to folate, MTX binds and inhibits the enzyme dihydrofolate reductase (DHFR), thereby preventing the formation of tetrahydrofolate, which is essential for purine and pyrimidine synthesis. Other approved folate analog metabolic inhibitors include trimethoprim, pyrimethamine, and pemetrexed. Methotrexate is currently approved for the following indications:

Indication	Route
Neoplastic diseases	oral, IM, IV, IA, IT
Adults with severe recalcitrant disabling psoriasis that is not adequately responsive to other forms of therapy	oral, IM, IV, SC
Adults with rheumatoid arthritis (RA) who have insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy*	Oral, SC
Polyarticular-course juvenile rheumatoid arthritis (JRA or pJIA) who have insufficient therapeutic response to, or are intolerant of, an adequate trial of first line therapy*	oral, IM, SC
* First line therapy for RA and JRA, as defined in the Indications and Usage section of the labels, includes full dose Non-steroidal anti-inflammatory agents (NSAIDS).	

Polyarticular-course juvenile rheumatoid arthritis (JRA) is now called polyarticular juvenile idiopathic arthritis or 'pJIA', 'JIA' being the more up-to-date classification terminology used to describe what used to be called JRA. Therefore, the newer terminology of pJIA is used in this application instead of the older terminology of JRA, except when specifically referring to the existing labeling or indications for marketed and approved products.

Polyarticular juvenile idiopathic arthritis (pJIA) is a category of juvenile idiopathic arthritis (JIA). pJIA is similar to adult RA with articular manifestations being predominant. The prevalence of JIA has been estimated to be between 57 and 220 per 100,000 children younger than 16 years of age, with pJIA affecting approximately 2 to 17% of children with JIA.

The classes of therapies for pJIA include non-steroidal anti-inflammatory drugs (NSAIDs), systemic and intra-articular glucocorticoids, conventional disease-modifying anti-rheumatic drugs (DMARDs); and biologic DMARDs. DMARDS slow or prevent structural progression of the disease. In the last several decades, MTX has emerged as the most widely accepted traditional DMARD because of its potency and well understood long-term effects. NSAIDs, which formerly were considered a core therapy, are now considered adjunctive therapy. Additionally, a number of highly effective biologicals have been approved that can be used alone or in combination with MTX, allowing individual tailoring of treatment to fluctuations in disease activity and drug-related toxicities.

Biologic DMARDs have revolutionized the treatment of JIA over the past several decades. There are currently four biologic products approved for the treatment of pJIA (Table 1), two TNFα-inhibitors: adalimumab (Humira) and etanercept (Enbrel); one targeting the IL-6 signaling pathway: tocilizumab (Actemra); and one targeting the T-cell co-stimulatory signaling pathway: abatacept (Orencia). (b) (4)

Table 1. Approved biologics for treatment of polyarticular JIA in the United States

Drug	BLA (Sponsor)	Approval Date	Characteristics	Route of Administration
Etanercept (Enbrel ®)	103795 (Immunex)	5/27/1999	Fusion protein (TNF inhibitor)	SC
Abatacept (Orencia ®)	125118 (Bristol Myers Squibb)	4/7/2008	Fusion protein (CTLA-4)	IV
Tocilizumab (Actemra ®)	125276 (Genentech)	4/15/2011	Monoclonal antibody (IL-6 inhibitor)	IV
Adalimumab (Humira ®)	125057 (Abbvie)	2/21/2008	Monoclonal antibody (TNF inhibitor)	SC

Abbreviations: BLA=biologics licence application; ROA=route of administration; SC=subcutaneous; IV=intravenous
Source: FDA generated

2.3 Availability of Proposed Active Ingredient in the United States

Methotrexate is available as oral tablets (in multiple strengths) and as an injectable solution (both preservative-free and with a preservative, in several strengths). Multiple proprietary and generic formulations are available. Please consult the Orange Book (http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm) for the current listings. Additionally, it should be noted that two single-dose auto-injector presentations of MTX have recently been approved for patient self-administration (Otrexup, NDA 204824, Antares, approved on October 11, 2013; and Rasuvo, NDA 205776, Medac, approved July 10, 2014). There are no approved oral solution formulations. In practice, when an oral solution formulation is needed, most practitioners use one of the injectable solutions as the basis of compounding an extemporaneous mixture.

This NDA references the MTX tablets from Dava Pharmaceuticals (NDA 08085), which is listed as an RLD in the Orange Book.

2.4 Important Safety Issues with Consideration to Related Drugs

NA

2.5 Summary of Presubmission Regulatory Activity Related to Submission

During drug development, Silvergate had two meetings with Division of Hematology Products (DHP), a Type B pre-IND meeting on May 21, 2013, and a Type C CMC meeting on April 7, 2015. No meetings were held with the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) prior to the submission of this application.

2.6 Other Relevant Background Information

2.6.1 Proprietary/Trade Name

This product will have the proprietary name of Xatmep™. On October 2, 2015, Silvergate requested review of the proprietary name (trade name) (b) (4). Upon review, the Division of Medication Error Prevention and Analysis (DMEPA) in the Office of Surveillance and Epidemiology (OSE) found that proposed name was not acceptable, and denied their request on November 27, 2015. Silvergate submitted a second request for review of the proprietary name Xatmep™ on December 23, 2015, which was reviewed and granted by DMEPA on February 29, 2016.

2.6.2 Pediatric Issues

As noted above, Silvergate is requesting to limit the indications for their product to two pediatric indications: (1) pediatric patients with acute lymphoblastic anemia (ALL), as part of a combination regimen, and (2) the management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full-dose nonsteroidal anti-inflammatory agents (NSAIDs).

The applicant has previously received Orphan Drug designations for both ALL and pJIA (ALL: May 28, 2015, 15-4796; pJIA: August 25, 2015, 15-4795). At this time, applications for drug products with Orphan Drug indications do not trigger PREA, so a PSP was neither required nor submitted.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No ethical or data integrity issues were noted during the review of this application.

3.2 Compliance with Good Clinical Practices

The applicant states that the studies submitted to this NDA were conducted in accordance with the Declaration of Helsinki and with all applicable laws and regulation, and were in compliance with Good Clinical Practice Guidelines. The protocols and informed consent documents were reviewed by Institutional Review Boards for each center prior to initiation of the study.

3.3 Financial Disclosures

Financial disclosure forms were submitted and reviewed for the two biopharmaceutical studies. No issues were noted.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The OPQ (CMC) team recommends Approval of the proposed oral solution formulation. No review issues were noted. The company has provided stability data and requested 24 months expiry dating.

At the time of completion of this review, the Divisions are aware that one or more Form 483 documents have been issued by the FDA based on a recent facilities inspection. However, the final status of the facilities inspection and its impact on the regulatory decision for this application is not known.

4.2 Clinical Microbiology

No microbiological issues were noted in the application.

4.3 Preclinical Pharmacology/Toxicology

No pharmacology/toxicology information was submitted with this application.

4.4 Clinical Pharmacology

The clinical pharmacology teams recommend Approval of the proposed oral solution formulation.

The clinical pharmacology of this product was assessed in 2 open-label, randomized, single dose, 2-way crossover relative bioavailability studies in healthy adult males, Study SG02-3 and Study SG02-4 (Table 2). No drug-drug interaction studies were required or conducted to support the application.

Study SG02-3 was a single dose bioavailability study that compared the systemic methotrexate exposure of 2.5 mg of the oral solution with 2.5 mg of the Dava tablets in the fasted state. Study SG02-4 was a single dose bioavailability study that compared the systemic methotrexate exposure of 2.5 mg of the oral solution in the fasted and fed states.

Results of SG02-3 showed similar systemic exposure between the oral solution and the tablet formulations. Results of SG02-4 showed that the presence of food results in a 50% reduction in Cmax and a 1.5 hour delay in Tmax compared to the fasted state, but does not significantly alter the total systemic exposure to methotrexate. Specifics of the study results are shown within Section 5.3.1 of this review.

While these studies used the smallest dose of methotrexate available, the clinical pharmacology teams considered that this was acceptable. Additionally, it is well known that the IV injection solution is widely used as an oral solution preparation for pediatric patients who have difficulty swallowing the tablets. In response to an IR, the Applicant provided literature reports to show that methotrexate prepared as oral solution or syrup using the IV injection solution has similar PK to IR tablets for doses up to 25 mg/m^2. Lastly, since patients are monitored clinically and dosing is titrated to effect, minor differences in systemic exposure due to a particular formulation would likely not be clinically relevant.

4.4.1 Mechanism of Action

No new information was submitted with this application.

4.4.2 Pharmacodynamics

No new information was submitted with this application.

4.4.3 Pharmacokinetics

See Section 5.3.1 of this review for details of the BA/BE studies performed for this application.

5 Sources of Clinical Data

5.1 Table of Studies

Table 2. Clinical Pharmacology Studies

Study	Type	Design	Product	Doses (mg)	N
SG02-3	BA	R, OL, SD, fasting, 2-way crossover in healthy male adults	MTX oral solution Dava MTX tablets	2.5 mg fasted 2.5 mg fasted	R 34 C 31
SG02-4	BA	R, OL, SD, 2-way crossover food effect study in healthy male adults	MTX oral solution MTX oral solution	2.5 mg. fasted 2.5 mg. fed	R 24 C 21
BA= bioavailability					

Source: tabular-listing.pdf

5.2 Review Strategy

No clinical trials were performed for this application. The application includes a literature review summarizing the safety and effectiveness of MTX, and a development program that included two clinical pharmacology studies, as shown in Table 2. The Division does not consider any of these studies to be clinical trials for the purposes of exclusivity determination. The studies submitted to the application were reviewed along with the literature supports submitted to the application.

5.3 Discussion of Individual Studies

5.3.1 Clinical Pharmacology Studies

Clinical pharmacology was assessed in 2 open-label, randomized, 2-way crossover studies (Study SG02-3 and Study SG02-4).

Both of these studies were conducted at Worldwide Clinical Trials (WCT) in Texas. Of note, the Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) conducted a surveillance inspection at (b) (4) (b) (4), specifically auditing the analytical portions of bioequivalence studies conducted by (b) (4) to support this and other applications. OSIS recommended that the bioanalytical data from these studies be accepted by the Agency for further review.

5.3.1.1 Study SG02-3

Initiation Date:	January 25, 2015
Completion Date:	January 31, 2015
Investigation Site:	PI: Cynthia Zamora, MD Worldwide Clinical Trials Early Phase Services, LLC 2455 NE Loop 410, Suite 150 San Antonio, Texas 78217
Bioanalytical Laboratory:	Not specified

Study SG02-3 was an open-label, single-dose, two period, two-treatment, two-way crossover PK study that compared the systemic MTX exposure following oral administration of 2.5 mg of the proposed MTX oral solution with 2.5 mg of the Dava MTX tablets under fasted conditions in 34 healthy adult males, 18-55 years of age with a BMI between 18 and 30 kg/m^2 and a minimum weight of 50 kg (110 lb). There was a 7-day washout between treatments. Blood (plasma) PK samples were drawn predose, and at 15, 30, 40, and 50 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, and 24 hours postdose. Safety assessments included screening with hematology, serum chemistries, urinalysis, serology for HBsAg, Hepatitis C antibody and HIV, and urine drug tests; physical examinations and ECGs at screening and at the end of the study; vital signs; and adverse events (AEs).

The study was performed at a single clinical site in the United States and is stated to have been conducted under an independent IRB and carried out in accordance with the principles defined in the Declaration of Helsinki and the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use. Written informed consent was obtained from each subject. However, the informed consent document was not reviewed herein. There were no protocol amendments or changes to the planned conduct of the study or analyses.

A total of 34 subjects were randomized, of whom 31 completed both study periods. Three subjects were withdrawn at check-in for Period 2, two for protocol noncompliance, and one for a fungal skin infection. The study population was all male, 50% white, 41% African American, 38% Hispanic, with a mean age, weight, and BMI of 34 years, 79 kg, and 26.2 kg/m^2, respectively.

There were no deaths and no serious adverse events (SAEs). AEs were reviewed, and there were no AEs reported that were new or of consequence, and there were no differences in the safety profiles of the two formulations tested.

PK parameters are shown in Table 3 and shown graphically in Figure 1 and Figure 2. Systemic exposure following administration of the oral solution and tablets was bioequivalent based on upper and lower 90% confidence intervals (CI) for the geometric LS means falling within the bounds of 80 to 125%.

Table 3. SG02-03, PK parameters

Parameter Mean (SD)	MTX Oral Solution	MTX Tablets
N	31	31
C_{max} (ng/mL/mg)	86.0 (18.1)	80.2 (17.7)
T_{max} (hr)	0.75 (0.25)	0.86 (0.34)
½ life (hr)	3.58 (0.79)	3.21 (0.46)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	251.5 (52.34)	253.5 (41.86)

Source: T11.4.3.2, p45; report-body.pdf

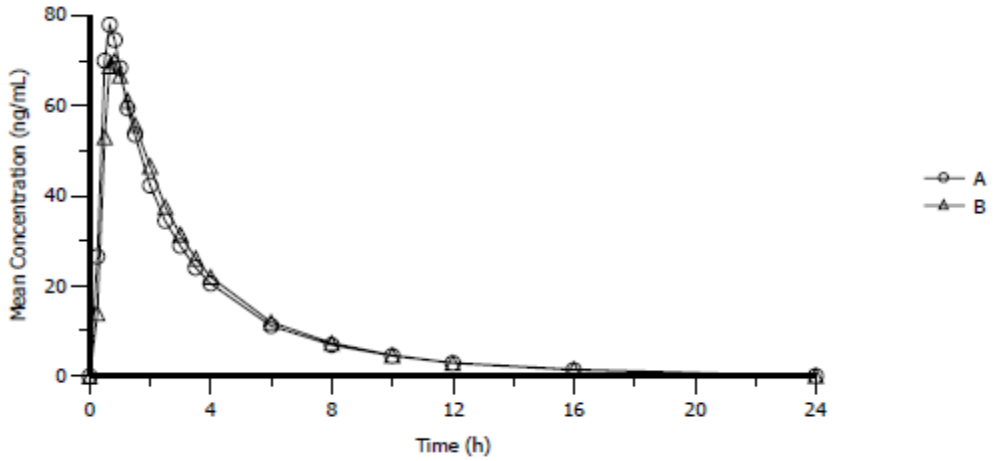

Figure 1. SG02-03, Mean MTX concentration vs time, original scale

Source: F11.4.3.1, p44; report-body.pdf

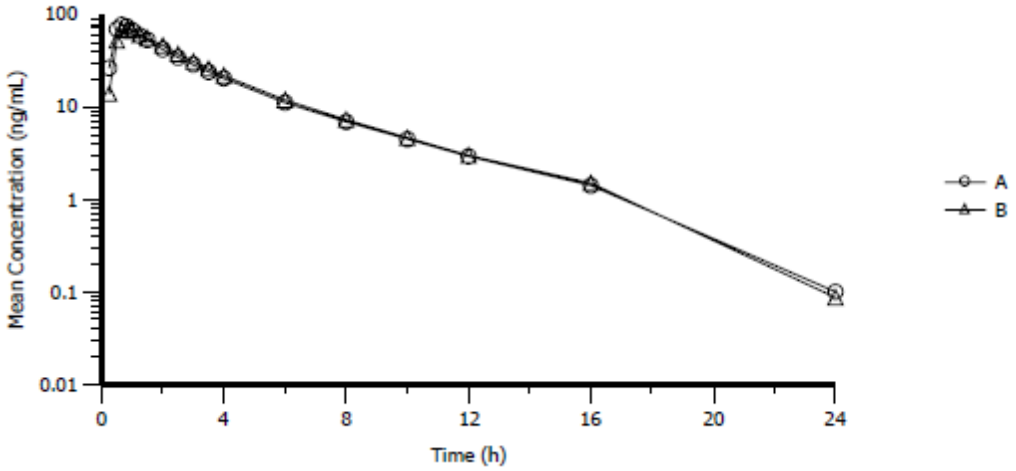

Figure 2. SG02-03, Mean MTX concentration vs time, log scale

Source: F11.4.3.1, p44; report-body.pdf

Conclusion

This open-label PK study demonstrated bioequivalence between 2.5 mg of each of the proposed MTX oral solution and approved tablet formulations.

5.3.1.2 Study SG02-04

Initiation Date:	March 10, 2015
Completion Date:	March 18, 2015
Investigation Site:	PI: Cynthia Zamora, MD Worldwide Clinical Trials Early Phase Services, LLC 2455 NE Loop 410, Suite 150 San Antonio, Texas 78217
Bioanalytical Laboratory:	Not specified

Study SG02-4 was food effect PK study. It used an open-label, single-dose, two-period, two-treatment, two-way crossover design to compare the systemic MTX exposure following oral administration of 2.5 mg of the proposed MTX oral solution under fasted and fed conditions in 24 healthy adult males, 18-55 years of age with a BMI between 18 and 30 kg/m^2 and a minimum weight of 50 kg (110 lb). There was a 7-day washout between treatments. Blood (plasma) PK samples were drawn predose, and at 15, 30, 40, and 50 minutes, and 1, 1.25, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, and 24 hours postdose. Safety assessments included screening with hematology, serum chemistries, urinalysis, serology for HBsAg, Hepatitis C antibody and HIV, and urine drug tests; physical examinations and ECGs at screening and at the end of the study; vital signs; and adverse events (AEs).

The study was performed at a single clinical site in the United States and is stated to have been conducted under an independent IRB and carried out in accordance with the principles defined in the Declaration of Helsinki and the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use. Written informed consent was obtained from each subject. However, the informed consent document was not reviewed herein. There were no protocol amendments or changes to the planned conduct of the study or analyses.

A total of 24 subjects were randomized, of whom 11 completed both study periods. Three subjects were withdrawn, one for protocol noncompliance (positive urine cotinine screen), and one due to an AE of a mouth injury noted at period 2 check-in, and one due to vomiting within 4 hours of dosing in period 1. The study population was all male, 63% white, 29% African American, 63% Hispanic, with a mean age, weight, and BMI of 37 years, 80 kg, and 26.4 kg/m^2, respectively.

There were no deaths and no serious adverse events (SAEs). AEs were reviewed, and there were no AEs reported that were new or of consequence.

PK parameters are shown in Table 4 and shown graphically in Figure 3 and Figure 4.

Table 4. SG02-04, PK parameters

Parameter Mean (SD)	MTX Oral solution Fed	MTX Oral solution Fasted
N	21	21
C_{max} (ng/mL/mg)	82.5 (14.1)	41.5 (7.24)
T_{max} (hr)	0.76 (0.15)	2.32 (0.64)
½ life (hr)	3.21 (0.68)	2.92 (0.56)
$AUC_{0\text{-}inf}$ (ng•hr/mL/mg)	236.8 (40.54)	230.6 (34.84)

Source: T11.4.3.2, p45; report-body.pdf

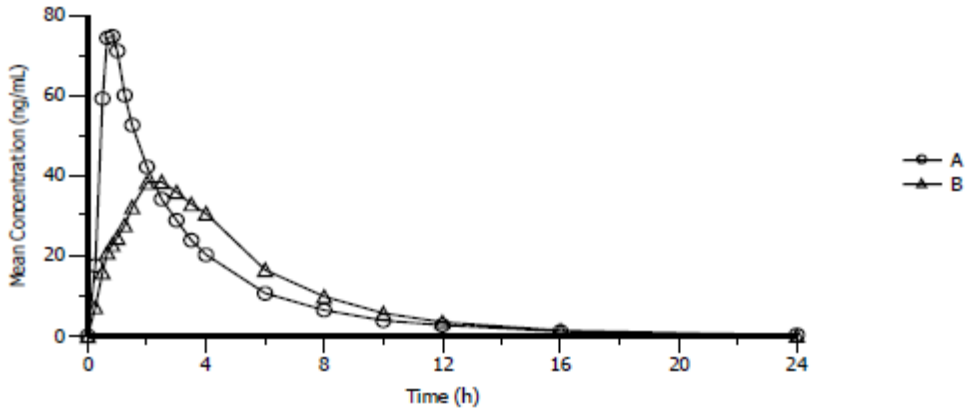

Figure 3. SG02-04, Mean MTX concentration vs time, original scale

Source: F11.4.3.1, p44; report-body.pdf

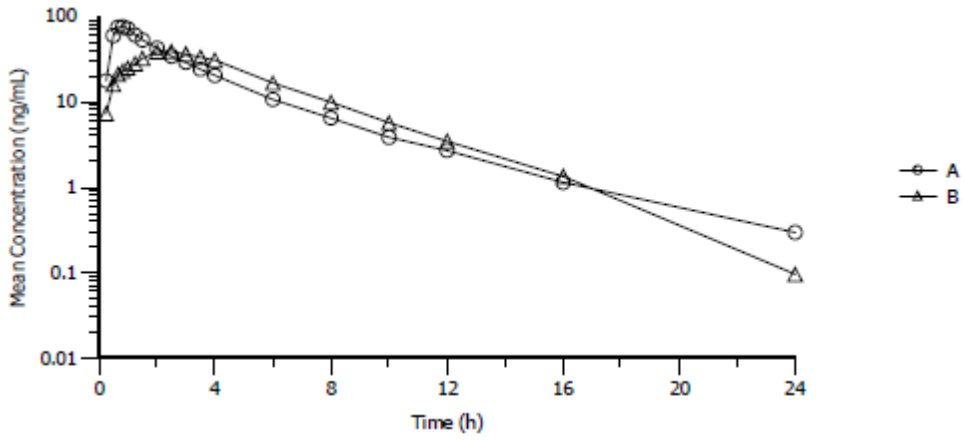

Figure 4. SG02-04, Mean MTX concentration vs time, log scale

Source: F11.4.3.1, p44; report-body.pdf

Conclusion

This open-label PK study demonstrated that the presence of food results in a 50% reduction in Cmax and a 1.5 hour delay in Tmax compared to dosing of methotrexate oral solution on an empty stomach. However, the presence of food does not significantly alter the AUC (i.e., total systemic exposure) to methotrexate.

6 Review of Efficacy

6.1 Efficacy Summary

Support for approval of this application is based on the Agency's previous findings of safety and effectiveness of MTX in patients with pJIA.

7 Review of Safety

7.1 Safety Summary

Two relative bioavailability studies are submitted. Both were single dose studies that used the lowest available doses of MTX (2.5 mg) in healthy adults, and no unexpected safety findings were noted. Methotrexate is already labeled for oral use in patients with RA and pJIA.

7.1 Methods

NA

7.2 Adequacy of Safety Assessments

NA

7.3 Major Safety Results

NA

7.4 Supportive Safety Results

NA

7.5 Other Safety Explorations

NA

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No new information is submitted with this NDA. Methotrexate is already labeled as causing chromosomal damage, although the risk of neoplasia in humans is unknown.

7.6.2 Human Reproduction and Pregnancy Data

No new information is submitted with this NDA. Methotrexate is already labeled as Pregnancy Category X, with a contraindication for use in pregnancy and in breastfeeding mothers.

7.6.3 Assessment of Effects on Growth

No new information is submitted with this NDA.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No new information is submitted with this NDA. Methotrexate is already labeled for much higher doses when used for treatment of neoplastic diseases, and for use of leucovorin to diminish the toxicity and counteract the effects in overdosage.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

NA

9 Appendices

9.1 Literature Review References

NA

9.2 Labeling Recommendations

Labeling revisions are ongoing at the time of completion of this document. Therefore, this section only provides a brief summary of the main issues found during initial review of the labeling, and is not intended as a complete review. The only labeling submitted with the application were the Prescribing Information (PI) and container labeling. No carton or patient labeling was submitted. All of the draft labeling included TRADENAME as a placeholder, which will be replaced by the applicant's trade name (Xatmep) before approval.

The proposed PI is in Physician Labeling Rule (PLR) format, whereas the listed product referenced in the application is not. Two recently approved methotrexate auto-injector products are approved in PLR format. The proposed labeling is also Pregnancy and Lactation Labeling Rule (PLLR) compliant, whereas previously approved products are not in PLLR format. The Pediatric and Maternal Health Team (PMHS) requested additional data to support the proposed PLLR labeling, which was submitted on April 7, 2016.

During the review, the team has been working to modify the language in the proposed labeling to be consistent with current labeling practice and to be scientifically up-to-date. Modifications to the labeling were challenging, as the safety and other information in the current methotrexate labels pertains to all indications, dosages, and routes of administration, and it is often difficult to separate out where that information originates and to which indication it applies. As a result, the clinical and other review teams are in the process of culling through the proposed PI and updating information as appropriate, or removing information that does not specifically relate to the limited indications or route of administration of this product. For example, information about high-dose methotrexate that can only be achieved with other dosage forms or routes of administration, or information about use in patients with RA or psoriasis, will be deleted. Further, the D&A, Warnings, Drug Interactions, and other sections will be updated to eliminate scientifically outdated information, thereby providing up-to-date and more user-friendly labeling while retaining the critical information needed for safe and effective use.

(b) (4) There are two aspects to these proposed changes. First, the term 'children' would be changed to 'pediatric patients', an editorial change that reflects best labeling practice. Second and more importantly, (b) (5) [2]

DPARP also plans to shorten the pJIA subsection within the Dosage and Administration section to delete material that is currently in that section but does not actually reflect on the safe and effective dosage and administration of methotrexate oral solution for pJIA.

9.3 Advisory Committee Meeting

An Advisory Committee meeting was not held during the review of this product.

2 Reference: *Singh JA, et al. 2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Disease-Modifying Antirheumatic Drugs and Biologic Agents in the Treatment of Rheumatoid Arthritis. Arthritis Care & Research 202;64(5);625-639.*

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/s/

PETER R STARKE
05/26/2016

JANET W MAYNARD
05/26/2016

CLINICAL REVIEW

Application Type	NDA (505(b)(2))
Application Number(s)	208400
Priority or Standard	Standard
Submit Date(s)	8/31/15
Received Date(s)	8/31/15
PDUFA Goal Date	6/30/16
Division / Office	DHP/OHOP
Reviewer Name(s)	Patricia Dinndorf
Review Completion Date	5/24/16
Established Name	Methotrexate
(Proposed) Trade Name	Xatmep
Therapeutic Class	Folate analog metabolic inhibitor
Applicant	Silvergate Pharmaceuticals
Formulation(s)	Oral solution (2.5 mg/mL)
Dosing Regimen	Multiple
Indication(s)	Acute Lymphoblastic Leukemia (ALL) Polyarticular juvenile idiopathic Arthritis (pJIA)
Intended Population(s)	Pediatric patients with ALL Pediatric patients with pJIA

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Table of Abbreviations

AE	Adverse event
ALC	Absolute lymphocyte count
ALL	Acute lymphoblastic leukemia
ANC	Absolute neutrophil count
BA	Bioavailability
BMI	Body mass index
CCG	Childrens Cancer Group (precursor to COG)
COG	Childrens Oncology Group
CS	Clinically significant
ECG	Electrocardiogram
eCTD	Electronic common technical document
FDA	Food and Drug Administration
GCP	Good clinical practice
HIV	Human immunodeficiency virus
IND	Investigational new drug
OTC	Over the counter
pJIA	Polyarticular juvenile idiopathic arthritis
PK	Pharmacokinetic
POG	Pediatric Oncology Group (precursor to COG)
PT	Preferred term
SOC	System Organ Class

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This review will focus on the proposed indication:

> Treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as a component of a combination maintenance therapy regimen

I recommend this 505(b)(2) application for Xatmep be approved for pediatric patients with ALL as a component of a combination maintenance therapy regimen. This recommendation is based on the clinical pharmacology review of trial GS02-03, a bioequivalence study. This trial was conducted using a 2 x 2 crossover design comparing 2.5 mg tablets to 1 ml of 2.5 mg/ml solution. The clinical pharmacology reviewer determined that the tablet and the oral solution were bioequivalent. This formulation of methotrexate will improve the ability to reliably provide the appropriate dose of this essential medication to children with acute lymphoblastic leukemia (ALL).

1.2 Risk Benefit Assessment

Table 1: Risk Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood with a peak incidence at the age of 3 years.	**Summary of evidence:** Oral methotrexate has been an integral component of ALL therapy since it was approved in 1953. Successive clinical trials have demonstrated its contribution to successful maintenance therapy and improved survival of patients with ALL.	**Conclusions (implications for decision):** 1. A formulation that provides more accurate dosing is a significant contribution to ALL therapy, especially in younger patients unable to swallow pills. 2. An alternative formulation also ensures better drug availability in the event of a drug shortage.
Unmet Medical Need Oral methotrexate is a component of maintenance chemotherapy for ALL. The 2.5 mg tablet or oral administration of methotrexate for injection are not ideal formulations for younger children or children who have difficulty swallowing pills.	**Summary of evidence**: • The solution is an appropriate formulation for young children or children who have difficulty swallowing pills. • The formulation of an oral solution of 2.5 mg/ml is an appropriate presentation of a medicine for children who are receiving doses of 20 to 40 mg/m^2 weekly. • The dose of methotrexate is modified to maintain an absolute neutrophil count (ANC) between 500 to 1500/µL and platelet count > 75,000/ µL. The oral solution is a formulation that facilitates dose adjustments.	**Conclusions (implications for decision):** The methotrexate solution is an appropriate formulation which is superior to the 2.5 mg tablet or use of methotrexate for injection orally, especially for children less than 5 years of age. The solution is a superior presentation to pills to allow dose adjustments.
Clinical Benefit See Unmet Medical Need		
Risk No risk in excess of the available tablet formulation	**Summary of evidence**: The solution is a superior presentation for children it allows straightforward provision of the appropriate dose.	**Conclusions (implications for decision):** This is a superior presentation compared to tablets for children who have difficulty swallowing pills.
Risk Management Ensure caregivers have adequate instructions to accurately measure and administer the correct dose	**Summary of evidence**:	**Conclusions (implications for decision):** 1. Label information and a Med Guide to provide instructions for correct administration
Benefit-Risk Summary and Assessment Xatmep is a superior presentation of methotrexate for children unable to swallow tablets. This formulation provides a superior presentation to tablets that are broken, crushed or extemporaneously formulated.		

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

- Label information
- Medication Guide

1.4 Recommendations for Postmarket Requirements and Commitments

None recommended.

2 Introduction and Regulatory Background

This is a 505(b)(2) application. Approval is based on the results of a bioequivalence study comparing Dava Pharmaceuticals Inc Methotrexate Sodium tablets (Reference Product NDA 8085) to the 2.5 mg/mL solution of methotrexate. The applicant also conducted a food effect study.

Methotrexate was originally approved December 7, 1953.

The clinical pharmacology reviewer has evaluated the acceptability of the results of the studies submitted to support this application. The clinical pharmacology review supports approval.

2.1 Product Information

Proprietary Name of the Drug Product	Xatmep Oral Solution
Nonproprietary Name of Drug Product	Methotrexate Oral Solution
Nonproprietary Name of Drug Substance	Methotrexate sodium
Dosage Form	Oral solution
Strength	2.5 mg/mL (methotrexate) Each bottle contains 120 mL of the oral solution.

2.2 Tables of Currently Available Treatments for Proposed Indications

Methotrexate is a component of multi-agent combination chemotherapy regimen for the treatment of acute lymphoblastic leukemia (ALL) and other lymphoid malignancies.

2.3 Availability of Proposed Active Ingredient in the United States

Methotrexate is available as a 2.5 mg tablet.

2.4 Important Safety Issues With Consideration to Related Drugs

(copied from DAVA Label 7/15)
Most common adverse reactions reported with oral methotrexate are ulcerative stomatitis, leukopenia, nausea, and abdominal distress. Other frequently reported adverse effects include malaise, fatigue, chills, fever, dizziness, and decreased resistance to infection.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 2: Regulatory History

Regulatory History		
Date	**Item**	**Discussion**
5/21/13	Pre-IND Meeting	• Sponsor plans to reference nonclinical section of DAVA methotrexate to support 505(b)(2) • FDA response - in general acceptable
		• Sponsor plans to conduct a randomized, parallel, single-dose pivotal comparative bioavailability study of its methotrexate product to DAVA's Methotrexate Sodium 2.5-mg Tablet in 60 healthy adult male subjects under fasted condition to assess bioequivalence. • FDA response – o In general acceptable o PK sampling inadequate o Must assess food effect
		• Sponsor plans to use the 80-125% bounds for the bioavailability study. • FDA – noted no objection
		• Sponsor plans to restrict label indication to the pediatric population • FDA response – no objection
11/7/14	IND 117387	Methotrexate Pediatric Oral Solution Original protocol submitted to IND on 10/9/14 as discussed at Pre IND meeting was the parallel trial in 60 subjects. On 10/17/14 the sponsor queried the agency concerning revising the protocol to a crossover design in 30 subjects. FDA informed sponsor a second protocol could be submitted after the 30 day letter had been issued for the current submission.
11/21/14	New protocol IND 117387 submitted	SG02-03 with cross-over design (n=34) with the same dose and PK time points as SG02-01 was submitted. The clinical pharmacology reviewer determined the protocol was acceptable.
4/4/15	Type C CMC Meeting	To discuss CMC requirements for a methotrexate pediatric oral solution regarding the active pharmaceutical ingredient and drug product specifications, as well as the stability requirements for submission of the 505(b)(2) NDA.
5/28/15	Orphan Designation (15-4796)	Treatment of ALL in pediatric patients The oral solution is an improved presentation making it superior to the currently available methotrexate tablets and injectable formulations approved for use in pediatric patients with ALL.
8/28/15	Orphan Designation (15-4795)	Treatment of oligoarticular JIA (which includes persistent oligoarthritis, psoriatic JIA, enthesitis-related arthritis, or undifferentiated arthritis) and polyarticular JIA pediatric patients The oral solution is an improved presentation making it superior to the currently available methotrexate tablets and injectable formulations approved for use in pediatric patients with ALL.
8/31/15	NDA 208400 submitted	

2.6 Other Relevant Background Information

ALL is the most common form of cancer in children and young adults. With current therapies the overall survival rate is over 85%. Successful treatment of children and young adults with ALL involves administration of a multi-drug regimen that that that are administered in several distinct phases, including induction, consolidation, delayed intensification and maintenance.

The first description of temporary remissions reported in children with ALL were induced by aminopterin, an anti-folate closely related to methotrexate (Farber 1948). Methotrexate, an antifolate related to aminopterin, began to replace aminopterin in the 1950s because of a more favorable toxicity profile. Continued improvement in survival in patients with ALL was achieved by the introduction of multi-agent chemotherapy regimens evaluated in cooperative group randomized trials. As prognostic factors were identified trials subsequent trials included stratification of treatment intensity according to the clinical features of the patient, the biologic features of the leukemia cells, and the early response to treatment. Collectively, these advances have increased the survival rate from less than 10% in the 1960s to greater than 90% with current therapies. See Figure 1. (Hunger 2015)

Figure 1: Survival of Successive Cohorts of Patients with ALL in COG Clinical Trials 1968 to 2009

Current therapy (derived from Hunger 2015)
The basic components of contemporary therapies for children and young adults with ALL include induction therapy which lasts 4 to 6 weeks and includes a glucocorticoid

(prednisone or dexamethasone), vincristine, an asparaginase preparation, optional use of an anthracycline, and intrathecal chemotherapy. Almost all patients attain remission, but this is not a cure, since relapse will occur universally without additional therapy.

After induction of remission, treatment includes 6 to 8 months of intensive combination chemotherapy that is designed to consolidate remission and prevent development of overt CNS leukemia. Treatment in an 8 week delayed intensification phase, based on the 8 week Berlin–Frankfurt–Münster protocol (Riehm 1980), is then administered. Repeated courses of intravenous methotrexate, administered either through short intravenous infusion or at high doses over 24 hours followed by administration of folinic acid to "rescue" normal tissues from toxic effects, are a critical component of this intensification therapy utilized in contemporary ALL regimens.

Patients then begin maintenance therapy low intensity "anti-metabolite" based therapy for 18 to 30 months. This therapy consists of daily oral mercaptopurine or thioguanine and weekly oral methotrexate. Some regimens also include periodic 5 to 7 day "pulses" of glucocorticoids and vincristine. The exact reasons why maintenance therapy is required and the most effective composition and duration of chemotherapy are unknown.

The dose of weekly oral methotrexate during maintenance therapy in pediatric cooperative group trials has been 20 mg/m^2 for several decades. A representative list of trials conducted by the Childrens Cancer Group (CCG), the Pediatric Oncology Group (POG) and the Childrens Oncology Group (COG) follows. The POG and the CCG groups were merged to form COG in 2000. (Matloub 2011 [CCG 1991 Trial], Bowman 2011[POG 9906 Trial], Schultz 2009 [COG AALL0031 Trial], Borowitz 2015 [COG AALL0232 Trial], Angiolillo 2014 [COG AALL07P4], Dreyer 2011 [CCG Trial 1953].

The current open protocol in the COG for the treatment of B-lineage ALL is comparing 2 doses of oral methotrexate during maintenance, 20 mg/m^2/week (standard) and 40 mg/m^2/week (experimental). During the course of maintenance therapy, the dose of oral methotrexate is adjusted to maintain an absolute neutrophil count (ANC) ≥ 500 /µL and < 1500/µL and a platelet count ≥ 50,000/µL.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was submitted in eCTD format. The application included all the required section. The reports and data sets submitted were adequate to allow substantive review.

3.2 Compliance with Good Clinical Practices

The study report for Study SG02-03 includes the statement: This study was conducted in accordance with Good Clinical Practice (GCP), including the archiving of essential documents.

The study report for Study SG02-04 includes the statement: This study was conducted in accordance with Good Clinical Practice (GCP), including the archiving of essential documents.

3.3 Financial Disclosures

The applicant checked the first box of form 3454.

As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

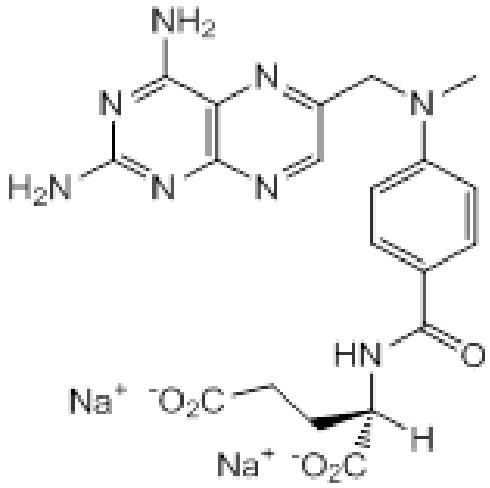
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

(copied from midcycle meeting slides)
Drug substance

- DMF [redacted] is referenced, adequate
- Methotrexate Sodium is a yellow to orange crystalline powder.
- It is freely soluble in water.

Figure 2: Methothrexate Structure



Drug Product

- Methotrexate Oral Solution, 2.5 mg/mL, is a ready-to-use aqueous solution, which is a clear, yellow to orange colored.
- In addition to the API, methotrexate sodium, the drug product contains citric acid, sodium citrate, methylparaben sodium, propylparaben sodium and sucralose, [redacted] water.
- The pH of the product is adjusted [redacted] with NaOH and HCl

The following issues were identified at the midcycle meeting:

- Extractables/leachables studies are needed for the cap liner.
- Your extractable studies on the bottle with printed label must be conducted with the drug product.

- Updated stability data on the drug product must be submitted within four months of the submission of the NDA. (per agreement with Agency, April 7, 2015 meeting)

4.2 Clinical Microbiology

(copied from midcycle meeting slides)
The following issues were identified at the midcycle meeting:

- The applicant needs to provide data from Antimicrobial Effectiveness studies using the drug product formulated with the (b) (4) content (i.e. (b) (4) (b) (4) %) established in the release or stability specifications
- Non-sterile aqueous drug products may potentially be contaminated with organisms in the Burkholderia cepacia complex (BCC). In order to control for the presence of BCC in the product, the applicant should:
  - identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product.
  - Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC.

4.3 Preclinical Pharmacology/Toxicology

Rely on reference product.

4.4 Clinical Pharmacology

Mechanism of Action

Methotrexate is a folic acid analogue. Methotrexate inhibits purine and pyrimidine synthesis.

Pharmacodynamics

Rely on reference product.

Pharmacokinetics

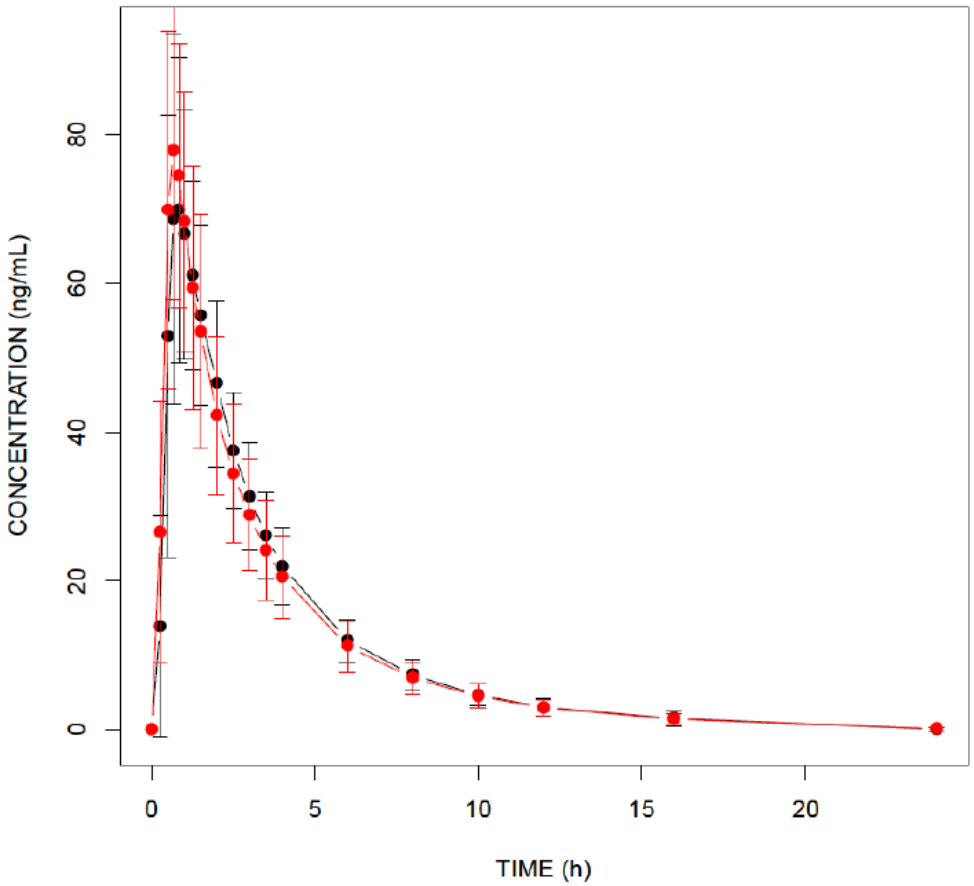
(copied from midcycle meeting slides)
The pivotal trial SG02-03 was a bioequivalence study. It was a 2 x 2 crossover design comparing 2.5 mg tablets to 1 ml of 2.5 mg/ml solution.

Results:

Table 3: SG02-03 PK Results - Bioequivalence Trial

Parameter	Ration (% of Reference)	90% CI
AUC_{inf}	98	[95, 105]
C_{max}	107	[100, 115]

Figure 3: SG02-03 Comparison of Mean PK Profiles – Bioequivalence Trial



Conclusion:
The clinical pharmacology reviewer concluded that the tablet and the oral solution were bioequivalent.

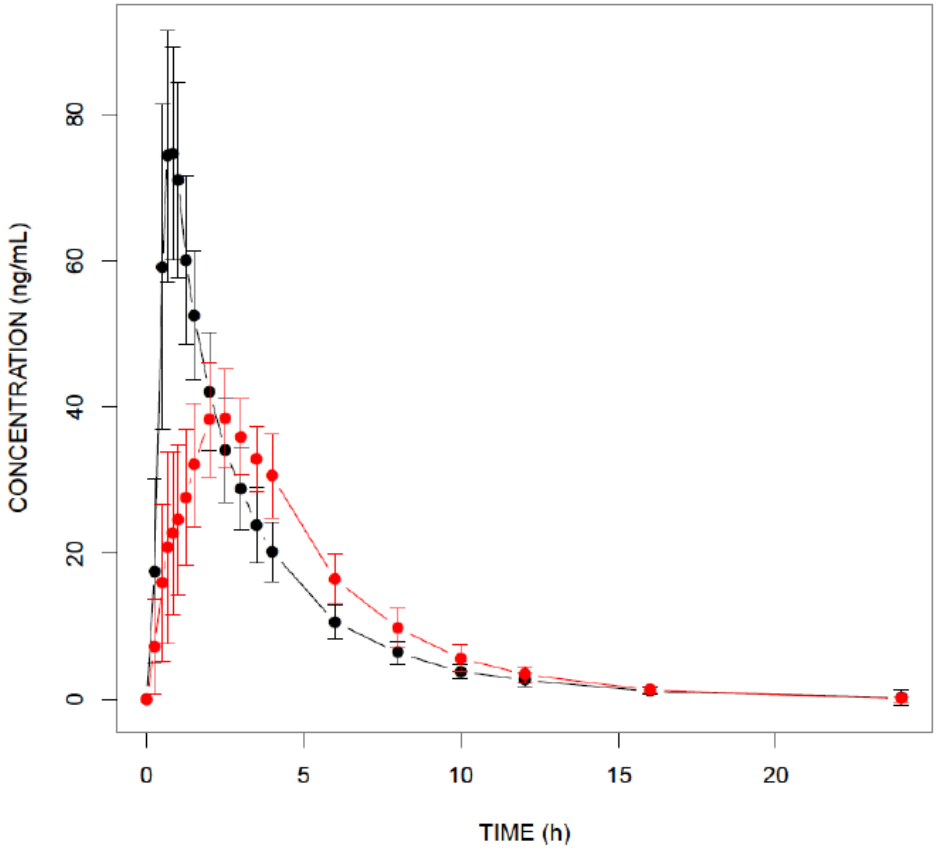
The sponsor also conducted a food effect study, SG 02-04. The rationale for this trial was that the drug label indicates there is a food effect, specifically a decreased C_{max} and T_{max}. This was 2 x 2 crossover design of 21 patients comparing administration after a 10 hour fast and after a standard high fat meal.

Results:

Table 4: SG02-04 PK Results - Food Effect Trial

Parameter	Ration (% of Reference)	90% CI
AUC_{inf}	96	[91, 102]
C_{max}	50	[47, 54]

Figure 4: SG02-04 Comparison of Mean PK Profiles – Food Effect Trial



Conclusion:
The clinical pharmacology reviewer concluded that administration with high fat meal resulted in an approximately 50% decrease in the C_{max}, and prolonged the T_{max} from 0.83 hours fasted to 2 hours fed. However, the AUC_{inf} was comparable.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

(copied from eCTD submission section 5.2 Tabular Listing of all Clinical Studies page 2 of 2)

Table 5: Tabular Listing of all Clinical Studies

Table 5.2-1. Listing of All Clinical Studies						
Type of Study	**Study Identifier**	**Objective(s) of the Study**	**Study Design and Type of Control**	**Dosage Regimen Route of Administration Duration; Test Product(s)**	**Healthy Subjects or Diagnosis of Patients Number of Subjects**	**Study Status Type of Report**
BA	*SG02-03*	To assess the bioavailability of Methotrexate Oral Solution versus Methotrexate Tablets (DAVA) under fasted conditions	Single-dose, open-label, randomized, 2-period, 2-treatment, 2-way crossover	A: Single dose; oral; Methotrexate Oral Solution 2.5 mg (fasted) B: Single dose; oral; Methotrexate Tablets 2.5 mg (fasted)	Healthy adult male subjects 34 enrolled (31 completed)	Complete eCTD
BA	*SG02-04*	To assess the bioavailability of Methotrexate Oral Solution under fasted and fed conditions	Single-dose, open-label, randomized, 2-period, 2-treatment, 2-way crossover	A: Single dose; oral; Methotrexate Oral Solution 2.5 mg (fasted) B: Single dose; oral; Methotrexate Oral Solution 2.5 mg (fed)	Healthy adult male subjects 24 enrolled (21 completed)	Complete eCTD
BA = bioavailability; DAVA = DAVA Pharmaceuticals, Inc.; eCTD = electronic Common Technical Document.						

5.2 Review Strategy

The clinical pharmacology of these studies is presented in section 4.4.3. This section contains an analysis of the safety review of these studies.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 SG02-03

STUDY INFORMATION:

- Title: “A Randomized, Open-Label, Two-Period, Two-Treatment, Two-Way, Crossover Study to Determine the Relative Bioavailability of Methotrexate Pediatric Oral Solution vs Methotrexate Tablets USP, (DAVA) 2.5 mg under Fasted Conditions in Healthy Adult Male Volunteers”
- Phase: I
- Design: Open Label, single-dose, randomized, two-period two-treatment, two-way crossover
- Study Sites: Worldwide Clinical Trials Early Phase Services, San Antonio, Texas

Clinical Review
Patricia Dinndorf
NDA 208400 (505(b)(2)
Methotrexate Oral Solution; Xatmep

- Proposed Sample Size: 34
- Gender: Male
- Age Range: 18 to 55 years

Dose: 2.5 mg/mL (Silvergate); Methotrexate Tablet, 2.5 mg (DAVA)
Route: oral
Planned enrollment: 34
Actual enrollment: 34, 31 analyzed

Primary objective

- The objective of this study was to assess the relative bioavailability of a test formulation of methotrexate pediatric oral solution, 2.5 mg/mL (Silvergate) compared to an equivalent oral dose of the commercially available reference listed drug methotrexate tablet, 2.5 mg (DAVA), when administered under fasted conditions in healthy adult male subjects.

Eligibility Criteria
Inclusion Criteria:

- Subject was a male.
- Subject was between 18 and 55 years of age (inclusive).
- Subject's BMI was between 18 and 30 kg/m2 (inclusive), and the subject weighed a minimum of 50 kg (110 lbs.).
- Subject had a successful vasectomy at least 6 months prior to dosing or agreed to use a double-barrier local contraception (i.e., spermicidal gel plus condom) when engaging in sexual contact with a female who could have become pregnant, from screening through at least 3 months after completion of the study.
- Subjects agreed not to donate sperm from time of screening, during the study, and for at least 3 months after the last dose of study medication.
- Subject was capable of complying with mandatory contraceptive measures.
- Subject voluntarily consented to participate in this study and provided his written informed consent prior to start of any study-specific procedures.
- Subject was willing and able to remain in the study unit for the entire duration of each confinement period.

Exclusion Criteria

- History or presence of clinically significant (CS) cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, autoimmune, or psychiatric disease or any other condition that, in the opinion of the Investigator, would have jeopardized the safety of the subject or the validity of the study results.
- More specifically, history or presence of psoriasis, rheumatoid arthritis, peptic ulcer disease, ulcerative colitis, or presence of any active infection.
- Had a CS abnormal finding on the physical exam, medical history, electrocardiogram (ECG), or clinical laboratory results at screening.

- History or presence of allergic or adverse response to methotrexate or related drugs.
- Had been on a significantly abnormal diet during the 4 weeks preceding the first dose of study medication.
- Had donated blood or plasma within 30 days prior to the first dose of study medication.
- Had participated in another clinical trial (randomized subjects only) within 30 days prior to the first dose of study medication.
- Had used any over-the-counter (OTC) medication, including nutritional supplements, within 7 days prior to the first dose of study medication. Had used any prescription medication within 14 days prior to the first dose of study medication.
- Had received a live virus vaccine within 14 days of first dose of study medication.
- Had been treated with any known drugs that were moderate or strong inhibitors/inducers of CYP enzymes such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc., within 30 days prior to the first dose of study medication and that in the Investigator's judgment may have impacted subject safety or the validity of the study results.
- Had smoked or used any type of tobacco or nicotine based products (including e-cigarettes) within 60 days prior to the first dose of study medication.
- History of substance abuse or treatment (including alcohol) within the past 2 years.
- Subject was a female.
- Had a positive urine screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates), alcohol, or cotinine.
- Had a positive test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) at screening or had been previously treated for hepatitis B, hepatitis C, or HIV infection.
- Had any piercings of the tongue or had a lip piercing within 30 days prior to the first dose of study medication.
- Any CS dental issues noted during oral examination at screening and check-in for each study period.
- Presence of blisters, ulcers, sores, or lesions in the mouth at time of screening or check-in.

Treatment Plan:
(copied from eCTD submission section 5.3.1.2 SG02-03 page 21 of 136)
Adult male subjects were to receive a single dose of methotrexate pediatric oral solution, 2.5 mg/mL (Treatment A) in one period, and a separate single dose of methotrexate tablet, 2.5 mg (Treatment B) in another period.

Each treatment was administered after an overnight fast of at least 10 hours. Treatment A was administered via a 1 mL glass dosing syringe and followed with

240 mL of room temperature tap water. Treatment B was administered with 240 mL of room temperature tap water. The subjects fasted for 4 hours after dosing. Except for the 240 mL of room temperature water provided with the dose, no water was consumed for 1 hour prior prior to dose through 1 hour postdose. Each drug administration was separated by a washout period of at least 7 days.

During each study period, meals were the same and scheduled at approximately the same times relative to dose.

Results:
Disposition:
(copied from eCTD submission section 5.3.1.2 SG02-03 page 38 of 136)
A total of 34 subjects were randomized into the study; 31 of these subjects completed both periods of the study. Two subjects were withdrawn at Period 2 check-in due to protocol non-compliance.
[One subject was withdrawn at Period 2 check-in due to an AE of fungal skin infection.

Table 6: SG02-03 Demographics

(copied from eCTD submission section 5.3.1.2 SG02-03 page 40 of 136)

			Sequence	
Characteristic		**All (N= 34)**	**AB (N= 17)**	**BA (N= 17)**
Sex	Male	34 (100.0%)	17 (100.0%)	17 (100.0%)
Age (years)	N	34	17	17
	Mean (SEM)	34.41 (1.80)	37.24 (2.16)	31.59 (2.79)
	Std Dev	10.52	8.89	11.50
	Median	32.00	34.00	27.00
	Min, Max	19.00, 54.00	26.00, 53.00	19.00, 54.00
Ethnicity	Hispanic or Latino	13 (38.2%)	5 (29.4%)	8 (47.1%)
	Not Hispanic or Latino	21 (61.8%)	12 (70.6%)	9 (52.9%)
Race	American Indian or Alaska Native	2 (5.9%)	1 (5.9%)	1 (5.9%)
	Asian	1 (2.9%)	0 (0.0%)	1 (5.9%)
	Black or African American	14 (41.2%)	9 (52.9%)	5 (29.4%)
	White	17 (50.0%)	7 (41.2%)	10 (58.8%)
Height (cm)	N	34	17	17
	Mean (SEM)	173.81 (1.54)	172.21 (1.78)	175.41 (2.51)
	Std Dev	8.97	7.34	10.33
	Median	172.50	172.00	174.00
	Min, Max	159.00, 203.00	159.50, 183.00	159.00, 203.00
Weight (kg)	N	34	17	17
	Mean (SEM)	79.28 (1.74)	80.45 (2.54)	78.11 (2.43)
	Std Dev	10.16	10.48	10.00
	Median	80.20	80.80	79.60
	Min, Max	60.80, 99.60	61.30, 99.60	60.80, 93.30
BMI (kg/m^2)	N	34	17	17
	Mean (SEM)	26.20 (0.41)	27.05 (0.56)	25.35 (0.54)
	Std Dev	2.39	2.29	2.23
	Median	26.40	27.60	25.80
	Min, Max	21.90, 30.00	21.90, 30.00	22.20, 29.90

(copied from eCTD submission section 5.3.1.2 SG02-03 page 48 of 136)

Table 7: SG02-03 Treatment-emergent Adverse Events

Number of Subjects:	Treatment A (N=33)	Treatment B (N=32)
Treatment-emergent AE	2 (6.1%)	2 (6.3%)
Treatment-related Treatment-emergent AE	1 (3.0%)	1 (3.1%)
Serious Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Serious Treatment-related Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Treatment-emergent AE Leading to Study Discontinuation	1 (3.0%)	0 (0.0%)

(copied from eCTD submission section 5.3.1.2 SG02-03 page 49 of 136)

Table 8: SG02-03 Treatment-emergent Adverse Events by SOC and PT

System Organ Class	Preferred Term	Treatment A (N=33)	Treatment B (N=32)
Gastrointestinal disorders	Paraesthesia oral	0 (0.0%)	1 (3.1%)
Immune system disorders	Hypersensitivity	0 (0.0%)	1 (3.1%)
Infections and infestations	Fungal skin infection	1 (3.0%)	0 (0.0%)
Nervous system disorders	Headache	1 (3.0%)	1 (3.1%)
Respiratory, thoracic and mediastinal disorders	Nasal congestion	1 (3.0%)	0 (0.0%)
Skin and subcutaneous tissue disorders	Seborrhoeic dermatitis	1 (3.0%)	0 (0.0%)

Conclusions:
(copied from eCTD submission section 5.3.1.2 SG02-03 page 48 of 136)
Overall, methotrexate pediatric oral solution, 2.5 mg/mL and methotrexate tablet, 2.5 mg were well-tolerated in this study and the AE profiles were consistent with the known effects of both drugs.

The incidence of treatment-emergent AEs was 6.3% or less for both treatment groups; 4 subjects overall experienced treatment-emergent AEs.

Treatment-emergent AEs were reported by 2 (6.1%) subjects following administration of Treatment A, and by 2 (6.3%) subjects following Treatment B. Of these, 1 (3.0%) subject reported a treatment-related AE following Treatment A, and 1 (3.1%) subject reported a treatment-related AE following Treatment B.

There were no serious AEs.

5.3.2 SG02-04

STUDY INFORMATION:

- Title: "A Randomized, Open-Label, Single-Dose, Two-Period, Two-Treatment, Two-Way Crossover Relative Bioavailability Study of Methotrexate Pediatric Oral Solution under Fasted and Fed Conditions in Healthy Adult Male Volunteers"
- Phase: I
- Design: Open Label, single-dose, randomized, two-period two-treatment, two-way crossover
- Study Sites: Worldwide Clinical Trials Early Phase Services, San Antonio, Texas
- Proposed Sample Size: 24
- Gender: Male
- Age Range: 18 to 55 years

Dose: 2.5 mg/mL (Silvergate); Methotrexate Tablet, 2.5 mg (DAVA)
Route: oral
Planned enrollment: 24
Actual enrollment: 24 enrolled, 21 analyzed

Primary objective

- The objective of this study was to assess the effect of food on the relative bioavailability of a test formulation of methotrexate pediatric oral solution, 2.5 mg/mL (Silvergate).

Eligibility Criteria
Inclusion Criteria:

- Subject was a male.
- Subject was between 18 and 55 years of age (inclusive).
- Subject's BMI was between 18 and 30 kg/m^2 (inclusive), and the subject weighed a minimum of 50 kg (110 lbs.).
- Subject had a successful vasectomy at least 6 months prior to dosing or agreed to use a double-barrier local contraception (i.e., spermicidal gel plus condom) when engaging in sexual contact with a female who could have become pregnant, from screening through at least 3 months after completion of the study.
- Subjects agreed not to donate sperm from time of screening, during the study, and for at least 3 months after the last dose of study medication.
- Subject was capable of complying with mandatory contraceptive measures.
- Subject voluntarily consented to participate in this study and provided his written informed consent prior to start of any study-specific procedures.
- Subject was willing and able to remain in the study unit for the entire duration of each confinement period.
- Subject was willing and able to consume the entire high-calorie, high-fat breakfast meal in the designated timeframe during the fed study period.

Exclusion Criteria

- History or presence of clinically significant (CS) cardiovascular, pulmonary, hepatic, renal, hematologic, gastrointestinal, endocrine, immunologic, dermatologic, neurologic, oncologic, autoimmune, or psychiatric disease or any other condition that, in the opinion of the Investigator, would have jeopardized the safety of the subject or the validity of the study results.
- Had a clinically significant abnormal finding on the physical exam, medical history, electrocardiogram (ECG), or clinical laboratory results at screening.
- More specifically, history or presence of psoriasis, rheumatoid arthritis, peptic ulcer disease, ulcerative colitis, or presence of any active infection.
- History or presence of allergic or adverse response to methotrexate or related drugs.
- Had been on a significantly abnormal diet during the 4 weeks preceding the first dose of study medication.
- Had donated blood or plasma within 30 days prior to the first dose of study medication.
- Had participated in another clinical trial (randomized subjects only) within 30 days prior to the first dose of study medication.
- Had used any over-the-counter (OTC) medication, including nutritional supplements, within 7 days prior to the first dose of study medication. Had used any prescription medication within 14 days prior to the first dose of study medication.
- Had used any prescription medication within 14 days prior to the first dose of study medication.
- Had received a live virus vaccine within 14 days of first dose of study medication.
- Had been treated with any known drugs that were moderate or strong inhibitors/inducers of CYP enzymes such as barbiturates, phenothiazines, cimetidine, carbamazepine, etc., within 30 days prior to the first dose of study medication and that in the Investigator's judgment may have impacted subject safety or the validity of the study results.
- Had smoked or used any type of tobacco or nicotine based products (including e-cigarettes) within 60 days prior to the first dose of study medication.
- History of substance abuse or treatment (including alcohol) within the past 2 years.
- Subject was a female.
- Had a positive urine screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates), alcohol, or cotinine.
- Had a positive test for hepatitis B surface antigen, hepatitis C antibody, or human immunodeficiency virus (HIV) at screening or had been previously treated for hepatitis B, hepatitis C, or HIV infection.
- Had any piercings of the tongue or had a lip piercing within 30 days prior to the first dose of study medication.

- Any CS dental issues noted during oral examination at screening and check-in for each study period.
- Presence of blisters, ulcers, sores, or lesions in the mouth at time of screening or check-in.

Treatment Plan:
(copied from eCTD submission section 5.3.1.2 SG02-04 page 21 of 144)
Healthy adult male subjects were to receive a single dose of the study treatment, methotrexate pediatric oral solution, 2.5 mg/mL, after a 10-hour overnight fast in one period and a single dose of the study treatment after consuming a Food and Drug Administration (FDA) standard high-calorie, high-fat breakfast meal in another period.

During the study period in which a subject was given the fed treatment, the subject fasted overnight for at least 10 hours, then began consuming the high-calorie, high-fat breakfast meal 30 minutes prior to administration of the study drug. With the exception of the high-calorie, high-fat breakfast served in the fed treatment period, meals were the same and scheduled at approximately the same times relative to dose.

Each dose was administered via a 1 mL glass dosing syringe and followed with 240 mL of room temperature water. The subjects fasted for 4 hours after dosing. Except for the 240 mL of room temperature water provided with the dose, no water was consumed for 1 hour prior to dose through 1 hour postdose. Each drug administration was separated by a washout period of 7 days.

Results:
Disposition:
(copied from eCTD submission section 5.3.1.2 SG02-04 page 38 of 144)
A total of 24 subjects participated in the study and 21 of these subjects completed both study periods. Three subjects discontinued from the study early, one due to a mouth injury, one due to vomiting 1 hour after treatment B, one due to non-compliance.

Table 9: SG02-04 Demographics

			Sequence	
Characteristic		**All (N= 24)**	**AB (N= 12)**	**BA (N= 12)**
Sex	Male	24 (100.0%)	12 (100.0%)	12 (100.0%)
Age (years)	Mean (SEM)	36.92 (2.43)	39.00 (3.48)	34.83 (3.45)
	Std Dev	11.93	12.05	11.95
	Median	34.00	34.00	35.00
	Min, Max	18.00, 55.00	20.00, 55.00	18.00, 54.00
Ethnicity	Hispanic or Latino	15 (62.5%)	7 (58.3%)	8 (66.7%)
	Not Hispanic or Latino	9 (37.5%)	5 (41.7%)	4 (33.3%)
Race	American Indian or Alaska Native	1 (4.2%)	0 (0.0%)	1 (8.3%)
	Asian	1 (4.2%)	0 (0.0%)	1 (8.3%)
	Black or African American	7 (29.2%)	3 (25.0%)	4 (33.3%)
	White	15 (62.5%)	9 (75.0%)	6 (50.0%)
Height (cm)	Mean (SEM)	174.73 (1.61)	175.29 (2.83)	174.17 (1.66)
	Std Dev	7.87	9.79	5.73
	Median	174.75	177.75	174.00
	Min, Max	153.00, 187.50	153.00, 187.50	167.50, 185.00
Weight (kg)	Mean (SEM)	80.29 (1.88)	80.28 (2.80)	80.30 (2.64)
	Std Dev	9.21	9.69	9.13
	Median	80.75	79.95	82.60
	Min, Max	60.70, 98.50	60.70, 98.50	64.20, 93.30
BMI (kg/m^2)	Mean (SEM)	26.35 (0.61)	26.23 (0.94)	26.48 (0.82)
	Std Dev	2.99	3.25	2.84
	Median	27.30	27.15	27.30
	Min, Max	18.80, 29.70	18.80, 29.60	22.40, 29.70

(copied from eCTD submission section 5.3.1.2 SG02-04 page 48 of 144)

Table 10: SG02-04 Treatment-emergent Adverse Events

Number of Subjects:	Treatment A (N=22)	Treatment B (N=23)
Treatment-emergent AE	0 (0.0%)	3 (13.0%)
Treatment-related Treatment-emergent AE	0 (0.0%)	1 (4.3%)
Serious Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Serious Treatment-related Treatment-emergent AE	0 (0.0%)	0 (0.0%)
Treatment-emergent AE Leading to Study Discontinuation	0 (0.0%)	1 (4.3%)

(copied from eCTD submission section 5.3.1.2 SG02-04 page 49 of 144)

Table 11: SG02-04 Treatment-emergent Adverse Events by SOC and PT

System Organ Class	Preferred Term	Treatment A (N=22)	Treatment B (N=23)
Gastrointestinal disorders	Vomiting	0 (0.0%)	1 (4.3%)
Injury, poisoning and procedural complications	Mouth injury	0 (0.0%)	1 (4.3%)
Nervous system disorders	Dizziness	0 (0.0%)	1 (4.3%)
	Hypoaesthesia	0 (0.0%)	1 (4.3%)
	Presyncope	0 (0.0%)	1 (4.3%)

Conclusions:
(copied from eCTD submission section 5.3.1.2 SG02-04 page 48 of 144)
Overall, methotrexate pediatric oral solution, 2.5 mg/mL was well-tolerated in this study under both fasted and fed conditions, and the AE profiles were consistent with the known effects of methotrexate.

There were no AEs reported after administration of Treatment A. Three (13%) subjects reported AEs after administration of Treatment B. Of the 3 subjects who reported treatment-emergent AEs after Treatment B, only 1 reported a treatment-related event.

There were no serious AEs.

One AE led to a subject discontinuation from the study.

6 Review of Efficacy

Efficacy Summary

Proposed Methotrexate Oral Solution is an acceptable alternative formulation based on reference product label evidence efficacy and demonstration of bioequivalence. See section 4.4.

7 Review of Safety

Safety Summary

Proposed Methotrexate Oral Solution is an acceptable alternative formulation based on reference product label evidence safety and demonstration of bioequivalence. There were no new safety signals identified in the PK studies of normal male volunteers. See sections 5.3.1, and 5.3.2.

8 Postmarket Experience

Oral methotrexate is a component of multi-agent combination chemotherapy regimen for the treatment of ALL and other lymphoid malignancies. Early in development methotrexate was one of the original agents determined to be successful in inducing complete remissions in children with ALL. Oral methotrexate has been proven to be an important component of multi-agent maintenance therapy since the 1960s and continues to be a component of maintenance therapy in contemporary therapy.

9 Appendices

9.1 Literature Review/References

Angiolillo AL, Schore RJ, Devidas M, Borowitz MJ, et al., 2014, Pharmacokinetic and pharmacodynamic properties of calaspargase pegol *E. coli* L-asparaginase in the treatment of patients with acute lymphoblastic leukemia: Results from Children's Oncology Group Study AALL07P4, J Clin Oncol, 32:3874-3882.

Borowitz MJ, Wood BL, Devidas M, Loh ML, et al., 2015, Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232, Blood.126:964-97.

Bowman WP, Larsen EC, Devidas M, Linda SB, et al., 2011 Augmented therapy improves outcome for pediatric high risk acute lymphocytic leukemia: Results of Children's Oncology Group trial P9906, Pediatr Blood Cancer; 57:569-577.

Dreyer Z, Dinndorf P, Camitta BM, Sather H, et al., 2011, Analysis of the role of hematopoietic stem-cell transplantation in infants with acute lymphoblastic leukemia in first remission and MLL gene rearrangements: A report from the Children's Oncology Group, J Clin Oncol, 29:214-222. PMCID: PMC3058277. 1953/CCG-1953, P9407 (POG-9407);

Farber S, Diamond LK, Mercer RD, Sylvester RF, Wolff JA, 1948, Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-Aminopteroyl-glutamic acid (Aminopterin), N Engl J Med, 238:787–793.

Hunger S, Mullighan C, 2015, Acute Lymphoblastic Leukemia in Children, N Engl J Med, 373:1541-1552.

Matloub Y, Bostrom BC, Hunger SP, Stork LC, Angiolillo A, et al., 2011, Escalating intravenous methotrexate improves event-free survival in children with standard-risk acute lymphoblastic leukemia: a report from the Children's Oncology Group, Blood, 118:243-251.

Riehm H, Gadner H, Henze G, Langermann H-J, Odenwald E,1980, The Berlin Childhood Acute Lymphoblastic Leukemia Therapy Study, 1970-1976, Am J Pediatr Hematol Oncol, 2:299-306.

Schultz KR, Bowman WP, Aledo A, Slayton WB et al., 2009, Improved early event-free survival with imatinib in philadelphia chromosome-positive acute lymphoblastic leukemia: A Children's Oncology Group study, J Clin Oncol, 27:5175-5181.

9.2 Labeling Recommendations

This application was supported by demonstration of bioequivalence to the DAVA 2.5 mg tablet. The DAVA label is not in the PLR format. Two methotrexate injectable products are labeled in the PLR format. The label for Xatmep is derived where appropriate from the label for “Rasuvo (methotrexate) injection, for subcutaneous use” most recently revised 8/2015.

The label was revised to be appropriate for the indications requested for oral methotrexate solution, ALL maintenance therapy and pJIA. It was converted to PLR format.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA A DINNDORF
05/24/2016

ALBERT B DEISSEROTH
05/24/2016

CLINICAL FILING CHECKLIST

NDA/BLA Number: 208400, Original 2 **Applicant:** Silvergate Pharmaceuticals, Inc.

Drug Name: Methotrexate Oral Solution **NDA/BLA Type:** 505(b)(2)

Stamp Date: August 31, 2015 **Review Date:** October 15, 2015

Reviewer: Peter Starke, MD, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Introduction and Summary

This is a 505(b)(2) application from Silvergate Pharmaceuticals, Inc. (Silvergate) for Methotrexate Oral Solution. The application references the Agency's previous findings of safety and effectiveness for the listed drug, Methotrexate Sodium Tablets, manufactured by DAVA Pharmaceuticals, Inc., NDA 8085. The development program consists of two comparative bioavailability studies, conducted by Silvergate, comparing their proposed oral solution with DAVA's Methotrexate Sodium Tablets.

During drug development, Silvergate had two meetings with Division of Hematology Products, a Type B pre-IND meeting on May 21, 2013, and a Type C CMC meeting on April 7, 2015.

The applicant is requesting two indications: (1) pediatric patients with acute lymphoblastic anemia (ALL), as part of a combination regimen, and (2) the management of children with active polyarticular juvenile idiopathic arthritis (pJIA) who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy, including full-dose nonsteroidal anti-inflammatory agents (NSAIDs). Both are pediatric indications for which the applicant has received Orphan Drug designations (ALL: May 28, 2015, 15-4796; pJIA: August 25, 2015, 15-4795). As a result, PREA is stated to not be triggered by the application and a PSP was not required. Restriction of the indications to pediatric only indications was noted to be acceptable to the Agency at the May 2013 pre-IND meeting. (b) (4)

Since two review divisions are involved in review of the application, the application has been administratively split into Original 1 for the ALL indication and Original 2 for the pJIA indication.

Reviewers Personal Comments

Disclaimer: These comments reflect the personal views of this reviewer, and do not necessarily reflect the views of the Agency.

This product will potentially provide benefit to many children who cannot swallow a tablet formulation of methotrexate. In current clinical practice, when a liquid formulation of methotrexate is needed for pediatric or adult patients, methotrexate injection is typically administered orally in a palatable oral solution. And in fact there are a number of highly reputable web sites that explain how do this; the drawback of this technique being that stability is limited and not assured by such administration.

CLINICAL FILING CHECKLIST

In the current application, Silvergate has intentionally limited this product to two pediatric indications for which they have obtained Orphan status. By doing so, Silvergate has avoided user fees, which will allow them to get this product to market with less expense. At the same time they may obtain Orphan exclusivity for this product, which will potentially block similar oral solution products from entering the market with these pediatric indications in the near future. Further, by focusing on only pediatric indications, the labeling will not include dosing for any of the adult indications for which an oral solution might be appropriate.

The FDA does not have the authority to regulate drug prices, so I await pricing information about this product should it be approved. If Silvergate prices this product reasonably and competitively with currently available alternatives, then they have used their savvy to create a marketing niche for their product while fulfilling a major part of the public health need for a marketed low-cost oral solution of methotrexate. If, however, Silvergate uses this as an opportunity to market this product at a price that is markedly different (i.e., higher) than the tablet and injectable products, while perfectly legal and understandable from a business perspective, such pricing will not be in the best interest of the public health. I can only hope that Silvergate will show that it is a good corporate citizen by choosing to follow the former rather than the latter path.

Fileability Determination

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?

Yes. See the checklist below.

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to the Applicant: NA

Potential review issues and 74-day letter comments: No clinical review issues.

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development	X			

CLINICAL FILING CHECKLIST

	Content Parameter	Yes	No	NA	Comment
	package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?				
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(B)(2)
505(b)(2) Applications					
13.	If appropriate, what is the relied upon listed drug(s)?	X			DAVA Methotrexate Tablets, NDA 8085
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?	X			
15.	Describe the scientific bridge (e.g., BA/BE studies)	X			2 relative bioavailability studies: SG02-03: 2-way crossover study comparing BA of oral solution with DAVA tablets under fasted conditions SG02-04: 2-way crossover study comparing BA of oral solution in fed and fasted states
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 Indication:			X	

CLINICAL FILING CHECKLIST

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #2 Indication:				
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?			X	
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			Safety data submitted is limited to the two indications being sought: pediatric ALL and pJIA
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST

	Content Parameter	Yes	No	NA	Comment
	terms?				
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?			X	There were no deaths and no SAEs in the two studies. One subject dropped out due to an AE (mouth injury 7 days post-dosing).
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			None submitted, but available upon request.

CLINICAL FILING CHECKLIST

	Content Parameter	Yes	No	NA	Comment
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			None submitted, but available upon request.
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			Form 3454 for the clinical investigators in the two studies.
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			The IRB for both studies was (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PETER R STARKE
10/15/2015

JANET W MAYNARD
10/15/2015