

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

203214Orig1s013

Trade Name: Xeljanz

Generic Name: Tofacitinib

Sponsor: Pfizer, Inc.

Approval Date: 02/08/2016

Indication: Xeljanz is an inhibitor of Janus kinases (JAKs) indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to methotrexate.

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CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	
Labeling	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	
Risk Assessment and Risk Mitigation Review(s)	X
Proprietary Name Review(s)	
Other Review(s)	
Administrative/Correspondence Document(s)	

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APPROVAL LETTER



NDA 203214/S-013

**SUPPLEMENT APPROVAL
RELEASE FROM REMS REQUIREMENT**

P F Prism C.V.
c/o Pfizer Inc.
500 Arcola Road
Collegeville, PA 19426

Attention: Alicia Holsey, M.S., RAC
Senior Manager, Worldwide Safety and Regulatory

Dear Ms. Holsey:

Please refer to your Supplemental New Drug Application (sNDA) dated and received January 20, 2016, submitted under section 505(b) for Xeljanz (tofacitinib) Tablets, 5 mg.

We also refer to our REMS Modification Notification letter dated January 13, 2016, and we acknowledge receipt of your risk evaluation and mitigation strategy (REMS) assessment dated November 6, 2015.

This prior approval supplemental application provides for proposed modification to the approved REMS and proposes to eliminate the requirement for the approved REMS for Xeljanz (tofacitinib).

We have completed our review of this supplemental application. It is approved, effective on the date of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

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.

Because none of these criteria apply to your application, you are exempt from this requirement.

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

The REMS for Xeljanz (tofacitinib) Tablets was originally approved on November 6, 2012,

and the most recent REMS modification was approved on June 19, 2015. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your proposed modifications consist of elimination of the communication plan, and therefore, release from the requirement for a REMS for Xeljanz (tofacitinib).

As communicated in the January 13, 2016 REMS Modification Notification Letter, we determined a communication plan is no longer necessary to include as an element of the approved REMS because the communication plan has been completed and the most recent assessment demonstrates that the communication plan has met its goals.

Therefore, because the communication plan is no longer necessary to ensure the benefits of the drug outweigh the risks, a REMS is no longer required for Xeljanz (tofacitinib).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Carol F. Hill, Senior Regulatory Health Project Manager for Safety, at (301) 796-1226.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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
02/08/2016

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
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**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**

**RISK EVALUATION AND MITIGATION STRATEGY (REMS) MODIFICATION
REVIEW**

Date: January 22, 2016

Reviewer: Erin M. Hachey, Pharm.D.
Risk Management Analyst
Division of Risk Management (DRISK)

Acting Team Leader: Jamie Wilkins Parker, Pharm.D., DRISK

Division Director: Cynthia LaCivita, Pharm.D., DRISK

Drug Name(s): Xeljanz (tofacitinib)

Therapeutic class: Janus kinase (JAK) inhibitor

Dosage forms: 5 mg oral tablet

OND Review Division: Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

Application Type/Number: NDA 203214, Supplement 13

Applicant/sponsor: PF Prism CV c/o Pfizer, Inc.

OSE RCM #: 2015-2179

*** This document contains proprietary and confidential information that should not be released to the public. ***

1. INTRODUCTION

The purpose of this review is to provide the Division of Risk Management's (DRISK) evaluation of the approved risk evaluation and mitigation strategy (REMS) for Xeljanz (tofacitinib), NDA 203214, and recommend modifications to the REMS, as appropriate. The evaluation of the approved REMS in meeting its goals uses the results of the REMS assessment reports submitted by PF Prism CV c/o Pfizer. The current REMS for Xeljanz was approved June 19, 2015, and consists of a communication plan (CP) and a timetable for submission of assessments.

1.1 PRODUCT BACKGROUND

Xeljanz (tofacitinib) is a Janus kinase (JAK) inhibitor approved for the treatment of moderate to severe rheumatoid arthritis (RA) in adult patients with an inadequate response or intolerance to methotrexate. The recommended dosage of Xeljanz is one 5 mg tablet administered orally twice daily. The dosage should be reduced to 5 mg once daily for patients receiving CYP3A4 inhibitors, patients with moderate-to-severe renal impairment, and patients with moderate hepatic impairment. It is recommended that Xeljanz not be initiated in patients with an absolute lymphocyte count less than 500 cells/mm³, an absolute neutrophil count (ANC) less than 1000 cells/mm³, or hemoglobin levels less than 9 g/dL. Dose interruption is recommended for management of lymphopenia, neutropenia, and anemia.

The original REMS for Xeljanz was approved on November 6, 2012, and the most recent REMS modification was approved on June 19, 2015. The goal of the current REMS is to mitigate the risk of serious infections, malignancies, lymphoproliferative disorders, increased cholesterol, and low blood cell counts associated with Xeljanz by informing healthcare prescribers and pharmacists about these risks. The REMS consists of a CP and a timetable for submission of assessments. The CP includes a Dear Healthcare Provider Letter (DHCPL) 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, a Dear Pharmacist Letter (DPL), dissemination of information through professional societies' scientific meetings and journals, and a Xeljanz REMS program website. The timetable for submission of assessments indicates that assessment reports be submitted at 18 months, 3 years, 5 years, and 7 years from the date of approval of the original REMS (November 6, 2012).

1.2 REGULATORY HISTORY

A brief summary of the key regulatory history relevant to the Xeljanz REMS is listed below, in chronological order.

November 6, 2012: Xeljanz (NDA 203214) was approved for the treatment of moderate-to-severe rheumatoid arthritis (RA) in adult patients with an inadequate response or intolerance to methotrexate. The approval included a REMS that consisted of a MG and CP.

July 11, 2013: Pfizer, Inc. informed the Agency of a change in ownership of NDA 203214.

August 28, 2013: The Agency issued a REMS Modification Notification Letter which requested the Sponsor submit a proposed REMS modification that reflects the change in ownership for Xeljanz.

September 25, 2013: The Sponsor submitted S-005, which requested revisions to the labeling to incorporate new safety information regarding viral hepatitis and the risk of non-melanoma skin cancer associated with Xeljanz and to align with recent labeling changes for the tumor necrosis factor (TNF) blockers. This submission also included a proposed REMS modification with revisions to the MG, DHCPL, DPL, and Journal Information Pieces to align the REMS materials with the proposed labeling.

September 27, 2013: The Sponsor submitted S-006, which included a proposed REMS modification based on the August 28, 2013 REMS Modification Notification Letter.

November 8, 2013: The Agency approved S-006, to reflect a change in ownership for Xeljanz.

March 26, 2014: The Agency approved S-005, which included approval of a REMS modification that revised the MG, DHCPL, DPL, and Journal Information Pieces to incorporate information regarding viral hepatitis and the risk of non-melanoma skin cancer associated with Xeljanz.

May 5, 2014: The Sponsor submitted the 18-month REMS Assessment Report.

July 2, 2014: DRISK review (dated June 30, 2014) of the 18-month REMS Assessment Report concluded that the REMS Assessment Report was complete and REMS goals were being met.

August 20, 2014: DRISK REMS Modification Review recommended a REMS modification to remove the MG from the REMS, revise the REMS goal to remove “and patients,” remove the Survey of Patient Knowledge and Understanding, and revise the REMS assessment plan accordingly, based on the DRISK review (dated June 30, 2014) of the 18-month REMS Assessment Report.

September 9, 2014: The Agency issued a REMS Modification Notification/REMS Assessment Plan Revision Letter, which requested removal of the MG as an element of the REMS.

November 7, 2014: The Sponsor submitted a proposed REMS modification (S-008) based on the September 9, 2014 REMS Modification Notification/REMS Assessment Plan Revision Letter.

December 19, 2014: The Sponsor submitted S-010 to the Agency, which contained a proposed REMS modification to align the REMS appended materials with changes proposed to the prescribing information. The changes to the REMS materials included the addition of a warning statement regarding the risk of Herpes Zoster (HZ) in Japanese patients treated with Xeljanz to the Serious Infections section of the DHCP letter.

February 11, 2015: The Agency approved S-008, which removed the MG from the REMS. The MG remained part of the approved labeling.

April 20, 2015: The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) sent the Sponsor an e-mail communication to request that the Sponsor withhold distribution of their May 2015 DHCP letter mailings prior to the approval of S-010.

June 19, 2015: The Agency approved S-010, which modified the approved REMS and REMS appended materials to align with changes to the prescribing information regarding the risk of HZ infection in Japanese patients treated with Xeljanz. It also modified the goal to the following:

The goal of the Xeljanz REMS is to mitigate the risk of serious infections, malignancies, lymphoproliferative disorders, and laboratory abnormalities associated with Xeljanz by:

- *Informing healthcare prescribers and pharmacists about the above risks.*

November 6, 2015: The Sponsor submitted the 3-Year REMS Assessment Report, dated October 27, 2015.

January 5, 2016: DRISK review of the 3-year REMS Assessment Report concluded that the REMS Assessment Report was complete and the REMS goal was being met.

January 12, 2016: DRISK REMS modification review concluded that the CP activities were complete and a REMS was no longer necessary for Xeljanz.

January 13, 2016: The Agency sent the Sponsor a REMS Modification Notification letter, informing them that a REMS was no longer required for Xeljanz.

January 20, 2016: The Sponsor submitted S-013 to the Agency, in response to the Agency's January 13, 2016 REMS Modification Notification letter.

2. MATERIALS REVIEWED

The following is a list of materials used to inform this review:

- Worthy K and Tavakoli A. DRISK Final REMS Review for Xeljanz, dated November 6, 2012.
- Booker N. DRISK REMS Modification Review for Xeljanz, dated October 23, 2013.
- Cvetkovich T. DRISK Review of 18-Month REMS Assessment Report for Xeljanz, dated June 30, 2014.
- Wilkins Parker J. DRISK REMS Modification Review for Xeljanz, dated August 20, 2014.
- Booker N. DRISK REMS Modification Review for Xeljanz, dated December 17, 2014.
- Tavakoli A. DRISK REMS Modification Review for Xeljanz, dated June 19, 2015.
- PF Prism CV c/o Pfizer, Inc., 3-Year REMS Assessment Report for Xeljanz, received November 6, 2015.
- Auth D. DRISK Review of 3-Year REMS Assessment Report for Xeljanz, dated January 5, 2016.
- Hachey E. DRISK REMS Modification Review for Xeljanz, dated January 12, 2016.
- Seymour S. DPARP. REMS Modification Notification letter, dated January 13, 2016.
- PF Prism CV c/o Pfizer, Proposed Major REMS Modification for Xeljanz, received January 20, 2016 (Seq. 0154).

3. DRISK EVALUATION OF THE XELJANZ REMS

3.1 CURRENTLY APPROVED REMS

The current Xeljanz REMS (dated June 19, 2015) includes a CP and a timetable for submission of assessments. The CP currently includes the following components:

- **A Dear Healthcare Provider Letter:** will be distributed twice annually for 2 years from the date of initial approval (11/2012), and once within 60 days of the date of the modification approval (6/2015), 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 through both traditional mailing and electronic mailing.

The initial letter will be distributed within 60 days of product approval. The Prescribing Information and a copy of the Medication Guide will also be distributed in this communication.

- **A Dear Pharmacist Letter:** will be distributed twice annually for 2 years from the date of initial approval (11/2012) and once within 60 days of the date of the modification approval (6/2015), through both traditional mailing and electronic mailing. The initial letter will be distributed within 60 days of product approval.
- **Dissemination of information about the known and potential serious risks associated with XELJANZ will be made to healthcare providers through certain professional societies' scientific meetings and journals.**
 - Display, for 2 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).
 - Quarterly, for 3 years following product approval, presentation as a printed information piece in the following journals: The Rheumatologist, Arthritis & Rheumatology, Arthritis Care & Research, Clinical Infectious Diseases, 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.
- **Xeljanz REMS Website:** Pfizer will ensure that all materials listed in or appended to the Xeljanz REMS program will be available through the Xeljanz REMS program website, www.XELJANZREMS.com. The Xeljanz REMS program website will exist for three years following approval of the REMS. The 3-year requirement for the website was included in the initial REMS approval; the intent was for the website to remain active for three years immediately following the *initial* REMS approval, though the REMS did not specify *initial*.

3.2 STATUS OF COMMUNICATION PLAN ACTIVITIES

The following table summarizes the status of each activity required for the Sponsor under the CP element of the REMS:

Activity	REMS Requirement	Complete (Y/N)
Distribution of Dear Healthcare Provider letters	Within 60 days of product approval. Twice annually for 2 years from the date of initial approval Once within 60 days of the date of the modification approval	Y
Distribution of Dear Pharmacist letters	Within 60 days of product approval Twice annually for 2 years from the date of initial approval Once within 60 days of the date of the modification	Y

	approval	
Dissemination of information through professional societies' scientific meetings and journals	Display for 2 years following product approval Disseminate quarterly for 3 years following product approval	Y
REMS Website	Exist for 3 years following the initial approval of the REMS	Y
Note: Product approval was November 6, 2012; REMS modification approval was June 19, 2015		

3.3 RESULTS OF XELJANZ REMS ASSESSMENT REPORTS

The 18-month REMS Assessment Report was submitted on May 5, 2014, and the findings were evaluated by DRISK in a review dated June 30, 2014. DRISK concluded that the REMS was complete and meeting its goal to inform healthcare providers and patients about the serious risks associated with Xeljanz. Survey results indicated that prescribers, pharmacists, and patients were reasonably well aware of the risks in the REMS for Xeljanz.

The 3-year REMS Assessment Report was submitted on November 6, 2015, and the findings were evaluated by DRISK in a review dated January 5, 2016. DRISK concluded that the REMS was complete and meeting its goal to inform healthcare prescribers and pharmacists about the risk of serious infections, malignancies, lymphoproliferative disorders, increased cholesterol, and low blood cell counts associated with Xeljanz. Survey results indicated that prescribers and pharmacists demonstrated knowledge of the risks in the REMS for Xeljanz.

3.4 ANALYSIS OF SAFETY INFORMATION

Based on a discussion with the Medical Officer on November 13, 2015, and e-mail communication from the Deputy Director for Safety on November 17, 2015, in the Division of Pulmonary, Allergy, and Rheumatology Products, there have been no identified or emerging safety issues since the last REMS modification and REMS assessment review that may require continued or new communication within the next six months. They also concur with DRISK thinking that the CP REMS is no longer necessary to ensure the benefits outweigh the risks for Xeljanz.

4. DRISK-RECOMMENDED REMS MODIFICATION

After review of the Sponsor's 18-month REMS Assessment Report, 3-year REMS Assessment Report, and available safety information, DRISK recommends that the Xeljanz REMS be modified to remove the CP as an element of the REMS, and therefore, remove the requirement for the REMS.

In accordance with CDER's current thinking¹, the following conditions must apply when considering a REMS modification to eliminate a CP from the REMS:

1. All activities for the CP have been completed, and/or the CP activities have been assessed at least once; and

¹ Safety Requirements Team Update, December 18, 2013.

2. If the CP has been assessed, the goal of the CP has been met and there is no need to further assess the current CP; If the CP has not been assessed, no assessment of the current CP is necessary; and
3. There are no identified or emerging safety issues that may require continued or new communication within the next 6 months; and
4. If the REMS includes ETASU, removal of the CP has no implication for those elements, and
5. The CP is no longer necessary as an element of the REMS to ensure that the benefits of the drug outweigh the risks.

The review team has determined that the above conditions have been met for Xeljanz.

5. DISCUSSION

5.1 CONSIDERATIONS FOR ELIMINATING A CP FROM THE REMS

All of the conditions necessary for eliminating a CP from a REMS have been met for Xeljanz. Per the REMS document, all requirements for the Sponsor under the CP of the REMS are complete as of November 6, 2015, and have been assessed in both the 18-month and 3-year REMS Assessment Reports. Based on the findings from the 18-month and 3-year REMS Assessment Reports, the review team determined that the goal of the REMS has been met. Additionally, further assessment of the current CP is not necessary. There have been no identified or emerging safety issues that may require continued or new communication within the next six months.

5.2 ASSESSMENT OF WHETHER A REMS IS STILL NECESSARY

The purpose of the CP for the Xeljanz REMS is to inform healthcare providers about the serious risks associated with Xeljanz. The 3-Year REMS Assessment Report confirms that all CP activities are complete as of November 6, 2015, and the assessment report demonstrates that prescribers and pharmacists are knowledgeable about the REMS risks. Therefore, DRISK and DPARP concur that a REMS is no longer necessary to ensure the benefits outweigh the risks for Xeljanz.

6. CONCLUSION AND RECOMMENDATIONS

Based on the status of the Communication Plan activities, the REMS assessment findings, and available safety data, DRISK believes the CP is no longer necessary to ensure that the benefits of Xeljanz outweigh the risks. Therefore, DRISK recommends the Sponsor be sent a REMS Modification Notification letter to request the removal of the CP.

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/s/

ERIN M HACHEY
01/22/2016

CYNTHIA L LACIVITA
01/22/2016
Concur