CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208400Orig1s000
208400Orig2s000

NON-CLINICAL REVIEW(S)

MEMORANDUM

TO: File for NDA 208400

FROM: Pedro L. Del Valle, PhD
Pharmacology-Toxicology Reviewer
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

THROUGH: Christopher Sheth, PhD
Pharmacology-Toxicology Supervisor
Division of Hematology Oncology Toxicology
Office of Hematology and Oncology Products

DATE: May 27, 2016

SUBJECT: Recommend Approval of NDA

Silvergate Pharmaceuticals, Inc. developed XATMEP, a methotrexate Oral Solution (2.5 mg/mL) product to be indicated for the treatment of acute lymphoblastic leukemia (ALL) in pediatric patients as part of a combination regimen and for polyarticular juvenile idiopathic arthritis in patients who are intolerant to or had an inadequate response to first-line therapy.

Silvergate Pharmaceuticals submitted a 505(b)(2) NDA for XATMEP on August 31, 2015. The application was administratively split into Original-1 (Division of Hematology Products [DHP]) and Original-2 (DPARP). The PDUFA goal date for NDA 208400 is June 30, 2016.

The sponsor referenced NDA 008085 (Methotrexate oral tablets, Dava Pharmaceuticals) to support the safety and effectiveness of methotrexate. No new nonclinical data were submitted for review in NDA 208400. The relevant nonclinical and clinical information are contained in NDA 008085. (b) (4). cross referenced the annotated PI to the relevant sections of NDA 008085. The Division of Pediatric and Maternal Health was also consulted regarding the conversion of labeling to meet the requirements of the Pregnancy and Lactation Labeling Rule (PLLR), with review by Medical Officer Carol Kasten. The reviewer has corresponded with Dr. Andrew Goodwin and Dr. Kasten regarding the nonclinical sections of the XATMEP labeling and is in agreement with the language.

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/s/

PEDRO L DEL VALLE
05/27/2016

CHRISTOPHER M SHETH
05/27/2016

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	208,400
Supporting document/s:	1
Applicant's letter date:	August 31, 2015
CDER stamp date:	August 31, 2015
Product:	XATMEP (methotrexate oral solution)
Indication:	Polyarticular juvenile idiopathic arthritis (pJIA)
Applicant:	Silvergate Pharmaceuticals
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer:	Andrew Goodwin, PhD
Team Leader:	Timothy Robison, PhD, DABT
Division Director:	Badrul Chowdhury, MD, PhD
Project Manager:	Sadaf Nabavian

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208,400 are owned by Silvergate Pharmaceuticals or are data for which Silvergate Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 208,400 that Silvergate Pharmaceuticals does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208,400.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Silvergate Pharmaceuticals submitted a 505(b)(2) NDA for XATMEP, a methotrexate oral solution product, on August 31, 2015. The application was administratively split into Original-1 (Division of Hematology Products [DHP]) and Original-2 (DPARP). The PDUFA goal date for NDA 208400 is June 30, 2016.

The sponsor referenced NDA 008,085 (Methotrexate oral tablets, Dava Pharmaceuticals) to support the safety and effectiveness of methotrexate. No nonclinical data were submitted for review in NDA 208400.

DHP is the label holder for methotrexate; therefore, the Division of Hematology and Oncology Toxicology (DHOT) review team of Dr. Pedro DelValle and Dr. Christopher Sheth led the nonclinical review. The Division of Pediatric and Maternal Health was also consulted regarding the conversion of labeling to meet the requirements of the Pregnancy and Lactation Labeling Rule (PLLR), with review by Medical Officer Carol Kasten.

The reviewer has corresponded with Dr. DelValle and Dr. Kasten regarding the nonclinical sections of the XATMEP labeling, and is in agreement with the language shown in Section 1.3.3 below.

1.3 Recommendations

1.3.1 Approvability

NDA 208400 (Original-2) is recommended for approval from the nonclinical perspective.

1.3.2 Additional Non Clinical Recommendations

None.

1.3.3 Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

In pregnant women with non-malignant disease, XATMEP is contraindicated. Consider the benefits and risks of XATMEP and risks to the fetus when prescribing XATMEP to a pregnant patient with a neoplastic disease. (b) (4) can cause embryo-fetal toxicity, fetal death, (b) (4) *[see Data]*. There are no animal data that meet current standards for nonclinical developmental toxicity studies.

The estimated background risk of major birth defects and miscarriage for the indicated populations(s) are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

Limited published literature report the presence of methotrexate in human milk in low amounts. The highest breast milk to plasma concentration ratio demonstrated was 0.08:1. No information is available on the effects of methotrexate on a breastfed infant or on milk production. Because of the potential for serious adverse reactions from methotrexate in breast fed infants, advise women not to breastfeed during XATMEP therapy.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Test for pregnancy prior to initiating therapy with XATMEP. (b) (4) (b) (4)

Contraception

Females

(b) (4) can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during and for 6 months after the final methotrexate dose.

Males

Methotrexate can cause chromosomal damage to sperm cells. Advise males to use effective contraception during and for at least 3 months after the final methotrexate dose.

Infertility

Females

Based on published reports of female infertility after therapy with methotrexate, advise females of reproductive potential that XATMEP can cause impairment of fertility and menstrual dysfunction during and after cessation of therapy. It is not known if the infertility may be reversed in all affected females.

Males

Based on published reports of male infertility after therapy with methotrexate, advise males of reproductive potential that XATMEP can cause oligospermia or infertility during and after cessation of therapy. It is not known if the infertility may be reversed in all affected males.

8.4 Pediatric Use

Safety and effectiveness of XATMEP in pediatric patients have been established for the treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as part of a multi-phase, combination chemotherapy maintenance regimen and for the management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) *[see Clinical Studies (14 (b) (4)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Methotrexate has been evaluated in a number of animal studies for carcinogenic potential with inconclusive results. Although there is evidence that methotrexate causes chromosomal damage to animal somatic cells and human bone marrow cells, the clinical significance remains uncertain.

(b) (4)

2 Drug Information

2.1 Drug

CAS Registry Number: 7413-34-5

Generic Name: Methotrexate

Code Name: 91 056 00

Chemical Names:

N-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-(+)-glutamic acid, disodium salt

N-[*p*-[(2,4-diamino-6-pteridinylmethyl)methylamino]benzoyl]-L-(+)-glutamic acid, disodium salt

4-amino-N_{10}-methylpteroyl-glutamic acid, disodium salt

4-amino-10-methylfolic acid, disodium salt

Molecular Formula/Molecular Weight: $C_{20}H_{20}N_8Na_2O_5$

Structure or Biochemical Description

APPEARS THIS WAY ON ORIGINAL

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/s/

ANDREW C GOODWIN
05/26/2016

TIMOTHY W ROBISON
05/26/2016
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 208400 **Applicant:** Silvergate Pharma **Stamp Date:** August 31, 2015 (Original-2)

Drug Name: Methotrexate oral solution **NDA/BLA Type:** 505(b)(2)

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		The applicant is relying upon approved, reference listed drugs (methotrexate oral tablets; NDA 8085) as well as published scientific literature. A written summary of Pharm-Tox information is provided in Module 2. Module 4 only contains the referenced publications. No new studies were conducted.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required and requested IND studies in accord with 505 (b)(1) and (b)(2) including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			No nonclinical studies were required or submitted. Literature references were submitted.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable. See Comment in #1.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not applicable. See Comment in #1.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable. See Comment in #1.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		A safety assessment of impurities was provided as requested by the Division of Hematology Products (pre-IND meeting minutes dated May 23, 2013) and will be reviewed.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	X		
10	Have any impurity, degradant, extractable/leachable, etc. issues been addressed? (New toxicity studies may not be needed.)	X		The Pharm-Tox Reviewer will consult with the CMC Reviewer regarding impurity issues.
11	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.
12	If the applicant is entirely or in part supporting the safety of their product by relying on nonclinical information for which they do not have the right to the underlying data (i.e., a 505(b)(2) application referring to a previous finding of the agency and/or literature), have they provided a scientific bridge or rationale to support that reliance? If so, what type of bridge or rationale was provided (e.g., nonclinical, clinical PK, other)?	X		A clinical PK bridging study was conducted comparing the oral solution to the reference oral tablets. The Pharm-Tox reviewer defers to the appropriate discipline reviewers as to the adequacy of the bridging data.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

NA.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

The reviewer notes that NDA 208400 includes a Pregnancy and Lactation Labeling Final Rule (PLLR) conversion which will be addressed by the interdisciplinary review team. Therefore, a subsequent nonclinical labeling review may or may not be filed.

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/s/

ANDREW C GOODWIN
10/28/2015

TIMOTHY W ROBISON
10/28/2015
I concur