CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203214Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

FINAL REMS REVIEW

Date:	November 6, 2012
To:	Badrul Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer(s)	Kendra Worthy, Pharm.D., Team Leader, Division of Risk Management (DRISK) Anahita Tavakoli, M.A., Health Communication Analyst, DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Subject:	Review of Risk Evaluation and Mitigation Strategy (REMS)
Drug Name	Xeljanz (Tofacitinib) 5 mg Tablet
Indication:	Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate.
Therapeutic Class:	Kinase Inhibitor (Janus Kinases JAKs family)
Application Type / Number:	NDA 20-3214
Applicant:	Pfizer
OSE RCM #:	2012-1430

CONTENTS

1 INTRODUCTION

This is a review of Pfizer's proposed Risk Evaluation and Mitigation Strategy (REMS) for Xeljanz (Tofacitinib) NDA 20-3214, submitted voluntarily October 25, 2011 (with subsequent revisions). The sponsor's final submission, received on November 5, 2012, is the subject of this review.

1.1. BACKGROUND

Regulatory History

Xeljanz (Tofacitinib) 5 mg tablet is proposed for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs). Tofacitinib is a new molecular entity in the Janus kinases (JAKs) family of Kinase Inhibitors.

An Arthritis Advisory Committee meeting was held on May 9, 2012 to discuss in part "potential limitations with regard to the safety data presentation and analyses to better determine the safety profile of tofacitinib."[1] There were issues with analyzing patients as randomized and not treated, which had the potential of a less precise assessment of adverse events (AEs). In addition, there was a question of whether the rules for capturing and reporting AEs were consistently applied throughout the clinical development program.[1] The sponsor was asked to provide additional analysis to address these concerns.

The sponsor's submission dated August 10, 2012 included sensitivity analyses on treatment emergent AEs and laboratory data, as well as exposure estimates and incidence rate tables, which constituted a major amendment by the Agency. The user fee date was extended to November 21, 2012.

2.1 Brief Efficacy Overview

Efficacy was demonstrated in five Phase 3 studies (N=3328) that "assesse[d] the effect of tofacitinib on signs and symptoms of disease and physical function, as measured by three primary efficacy endpoints (in sequence):

1. Signs and symptoms as measured by ACR 20 at Month 3 or at Month 6;
2. Physical function as measured by the HAQ-DI change from baseline at Month 3;
3. Incidence of DAS <2.6 at Month 3 or at Month 6.

Four studies assessed tofacitinib as an add-on in combination with MTX and in combination with traditional DMARDs. One study assessed tofacitinib as a monotherapy, following washout of other DMARDs."[2]

[1] Clinical review, Nikolay Nikolov, M.D., DPARP, dated July 6, 2012.
[2] Clinical review, Nikolay Nikolov, M.D., DPARP, June 26, 2012.

2.2 Safety Overview

Safety data is from two Phase 2 and five Phase 3 studies, covering approximately 3328 patients. The overall study population in the development program was representative of the target patient population of adult patients with established moderately-to-severely active RA who have had inadequate response to at least one DMARD.

As of the sponsor's safety update in February 2012, 49 deaths were reported in the development program; one in the placebo group (N=681), three in comparator adalimumab group (N=204), and 45 in tofacitinib-treated patients (N=3328). The breakdown of the 45 tofacitinib-deaths is as follows:

- 15 (33%) infections (12 pneumonias)
- 12 (27%) malignancies
- 11 CV (4 cardiac arrest, 2 CVA, 2 arrhythmia, 1 PE, 1 CHF, 1 PHTN)
- 7 other (2 suicides, 2 traumatic, 1 COPD, 1 aspiration, 1 unknown)

Most of the causes of death are consistent with the profile of immunosuppressive drugs.[3]

The proposed label, which is in the latter stages of completion, contains a boxed warning for serious infections and malignancy.

Serious infections:
There is "an increased risk of serious infections, including opportunistic infections, identifying a profile of tofacitinib as a major immunosuppressant.

- Serious infections associated with tofacitinib use were common in the RA program with pneumonia being the most common (occurring only in tofacitinib-treated patients).
- Tuberculosis occurred only in tofacitinib treated patients in a clearly dose-dependent fashion.
- Opportunistic infections were not uncommon and included cases of cryptococcal infections, Pneumocystis jiroveci pneumonia, and BK virus encephalitis, which are seen exclusively in severely immunocompromized patients."[4]

The proposed label states that:

- patients should be tested for latent tuberculosis before XELJANZ use and during therapy;
- patients invasive fungal infections may present with disseminated, rather than localized disease; and
- the risks and benefits of treatment with XELJANZ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Malignancies:
The boxed warning language in the draft label states that lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus- associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

[3] Clinical wrap-up meeting slides, Nikolay Nikolob, M.D., DPARP, June 18, 2012.
[4] Clinical review, Nikolay Nikolov, M.D., DPARP, September 26, 2012

"Risk of malignancy, excluding non-melanoma skin cancer, increased numerically in a dose and time-dependent fashion (from 0.8 events per 100 pt-yrs for <6 months exposure to 1.4 events per 100 pt-yrs for >24 months exposure)." [4]

Laboratory abnormalities, including hematologic parameters, lipid changes, liver enzymes, and serum creatinine elevation:

- Lymphopenia: Dose-dependent sustained progressive lymphopenia occurred (ALC <500/mm3), which was also associated with increased risk of infections.[3]
- Neutropenia: Dose-dependent sustained neutropenia occurred over the first month of treatment, none of which were life-threatening (ANC <500/mm^3).[3]
- Hemoglobin: Events of clinically significant hemoglobin decreases and severe or life-threatening values were small; however, since anemia may represent an off-target toxicity associated with tofacitinib use due to its mechanism of action warrants inclusion of hemoglobin monitoring in labeling.[2]
- Lipid changes: Dose-dependent elevations in total, LDL (mean increase by 15%), and HDL (mean increase by 10%) cholesterol, were observed during the first 3 months of exposure.

  Total cholesterol and LDL responded to lipid-lowering therapy. Few Major Adverse Cardiovascular Events (MACE) were observed; the incidence was similar among treatment groups and stable over time.[3]

"Gastrointestinal perforations and interstitial lung disease were observed in the clinical trials, however the relative risk and role of tofacitinib treatment in the development of these adverse events is not well defined." [4]

3 MATERIAL REVIEWED

The following REMS-related materials were reviewed:

- Proposed REMS submitted October 25, 2011
- Medical Officer Wrap-Up Meeting slides, June 18, 2012, Nikolay Nikolov, M.D., Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
- DRISK REMS Interim Comments dated July 17, 2012, October 24, 2012, October 31, 2012, and November 5, 2012
- Clinical reviews, Nikolay Nikolov, M.D., DPARP, September 26, 2012 and July 6, 2012, and June 26, 2012
- Revised proposed REMS amendments submitted October 2 and October 29, 2012
- DRISK Final REMS review, ACTEMRA (tocilizumab), Kathryn O'Connell, M.D., Ph.D., Medical Officer, January 2, 2010.

4 RESULTS OF REVIEW OF PROPOSED REMS

4.1 Need for a REMS

The sponsor voluntarily submitted a proposed REMS with the NDA on October 25, 2011. According to pre-NDA meeting minutes, there were no questions from the sponsor specific to REMS or discussion pertaining to risk management or a proposed REMS. DRISK and DPARP determined that a REMS consisting of a Medication Guide, communication plan and a timetable for submission of assessments is necessary to ensure that the benefits of tofacitinib outweigh the risks of serious infections, including opportunistic infections and tuberculosis, malignancy, increase in cholesterol, and decrease in blood counts. This approach is consistent with the initial REMS development approach taken with Actemra (tocilizumab), a Human Interleukin-6 Receptor Inhibitor indicated for the treatment of Rheumatoid Arthritis and Systemic Juvenile Idiopathic Arthritis. The adverse event profile of tofacitinib is similar to that of Actemra and other DMARDs.

The communication plan will be directed toward rheumatologists and rheumatology healthcare providers, infectious disease specialists (b) (4), family practitioners, general practitioners, internal medicine specialists, and emergency medicine specialists who may prescribe Xeljanz and/or treat serious risks associated with Xeljanz, as well as pharmacists. The communication plan will consist of a Dear Healthcare Provider Letter, a Dear Pharmacist Letter, and dissemination of information through certain professional societies' scientific meetings and journals.

4.2 Relevant REMS Background

DRISK reviewed the proposed REMS and had interim comments (Set #1) dated July 17, 2012 that specifically addressed the following:

- Revision of the REMS goals
- Broadening the audience of the communication plan
- Requesting submittal of the Dear Healthcare Provider Letters and Dear Pharmacist Letters for review
- Addition of a REMS website

DRISK subsequently reviewed the October 2, 2012 REMS amendment and met with DPARP to discuss and gain further clarification and agreement on certain aspects of the REMS.[5] Interim comments (Set #2) sent October 24, 2012 addressed:

- Additional revision of the REMS goals
- Removal of (b) (4) from the targeted prescribers in the communication plan

[5] Before the second set of comments was sent to the sponsor, further clarifications were made after discussion with DPARP:

- Revision to the clarification of the risks to be included within the REMS
- Revision of the DHCP Letters and Journal Information Pieces to change the header of the following language from "Contraindication" to "Limitation of Use", which is consistent with the most recent label:
  - XELJANZ should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

- Clarification of the risks to be included within the REMS:
  - Serious and other important infections
  - Changes in laboratory parameters, such as decreases in neutrophil counts, increases in [redacted] cholesterol [redacted], decreases in hemoglobin levels, and [redacted].
  - The risks of gastrointestinal perforation as well as malignancies and other lymphoproliferative disorders are not required to be included in the REMS and can be addressed via labeling.
- Editorial track changes to the REMS document and the attached materials.
- Addition of a survey of pharmacists' knowledge and understanding of the serious risks of tofacitinib.

The revised track changes to the REMS document sent to the sponsor on October 26, 2012 are appended in Attachment 2 of this review. There were subsequent comments sent to the sponsor on November 1, and November 2, 2012 regarding edits to the assessment plan, the REMS document and REMS appended materials to remain consistent with labeling.

4.3 Summary of November 5, 2012 Proposed REMS Amendment

4.3.1 REMS Goals

The goal of the XELJANZ REMS is to inform healthcare providers and patients about the serious risks associated with XELJANZ treatment.

4.3.2 REMS Elements

4.3.2.1 Medication Guide

In accordance with 21 CFR 208.24, a Medication Guide will be included in each XELJANZ package. This Medication Guide should be dispensed to each patient by the pharmacy with each XELJANZ prescription. The Medication Guide will also be available via sales representatives, the XELJANZ patient and professional websites, the XELJANZ REMS website, and a toll-free product information line.

4.3.2.2 Communication Plan

Pfizer will implement a communication plan to healthcare providers to support the implementation of the REMS. The communication plan will include:

1. A Dear Healthcare Provider Letter (DHCPL)
2. A Dear Pharmacist Letter
3. Dissemination of information through professional societies' scientific meetings and journals
4. REMS website

The DHCPL and Dear Pharmacist Letter will include information regarding the serious risks associated with XELJANZ and will be distributed twice annually for three years to pharmacists

and prescribers likely to prescribe XELJANZ or potential adverse effects associated with XELJANZ by traditional and electronic mail within 60 days of product approval.

Pfizer will distribute the letters to rheumatologists and rheumatology healthcare providers (including physician assistants and nurse practitioners), infectious disease specialists, family practitioners, general practitioners, internal medicine specialists, and emergency medicine specialists, and pharmacists.

Pfizer will display journal information pieces, for two years following product approval, as a panel/poster and distribution as printed material at major convention meetings of rheumatologists and other healthcare professionals specializing in rheumatology where the company has a sponsored booth (e.g., American College of Rheumatology, Congress of Clinical Rheumatology, and American Society of Health System Pharmacists annual meetings).

In addition, printed journal information pieces will be disseminated quarterly for three years following product approval to the following professional societies for wider dissemination in the following scientific journals: *The Rheumatologist, Arthritis &Rheumatism, Arthritis Care & Research, Clinical Infectious Disease, Annals of Emergency Medicine, American Family Physician, Annals of Internal Medicine, American Journal of Health-System Pharmacy*, and *Journal of the Academy of Managed Care Pharmacy*.

All of the REMS materials will be available through the XELJANZ program website www.XELJANZREMS.com, which will exist for 3 years following approval of the REMS.

See the following Attachments for the final XELJANZ REMS:

- Attachment 1: Xeljanz REMS document
    - Appendix A: Dear HealthCare Provider Letter
    - Appendix B: Dear Pharmacist Letter
    - Appendix C: Journal Information Piece For Rheumatologists or Rheumatology Healthcare Providers (including physician assistants and nurse practitioners)
    - Appendix D: Journal Information Piece For Infectious Disease Specialists
    - Appendix E: Journal Information Piece For Family Practitioners, General Practitioners, and Internal Medicine Specialists
    - Appendix F: Journal Information Piece For Emergency Medicine Specialists
    - Appendix G: Journal Information Piece For Pharmacists
    - Appendix H: Screenshot of the Proposed REMS Website
    - Appendix I: Medication Guide (The Medication Guide was reviewed separately and is not appended here.)
- Attachment 2: Comments and track changes sent to sponsor on Oct. 26, 2012

4.3.2.3 Timetable for Submission of Assessments

Pfizer will submit REMS Assessments to the FDA by at 18 months, by 3 years and in the 7th years from the date of approval of the REMS. To facilitate inclusion of as much information as

possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. Pfizer will submit each assessment so that it will be received by the FDA on or before the due date.

4.3.3 REMS Assessment Plan

Pfizer will submit REMS Assessments to FDA at 18 months, by 3 years and 7 years from the date of REMS approval.

The following information needed for assessments is included in the REMS supporting document:

1. A survey of the patients' knowledge and understanding of the serious risks of tofacitinib.

2. A survey of the prescribers' knowledge and understanding of the serious risks of tofacitinib.

3. A survey of the pharmacists' knowledge and understanding of the serious risks of tofacitinib.

4. An assessment and conclusions regarding the success of the REMS in meeting the stated goals.

5. An assessment of the communication plan including:

    a. The source(s) of the list of healthcare professionals to whom the DHCPL, Dear Pharmacist Letter are distributed
    b. Journal information pieces published, including date and journal name, volume, and issue.
    c. The date of launch of the communication plan (DHCPL, Dear Pharmacist Letter, website, and journal information pieces)
    d. The number of recipients of the DCHP and Dear Pharmacist letters
    e. Date(s) of distribution of the DHCP and Dear Pharmacist letters
    f. The number of returned and refused letters

5 DISCUSSION AND CONCLUSION:

DRISK and DPARP agree that a REMS consisting of a Medication Guide and communication plan is necessary to ensure that the benefits of tofacitinib outweigh the risks, and that prescriber, pharmacist, and patient knowledge should be assessed.

Pfizer's REMS proposal for XELJANZ addresses the requirements stipulated by FDA. The proposed REMS for XELJANZ includes a communication plan with a DHCPL, a Dear

Pharmacist letter, dissemination of information through professional societies' scientific meetings and journals, and a REMS website.

DRISK finds the proposed REMS for XELJANZ to be acceptable and recommends approval of this REMS.

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

---

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

/s/

KENDRA C WORTHY
11/06/2012

CLAUDIA B MANZO
11/06/2012
concur

Risk Evaluation and Mitigation Strategy (REMS) Memorandum

U.S. FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF DRUG EVALUATION II
DIVISION OF PULMONARY, ALLERGY, AND RHEUMATOLOGY PRODUCTS

NDA#:	203214
Products:	Xeljanz (tofacitinib), Tablets
APPLICANT:	Pfizer
FROM:	Sally Seymour, MD, Deputy Director for Safety
DATE:	October 25, 2012

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)]. Section 505-1(a)(1) provides the following factors:

(A) The estimated size of the population likely to use the drug involved;
(B) The seriousness of the disease or condition that is to be treated with the drug;
(C) The expected benefit of the drug with respect to such disease or condition;
(D) The expected or actual duration of treatment with the drug;
(E) The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug;
(F) Whether the drug is a new molecular entity (NME).

After consultations between the Office of New Drugs and the Office of Surveillance and Epidemiology, we have determined that a REMS is necessary for Xeljanz (tofacitinib) to ensure that the benefits of the drug outweigh the risks of serious infections, including opportunistic infections, tuberculosis, malignancy, increase in cholesterol, and decrease in blood counts. In reaching this determination, we considered the following:

A. The estimated number of patients in the United States with rheumatoid arthritis (RA) is 1.5 million. This estimate is based on data published in Arthritis Rheum. 2010 Jun;62(6):1576-82.

B. RA is a chronic systemic progressive disease associated with synovial inflammation resulting in joint pain and swelling, autoantibody production (rheumatoid factor and anti-citrullinated protein antibodies), bone erosions, joint space narrowing and joint destruction, and systemic features, including inflammation, cardiovascular, pulmonary, musculoskeletal, and other manifestations. Sustained RA activity results in irreversible joint destruction, functional impairment and increased morbidity and mortality, and significantly impacts society and the health care system.

C. Compared with placebo, tofacitinib has been shown to be effective on signs and symptoms and physical function in patients with established moderately-to-severely active RA, both as a monotherapy and in combination with methotrexate or other traditional disease-modifying anti-rheumatic drugs (DMARDs)

D. Tofacitinib is expected to be used alone or in a combination with methotrexate or other non-biologic DMARDs in patients with moderate to severe active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. The expected duration of therapy with tofacitinib is chronic and potentially life-long.

E. The review of tofacitinib NDA identified several areas of major safety concerns potentially associated with tofacitinib administration in patients with rheumatoid arthritis:

Malignancy: An increased risk of solid and hematologic malignancies, including lymphoproliferative disorder (LPD) was noted in the tofacitinib program. Malignancy was numerically higher in the tofacitinib group compared to placebo. Malignancy increased with prolonged tofacitinib exposure (from 0.8 events per 100 pt-yrs for <6 months exposure to 1.4 events per 100 pt-yrs for >24 months exposure). Seven cases of LPD occurred in the overall RA development program as of May 2012, all in tofacitinib-treated patients. Two of the cases occurred in highly atypical locations (CNS and breast). Five lymphoma cases in 218 (2.3%) renal transplant patients who had received 15 mg BID. Lymphomas occurred in the highest dose group (3 of 8, 37%) of the chronic toxicology study in monkeys.

Serious Infections: An increased risk of serious infections, including opportunistic infections, was noted in the tofacitinib program, identifying a profile of tofacitinib as a major immunosuppressant. Serious infections associated with tofacitinib use were common in the RA program with pneumonia being the most common (occurring only in tofacitinib-treated patients). Tuberculosis occurred only in tofacitinib treated patients in a clearly dose-dependent fashion. Opportunistic infections were not uncommon and included cases of cryptococcal infections, Pneumocystis jiroveci pneumonia, and BK virus encephalitis, which are seen exclusively in severely immunocompromized patients.

Increased cholesterol: Dose-dependent sustained elevations in total, LDL, and HDL cholesterol were noted in the tofacitinib program. Total and LDL cholesterol levels reversed with lipid-lowering therapy. These lipid abnormalities did not appear to translate into increases in cardiovascular events.

Decreased blood counts: Dose-dependent sustained neutropenia and progressive lymphopenia were noted in the tofacitinib program. Severe lymphopenia was also associated with increased risk of infections.

In addition to malignancy, serious infections, increased cholesterol, and decreased blood counts, tofacitinib is associated with elevation in liver enzymes, elevation in serum creatinine, and gastrointestinal perforations.

F. Xeljanz (tofacitinib) is a new molecular entity.

Xeljanz (tofacitinib) is a novel product (new molecular entity) and is a new oral disease modifying anti-rheumatic drug (DMARD). Consequently, this novel product may be widely used. These factors make it important for healthcare providers to be appropriately informed about the drug's serious risks. Similarly, because of the drug's novelty and anticipated chronic use, potentially life-long, patients should also be informed about the serious risks and their understanding of the risks should be assessed.

In accordance with section 505-1 of FDCA and under 21 CFR 208, FDA has determined that a Medication Guide is required for Xeljanz (tofacitinib). FDA has determined that Xeljanz (tofacitinib) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Xeljanz (tofacitinib). FDA has determined that Xeljanz (tofacitinib) is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use Xeljanz (tofacitinib).

Additionally, FDA has determined that a Medication Guide is necessary as an element of the REMS because maintaining the Medication Guide as part of labeling will not be adequate to address the serious and public health concern of adequately informing patients about the serious risks of Xeljanz (tofacitinib).

FDA has also determined that a communication plan is necessary to ensure that healthcare providers are adequately informed about the serious risks of Xeljanz (tofacitinib).

The elements of the REMS will be Medication Guide, communication plan, and a timetable for submission of assessments of the REMS.

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

/s/

SALLY M SEYMOUR
11/06/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Interim Comments on Amendments to the Risk Evaluation and Mitigation Strategy (REMS) Proposed for Tofacitinib

Date:	October 24, 2012
Reviewer(s):	Kendra Worthy, Pharm. D., Team Leader, DRISK Ana Tavakoli, M.A., Health Communication Analyst, DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Subject:	Interim Comments on the proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Tofacitinib
Therapeutic Class:	Kinase Inhibitor (JAK family)
Dosage and Route:	5 mg Tablet
NDA #/Supplement:	NDA 20-3214
Applicant:	Pfizer
OSE RCM #:	2012-1430

1 MATERIALS REVIEWED

- Revised proposed REMS submitted 10/2/2012
- DRISK REMS Interim Comments dated
- Proposed REMS submitted 10/25/2011
- Medical Officer Wrap-Up Meeting slides, June 18, 2012, Nikolay Nikolov, M.D., Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

2 INTRODUCTION AND BACKGROUND

This second interim review provides comments on the revised proposed Risk Evaluation and Mitigation Strategy (REMS) for Xeljanz (tofacitinib) submitted by Pfizer October 2, 2012.

Pfizer voluntarily submitted a REMS October 25, 2011, with the original NDA submission for the treatment of rheumatoid arthritis (RA). Tofacitinib is a new molecular entity that belongs to the class of kinase inhibitors (JAK family). Serious risks associated with Xeljanz include serious infections, and changes in laboratory parameters, such as decreases in neutrophil counts, increases in low density lipoprotein cholesterol (LDLc), decreases in hemoglobin levels, and transaminase elevations.

The proposed REMS goal is to inform healthcare providers and patients about the serious risks associated with Xeljanz treatment. The REMS consists of a Medication Guide and communication plan directed toward rheumatologists and rheumatology healthcare providers, infectious disease specialists, (b) (4), family practitioners, general practitioners, internal medicine specialists, and emergency medicine specialists who may prescribe Xeljanz and/or treat serious risks associated with Xeljanz. The communication plan consists of a Dear Healthcare Provider Letter, a Dear Pharmacist Letter, and dissemination of information through certain professional societies' scientific meetings and journals.

The Agency sent comments to Pfizer July 31, 2012 that addressed the following:

- Revision of the REMS goals
- Broadening the audience of the communication plan
- Requesting submittal of the Dear Healthcare Provider Letters and Dear Pharmacist Letters for review
- Addition of a REMS website

Pfizer submitted a revised REMS October 2, 2012, which is the subject of this review.

3 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments in Sections 4 through 4.5 be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review.

4 COMMENTS TO BE SENT TO THE APPLICANT

Your proposed REMS requires the following revisions. The REMS Supporting Document must be consistent with all changes made to the REMS.

4.1 GOAL

The goals have been further revised to the following:

"The goal of the XELJANZ REMS is to inform healthcare providers and patients about the serious risks associated with XELJANZ treatment."

4.2 COMMUNICATION PLAN

Revise the communication plan as follows:

1. The following risks have been identified as part of the REMS:
    - serious and other important infections
    - changes in laboratory parameters, such as decreases in neutrophil counts, increases in (b) (4) cholesterol (b) (4) decreases in hemoglobin levels, (b) (4).

    The risks of gastrointestinal perforation as well as malignancies and other lymphoproliferative disorders are not required to be included in the REMS and can be addressed via labeling.

2. The prescriber specialties of (b) (4) have been removed from the list of targeted prescribers.

3. See the attached REMS document, Dear Healthcare Provider Letter, Dear Pharmacist Letter, and Professional Society Letters for track changes.

4.3 REMS ASSESSMENT

Add the following to the REMS Assessment Plan:

1. A survey of pharmacists' knowledge and understanding of the serious risks oof tofacitinib.

4.4 GENERAL COMMENTS

Resubmission Requirements and Instructions Submit the revised proposed REMS with attached materials. Provide a track changes and a clean version of all revised materials and documents.

Format Request: Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

4.5 TRACK CHANGES FOR THE SPONSOR

(b) (4)

[redacted]

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

---

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

/s/

KENDRA C WORTHY
10/24/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Interim Comments on Amendments to the Risk Evaluation and Mitigation Strategy (REMS) Proposed for Tofacitinib

Date:	July 17, 2012
Reviewer(s):	Kendra Worthy, Pharm. D., Team Leader, DRISK Ana Tavakoli, M.A., Health Communication Analyst, DRISK
Division Director:	Claudia Manzo, Pharm. D., DRISK
Subject:	Interim Comments on the proposed Risk Evaluation and Mitigation Strategy (REMS)
Drug Name(s):	Tofacitinib
Therapeutic Class:	Kinase Inhibitor (JAK family)
Dosage and Route:	5 mg Tablet
NDA #/Supplement:	NDA 20-3214
Applicant:	Pfizer
OSE RCM #:	2012-1430

1 MATERIALS REVIEWED

- Proposed REMS, submitted 10/25/2011
- Medical Officer Wrap-Up Meeting slides, June 18, 2012, Nikolay Nikolov, M.D., Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

2 INTRODUCTION AND BACKGROUND

This interim review provides comments on the proposed proposed Risk Evaluation and Mitigation Strategy (REMS) for Tofacitinib voluntarily submitted by Pfizer on October 25, 2012, with the original NDA submission for the treatment of rheumatoid arthritis (RA). Tofacitinib is a new molecular entity that belongs to the class of kinase inhibitors (JAK family).

Efficacy of Tofacitinib was shown in five placebo controlled studies. The population in these studies was representative of adult patients with established, moderately-to-severely active RA and included patients with inadequate response to either TNF inhibitors and/or Disease-modifying antirheumatic drugs (DMARDs). The Phase 3 efficacy studies provided consistent evidence of a short-term treatment benefit with tofacitinib 5 mg and 10 mg twice daily. [1]
Dosages were associated with serious adverse events including:

- Malignancy (lymphoma)
- Infections (tuberculosis and opportunistic infections)
- Cardiovascular and Lipid disorders
- GI perforation
- Elevated serum creatinine
- Liver test abnormalities

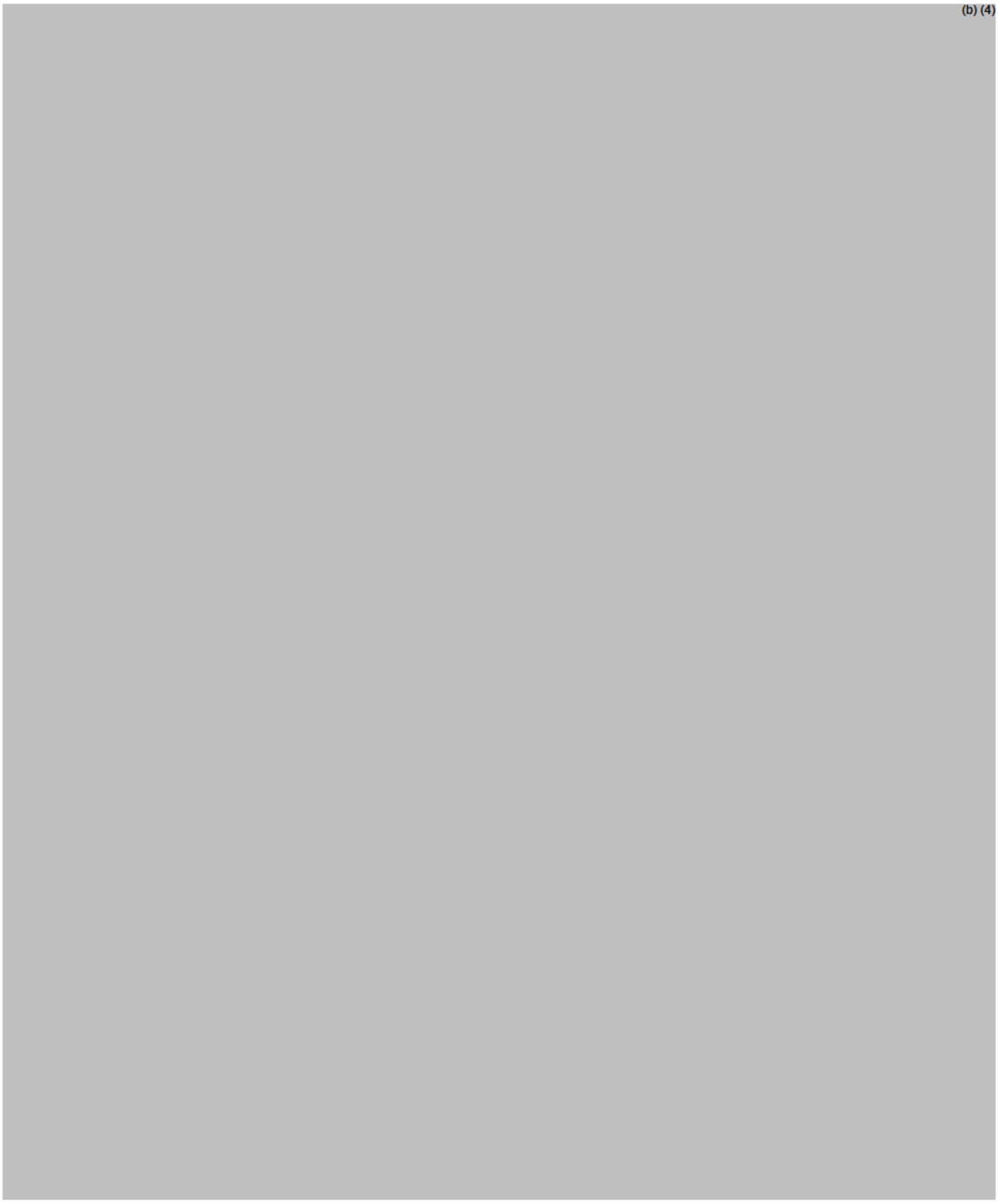
3 SUMMARY OF THE APPLICANT'S PROPOSED REMS

The proposed REMS contains the following elements:

(b) (4)

[redacted]

[1] Medical Officer Wrap-Up Meeting slides, June 18, 2012, Nikolay Nikolov, M.D., DPARP



4 RECOMMENDATIONS FOR THE REVIEW DIVISION

We recommend that the following comments on the REMS proposal be sent to the applicant. Please request that the applicant respond to these comments as soon as possible to facilitate further review.

The comments below are based on DRISK's preliminary review of the REMS proposal for tofacitinib tablets. The applicant should be reminded that the REMS Supporting Document must be consistent with all changes made to the REMS document.

5 COMMENTS TO BE SENT TO THE APPLICANT

Your proposed REMS requires the following revisions:

5.1 GOALS

Revise the goals of the REMS to be more consistent with current REMS goals and to leave open the potential to edit safety issues as necessary.

The goals of the tofacitinib REMS are:

- To inform healthcare providers about the serious risks associated with tofacitinib, (b) (4)
- To inform patients about the serious risks associated with tofacitinib treatment.

5.2 MEDICATION GUIDE

Comments pertaining to the Medication Guide will be provided under separate cover.

5.3 COMMUNICATION PLAN

Revise the communication plan as follows:

General

1. Broaden the audience to include the following practitioners:

   - (b) (4)
   - Primary care providers and Emergency care physicians who may treat infections, including serious, opportunistic, and tuberculosis.

Dear Healthcare Provider Letter and Dear Pharmacist Letter

2. Submit the Dear Healthcare Provider and Dear Pharmacist Letters to the Agency to review.

3. Provide a detailed description of the method(s) that information about the known and potential risks associated with tofacitinib will be disseminated to practitioners. For example; for the journal ad, define which journals will be targeted.

4. Provide a detailed description of the method(s) you propose to utilize to capture relevant prescribers for implementation of the communication plan. For example, will you use professional organizations or a third-party contact database of the HCPs for which the mailing list will be derived?

5. Describe how you will identify pharmacists and/or pharmacies.

REMS Website

6. Add a REMS website, tofacitinibrems.com, to the elements of the communication plan.

    a. We recommend that you include a prominent link on the product website's homepage for REMS materials. This link will direct users to a separate webpage that describes the REMS program and lists only approved REMS materials. For example, the link could state: "Important Safety Information and Risk Evaluation and Mitigation Strategy (REMS)", or "Healthcare Professionals click here for Risk Evaluation and Mitigation Strategy (REMS) information."

    b. In order to reach as many healthcare providers as possible, we suggest disseminating the DHCP letter through various media. For example, in addition to hardcopy, the letter could be sent electronically and be available on the product REMS website. If you do not choose to use electronic mailings, please provide a rationale for this decision.

7. The landing page of the separate REMS link should contain background information on the REMS along with the REMS communication materials.

    a. We recommend the following language as background information on the REMS landing page:

    A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage known or potential serious risks associated with a drug product and is required by the Food and Drug Administration to ensure that the benefits of the drug outweigh its risks. In order for Pfizer to communicate certain risks about Tofacitinib, the Sponsor has worked with the FDA to develop materials to communicate the risks of [list risks; bullet format if multiple].

8. The REMS-related webpage(s) should not be a means to promote tofacitinib or any other Pfizer product.

9. Submit for review the web screenshot(s) for the REMS.

10. The Agency requires that the REMS website be independent of links to the promotional and/ or commercial website and non-REMS materials about the product. Do not include a link from the REMS website page back to the www.tofacitinib.com website.

11. Please note, the tofacitinib REMS webpage should also be accessible directly through a search engine.

5.4 GENERAL COMMENTS

Resubmission Requirements and Instructions Submit the revised proposed REMS with attached materials. Provide a track changes and a clean version of all revised materials and documents.

Format Request: Submit your proposed REMS and other materials in WORD format. It makes review of these materials more efficient and it is easier for the web posting staff to make the document 508 compliant. It is preferable that the entire REMS document and attached materials be in a single WORD document. If certain documents such as enrollment forms are only in PDF format, they may be submitted as such, but the preference is to include as many as possible be in a single WORD document.

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

/s/

KENDRA C WORTHY
07/17/2012