

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*

**203214Orig1s008**

*Trade Name:* Xeljanz

*Generic Name:* Tofacitinib

*Sponsor:* Pfizer, Inc.

*Approval Date:* 02/11/2015

*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.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**203214Orig1s008**

## CONTENTS

### Reviews / Information Included in this NDA Review.

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

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**203214Orig1s008**

**APPROVAL LETTER**



NDA 203214/S-008

**SUPPLEMENT APPROVAL  
REMOVE REMS ELEMENT  
REMS ASSESSMENT PLAN REVISION**

PF PRISM C.V.  
c/o Pfizer, Inc.  
445 Eastern Road  
Groton, CT 06340

Attention: James T. Mayne, PhD, DABT  
Senior Director, Worldwide Safety and Regulatory

Dear Dr. Mayne:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 7, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xeljanz (tofacitinib) 5 mg tablets.

We also refer to our REMS Modification Notification letter, dated September 9, 2014, in which we notified you that the Medication Guide should be removed as an element of the REMS to decrease the burden on the healthcare delivery system of complying with the REMS. We also notified you that the REMS assessment plan should be revised.

This Prior Approval Supplemental New Drug Application proposes to eliminate the requirement for the approved Medication Guide as an element of the approved Xeljanz REMS.

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

**RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

The REMS for Xeljanz (tofacitinib) was originally approved on November 6, 2012, and REMS modifications were approved on November 8, 2013 and March 26, 2014. The REMS consists of a Medication Guide, communication plan, and timetable for submission of assessment of the REMS.

Your proposed modification to the REMS consists of eliminating the requirement for the Medication Guide as an element of the REMS.

We have determined that maintaining the Medication Guide as part of the approved labeling is adequate to address the serious and significant public health concern and meets the standard in

21 CFR 208.1. Therefore, it is no longer necessary to include the Medication Guide as an element of the approved REMS to ensure that the benefits of Xeljanz (tofacitinib) outweigh the risks.

Therefore, we agree with your proposal, and a Medication Guide is no longer required as part of the REMS for Xeljanz (tofacitinib).

Your proposed modified REMS submitted on November 7, 2014 and appended to this letter is approved.

The modified REMS consists of a communication plan and a timetable for submission of assessments for the REMS.

We remind you that the Medication Guide will continue to be part of the approved labeling for Xeljanz (tofacitinib) in accordance with 21 CFR 208.

The timetable for submission of assessments of the REMS will remain the same as that approved on November 6, 2012.

### **REMS ASSESSMENT PLAN**

Our March 26, 2014, Supplement Approval/REMS Modification Approval, letter described the REMS assessment plan. As described in our September 9, 2014, letter, the REMS assessment plan should be revised to remove the Survey of Patient Knowledge and Understanding since the REMS goals will be revised to only include healthcare providers.

The revised REMS assessment plan should include, but is not limited to the following:

- i. A survey of physicians' knowledge and understanding of the serious risks of tofacitinib will be made.
- ii. A survey of pharmacists' knowledge and understanding of the serious risks of tofacitinib will be made.
- iii. An assessment and conclusions regarding the success of the REMS in meeting the stated goals will be made.
- iv. An assessment of the communication plan including:
  - o The source(s) of the list of healthcare professionals to whom the Dear Healthcare Provider Letter, Dear Pharmacist Letter are distributed
  - o Journal information pieces published, including date and journal name, volume, and issue
  - o The date of launch of the communication plan (Dear Healthcare Provider Letter, Dear Pharmacist Letter, website, and journal information pieces)

- The number of recipients of the Dear Healthcare Provider and Dear Pharmacist Letters
- Date(s) of distribution of the Dear Healthcare Provider and Dear Pharmacist Letters
- The number of returned and refused letters

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

In addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment and may propose a modification to the approved REMS when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**NDA 203214 REMS CORRESPONDENCE  
(insert concise description of content in bold capital letters, e.g.,  
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT  
METHODOLOGY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

Prominently identify the submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

**NDA 203214 REMS ASSESSMENT  
  
NEW SUPPLEMENT FOR NDA 203214  
PROPOSED REMS MODIFICATION  
  
NEW SUPPLEMENT (NEW INDICATION FOR USE)**

**FOR NDA 203214  
REMS ASSESSMENT  
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

**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.

**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, Safety Regulatory Health Project Manager, 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

ENCLOSURES:  
REMS

**REMS**

Initial REMS Approval: 11/06/2012

Most Recent Modification: February/2015

**NDA 203,214 XELJANZ<sup>®</sup> (TOFACITINIB)**

**PF PRISM C.V.**

**c/o Pfizer Netherlands, Rivium Westlaan 142  
2909 LD Capelle aan den IJssel**

**NETHERLANDS**

**Authorized U.S. Agent: Pfizer Inc, NY**

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

**GOAL**

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

**REMS ELEMENTS:**

**Communication Plan**

Pfizer Inc will implement a communication plan to the following healthcare providers:

- Rheumatologists and rheumatology healthcare providers (including physician assistants and nurse practitioners) who are likely to prescribe XELJANZ,
- Infectious disease specialists who may be consulted about and treat serious infections including herpes zoster, tuberculosis, and other opportunistic infections,
- Family practitioners, general practitioners, and internal medicine specialists who may be consulted about and be involved in treating serious infections, decreases in neutrophil counts, decrease in lymphocyte counts, decreases in hemoglobin, and lipid elevations and hyperlipidemia,
- Emergency medicine specialists who may evaluate and treat serious infections including herpes zoster, and tuberculosis and other opportunistic infections in emergency care settings, and
- Pharmacists who will dispense XELJANZ.

Elements of the communication plan include the following:

1. A Dear Healthcare Provider Letter will be distributed twice annually for 3 years 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 Dear Healthcare Provider letter is enclosed in [Appendix A](#).

The Prescribing Information and a copy of the Medication Guide will also be distributed in this communication.

2. A Dear Pharmacist letter will be distributed to pharmacists twice annually for 3 years through both traditional mailing and electronic mailing. The initial letter will be distributed within 60 days of product approval. The Dear Pharmacist Letter is enclosed in [Appendix B](#).
3. 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 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*. The drafts of the important drug warning that will be printed in the aforementioned scientific journals are enclosed in [Appendices C](#) through [Appendix G](#).
4. 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](http://www.XELJANZREMS.com). The XELJANZ REMS program website will exist for 3 years following approval of the REMS. The landing page for the XELJANZ REMS website is appended (see [Appendix H](#)).

### **Timetable for Submission of Assessments**

Pfizer will submit REMS Assessments to the FDA at 18 months, by 3 years and 7 years from the date of approval of the REMS (11-06-2012). 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.

## Appendix A: Dear HealthCare Provider Letter

### IMPORTANT DRUG WARNING

**Subject: Risk of serious infections, malignancies, decreases in peripheral lymphocyte counts, neutrophil counts, hemoglobin, and increases in lipid parameters in peripheral blood with XELJANZ<sup>®</sup> (tofacitinib)**

Dear Healthcare Provider,

The purpose of this letter is to inform you of important safety information for XELJANZ<sup>®</sup> (tofacitinib citrate), an inhibitor of Janus kinases (JAKs) approved by the Food and Drug Administration (FDA) for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). The recommended dose of XELJANZ is 5 mg twice daily.

The safety and efficacy of XELJANZ<sup>®</sup> for conditions other than RA have not yet been established.

FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for XELJANZ to ensure that the benefits of the drug outweigh the potential risks.

#### **Limitations of Use**

XELJANZ is not recommended to be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

#### **Patient Counseling**

You must discuss the risks associated with XELJANZ therapy with patients and in applicable instances with their caregivers.

#### **Serious Risks of XELJANZ<sup>®</sup> (tofacitinib)**

##### ***Serious Infections***

- Patients treated with XELJANZ are at increased risk for developing serious infections leading to hospitalization or death, including active tuberculosis (TB), invasive fungal infections, bacterial, viral and other infections due to opportunistic pathogens. Most patients

who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

- Avoid use of XELJANZ in patients with an active infection, including localized infections. If a serious infection develops, XELJANZ should be interrupted until the infection is controlled.
- Prior to initiating XELJANZ, a test for latent TB should be performed. If the test is positive, treatment for TB should be started prior to starting XELJANZ. All patients should be monitored for active TB during treatment, including patients who tested negative for latent TB prior to initiating therapy.
- Cases of viral reactivation were observed in clinical studies with XELJANZ. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ.

### ***Malignancies and Lymphoproliferative Disorders***

- Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. Lymphoma and other malignancies have been reported in patients treated with XELJANZ.
- In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving XELJANZ with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with XELJANZ.
- In Phase 2B, controlled dose-ranging studies in de-novo renal transplant patients, all of whom received induction therapy with basiliximab, high dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine.
- Non-melanoma skin cancers have been reported in patients treated with XELJANZ and identified as an adverse drug reaction. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

### ***Important Information on Laboratory Abnormalities***

- Lymphocytes, neutrophils, hemoglobin, and lipids should be monitored, as abnormalities in these parameters were associated with XELJANZ treatment in Phase 3 clinical trials.

### **Medication Guide**

The Medication Guide contains information that can be used to facilitate discussions about the known and potential risks of therapy. A copy is enclosed. The XELJANZ Medication Guide must be provided to patients being treated with XELJANZ or to their caregiver at the time of first dose or if the Medication Guide is materially changed. Additional copies of the Medication Guide may be obtained from the XELJANZ REMS web site ([www.XELJANZREMS.com](http://www.XELJANZREMS.com)) or by calling Pfizer at 1-800-438-1985.

### **Reporting Adverse Events**

To report any adverse events with the use of XELJANZ, contact:

- Pfizer Safety at 1-800-438-1985
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This letter is not a comprehensive description of the risks associated with the use of XELJANZ. Please read the accompanying Prescribing Information, including **BOXED WARNING**, and Medication Guide for a complete description of these risks.

For more information, please call Pfizer Medical Information at 1-800-438-1985 or visit the XELJANZ REMS web site ([www.XELJANZREMS.com](http://www.XELJANZREMS.com)).

Sincerely,

Chief Medical Officer  
Pfizer

Enclosure

## Appendix B: Dear Pharmacist Letter

### IMPORTANT DRUG WARNING

Dear Pharmacist,

The purpose of this letter is to inform you of important safety information for XELJANZ<sup>®</sup> (tofacitinib citrate), an inhibitor of Janus kinases (JAKs) approved by the Food and Drug Administration (FDA) for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). The recommended dose of XELJANZ is 5 mg twice daily.

The safety and efficacy of XELJANZ<sup>®</sup> for conditions other than RA have not yet been established.

FDA has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for XELJANZ to ensure that the benefits of the drug outweigh the potential risks.

#### **Limitations of Use**

XELJANZ is not recommended to be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

#### **Serious Risks of XELJANZ<sup>®</sup> (tofacitinib)**

##### ***Serious Infections***

- Patients treated with XELJANZ are at increased risk for developing serious infections leading to hospitalization or death, including active tuberculosis (TB), invasive fungal infections, bacterial, viral and other infections due to opportunistic pathogens. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.
- Avoid use of XELJANZ in patients with an active infection, including localized infections. If a serious infection develops, XELJANZ should be interrupted until the infection is controlled.
- Prior to initiating XELJANZ, a test for latent TB should be performed. If the test is positive, treatment for TB should be started prior to starting XELJANZ. All patients should be

monitored for active TB during treatment, including patients who tested negative for latent TB prior to initiating therapy.

- Cases of viral reactivation were observed in clinical studies with XELJANZ. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ.

### ***Malignancies and Lymphoproliferative Disorders***

- Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. Lymphoma and other malignancies have been reported in patients treated with XELJANZ.
- In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving XELJANZ with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with XELJANZ.
- In Phase 2B, controlled dose-ranging studies in de-novo renal transplant patients, all of whom received induction therapy with basiliximab, high dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine.
- Non-melanoma skin cancers have been reported in patients treated with XELJANZ and identified as an adverse drug reaction. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

### ***Important Information on Laboratory Abnormalities***

- Lymphocytes, neutrophils, hemoglobin, and lipids should be monitored, as abnormalities in these parameters were associated with XELJANZ treatment in Phase 3 clinical trials.

### **Medication Guide**

The FDA requires that a copy of the enclosed XELJANZ Medication Guide be distributed to patients who receive XELJANZ or to their caregiver at the time of dispensing or if the Medication Guide is materially changed. Additional copies of the Medication Guide may be obtained from the XELJANZ REMS web site ([www.XELJANZREMS.com](http://www.XELJANZREMS.com)) or by calling Pfizer at 1-800-438-1985.

### **Reporting Adverse Events**

To report any adverse events with the use of XELJANZ, contact:

- Pfizer Safety at 1-800-438-1985

- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This letter is not a comprehensive description of the risks associated with the use of XELJANZ. Please read the accompanying Prescribing Information, including **BOXED WARNING**, and Medication Guide for a complete description of these risks.

For more information, please call Pfizer Medical Information at 1-800-438-1985 or visit the XELJANZ REMS web site ([www.XELJANZREMS.com](http://www.XELJANZREMS.com)).

Sincerely,

Chief Medical Officer  
Pfizer

Enclosure

## **Appendix C: Journal Information Piece For Rheumatologists or Rheumatology Healthcare Providers (including physician assistants and nurse practitioners)**

### **Important Drug Warning for Rheumatologists and Rheumatology Healthcare Providers (including physician assistants and nurse practitioners) about Risks and Potential Risks with XELJANZ**

XELJANZ<sup>®</sup> (tofacitinib citrate) is an inhibitor of Janus kinases (JAKs) approved by the Food and Drug Administration (FDA) for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). The recommended dose of XELJANZ is 5 mg twice daily.

The safety and efficacy of XELJANZ<sup>®</sup> for conditions other than RA have not yet been established.

#### **Limitations of Use**

XELJANZ is not recommended to be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

#### **Serious Risks of XELJANZ<sup>®</sup> (tofacitinib)**

**Serious Infections:** Patients treated with XELJANZ are at increased risk for developing serious infections leading to hospitalization or death, including active tuberculosis (TB), invasive fungal infections, bacterial, viral and other infections due to opportunistic pathogens. Avoid use of XELJANZ in patients with an active infection, including localized infections. If a serious infection develops, XELJANZ should be interrupted until the infection is controlled.

**Malignancies and Lymphoproliferative Disorders:** Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. Lymphoma, solid cancers, and NMSC have been reported in patients treated with XELJANZ. NMSC has been identified as an adverse drug reaction.

**Laboratory Abnormalities:** Lymphocytes, neutrophils, hemoglobin, and lipids should be monitored, as abnormalities in these parameters were associated with XELJANZ treatment in Phase 3 clinical trials. Please see the full Prescribing Information for more information.

#### **Reporting Adverse Events**

To report any adverse events with the use of XELJANZ, contact:

- Pfizer Safety at 1-800-438-1985
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This is not a comprehensive representation of the potential risks associated with use of XELJANZ. For a complete description of these potential risks, please visit the XELJANZ REMS web site ([www.XELJANZREMS.com](http://www.XELJANZREMS.com)) for Prescribing Information and Medication Guide.

## Appendix D: Journal Information Piece For Infectious Disease Specialists

### Important Drug Warning for Infectious Disease Specialists about Risks and Potential Risks with XELJANZ

XELJANZ<sup>®</sup> (tofacitinib citrate) is an inhibitor of Janus kinases (JAKs) approved by the Food and Drug Administration (FDA) for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). The recommended dose of XELJANZ is 5 mg twice daily.

The safety and efficacy of XELJANZ<sup>®</sup> for conditions other than RA have not yet been established.

#### Limitations of Use

XELJANZ is not recommended to be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

#### Serious Risks of XELJANZ<sup>®</sup> (tofacitinib)

**Serious Infections:** Patients treated with XELJANZ are at increased risk for developing serious infections leading to hospitalization or death, including active tuberculosis (TB), invasive fungal infections, bacterial, viral and other infections due to opportunistic pathogens. Avoid use of XELJANZ in patients with an active infection, including localized infections. If a serious infection develops, XELJANZ should be interrupted until the infection is controlled.

**Malignancies and Lymphoproliferative Disorders:** Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. Lymphoma, solid cancers, and NMSC have been reported in patients treated with XELJANZ. NMSC has been identified as an adverse drug reaction.

**Laboratory Abnormalities:** Lymphocytes, neutrophils, hemoglobin, and lipids should be monitored, as abnormalities in these parameters were associated with XELJANZ treatment in Phase 3 clinical trials. Please see the full Prescribing Information for more information.

#### Reporting Adverse Events

To report any adverse events with the use of XELJANZ, contact:

- Pfizer Safety at 1-800-438-1985
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This is not a comprehensive representation of the potential risks associated with use of XELJANZ. For a complete description of these potential risks, please visit the XELJANZ

REMS web site ([www.XELJANZREMS.com](http://www.XELJANZREMS.com)) for Prescribing Information and Medication Guide.

## **Appendix E: Journal Information Piece For Family Practitioners, General Practitioners, and Internal Medicine Specialists**

### **Important Drug Warning for Family Practitioners, General Practitioners, and Internal Medicine Specialists about Risks and Potential Risks with XELJANZ**

XELJANZ<sup>®</sup> (tofacitinib citrate) is an inhibitor of Janus kinases (JAKs) approved by the Food and Drug Administration (FDA) for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). The recommended dose of XELJANZ is 5 mg twice daily.

The safety and efficacy of XELJANZ<sup>®</sup> for conditions other than RA have not yet been established.

#### **Limitations of Use**

XELJANZ is not recommended to be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

#### **Serious Risks of XELJANZ<sup>®</sup> (tofacitinib)**

**Serious Infections:** Patients treated with XELJANZ are at increased risk for developing serious infections leading to hospitalization or death, including active tuberculosis (TB), invasive fungal infections, bacterial, viral and other infections due to opportunistic pathogens. Avoid use of XELJANZ in patients with an active infection, including localized infections. If a serious infection develops, XELJANZ should be interrupted until the infection is controlled.

**Malignancies and Lymphoproliferative Disorders:** Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. Lymphoma, solid cancers, and NMSC have been reported in patients treated with XELJANZ. NMSC has been identified as an adverse drug reaction.

**Laboratory Abnormalities:** Lymphocytes, neutrophils, hemoglobin, and lipids should be monitored, as abnormalities in these parameters were associated with XELJANZ treatment in Phase 3 clinical trials. Please see the full Prescribing Information for more information.

#### **Reporting Adverse Events**

To report any adverse events with the use of XELJANZ, contact:

- Pfizer Safety at 1-800-438-1985
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This is not a comprehensive representation of the potential risks associated with use of XELJANZ. For a complete description of these potential risks, please visit the XELJANZ REMS web site ([www.XELJANZREMS.com](http://www.XELJANZREMS.com)) for Prescribing Information and Medication Guide.

## Appendix F: Journal Information Piece For Emergency Medicine Specialists

### Important Drug Warning for Emergency Medicine Specialists about Risks and Potential Risks with XELJANZ

XELJANZ<sup>®</sup> (tofacitinib citrate) is an inhibitor of Janus kinases (JAKs) approved by the Food and Drug Administration (FDA) for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). The recommended dose of XELJANZ is 5 mg twice daily.

The safety and efficacy of XELJANZ<sup>®</sup> for conditions other than RA have not yet been established.

#### Limitations of Use

XELJANZ is not recommended to be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

#### Serious Risks of XELJANZ<sup>®</sup> (tofacitinib)

**Serious Infections:** Patients treated with XELJANZ are at increased risk for developing serious infections leading to hospitalization or death, including active tuberculosis (TB), invasive fungal infections, bacterial, viral and other infections due to opportunistic pathogens. Avoid use of XELJANZ in patients with an active infection, including localized infections. If a serious infection develops, XELJANZ should be interrupted until the infection is controlled.

**Malignancies and Lymphoproliferative Disorders:** Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. Lymphoma, solid cancers, and NMSC have been reported in patients treated with XELJANZ. NMSC has been identified as an adverse drug reaction.

**Laboratory Abnormalities:** Lymphocytes, neutrophils, hemoglobin, and lipids should be monitored, as abnormalities in these parameters were associated with XELJANZ treatment in Phase 3 clinical trials. Please see the full Prescribing Information for more information.

#### Reporting Adverse Events

To report any adverse events with the use of XELJANZ, contact:

- Pfizer Safety at 1-800-438-1985
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This is not a comprehensive representation of the potential risks associated with use of XELJANZ. For a complete description of these potential risks, please visit the XELJANZ REMS web site ([www.XELJANZREMS.com](http://www.XELJANZREMS.com)) for Prescribing Information and Medication Guide.

## Appendix G: Journal Information Piece For Pharmacists

### Important Drug Warning for Pharmacists about Risks and Potential Risks with XELJANZ

XELJANZ<sup>®</sup> (tofacitinib citrate) is an inhibitor of Janus kinases (JAKs) approved by the Food and Drug Administration (FDA) for adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). The recommended dose of XELJANZ is 5 mg twice daily.

The safety and efficacy of XELJANZ<sup>®</sup> for conditions other than RA have not yet been established.

#### Limitations of Use

XELJANZ is not recommended to be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

#### Serious Risks of XELJANZ<sup>®</sup> (tofacitinib)

**Serious Infections:** Patients treated with XELJANZ are at increased risk for developing serious infections leading to hospitalization or death, including active tuberculosis (TB), invasive fungal infections, bacterial, viral and other infections due to opportunistic pathogens. Avoid use of XELJANZ in patients with an active infection, including localized infections. If a serious infection develops, XELJANZ should be interrupted until the infection is controlled.

**Malignancies and Lymphoproliferative Disorders:** Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. Lymphoma, solid cancers, and NMSC have been reported in patients treated with XELJANZ. NMSC has been identified as an adverse drug reaction.

**Laboratory Abnormalities:** Lymphocytes, neutrophils, hemoglobin, and lipids should be monitored, as abnormalities in these parameters were associated with XELJANZ treatment in Phase 3 clinical trials. Please see the full Prescribing Information for more information.

#### Reporting Adverse Events

To report any adverse events with the use of XELJANZ, contact:

- Pfizer Safety at 1-800-438-1985
- MedWatch (FDA safety information and adverse event reporting program) at 1-800-332-1088 or online at [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)

This is not a comprehensive representation of the potential risks associated with use of XELJANZ. For a complete description of these potential risks, please visit the XELJANZ REMS web site ([www.XELJANZREMS.com](http://www.XELJANZREMS.com)) for Prescribing Information and Medication Guide.

## Appendix H: Screenshot of the Proposed REMS Website



### Risk Evaluation and Mitigation Strategy (REMS)

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 (FDA) to ensure that the benefits of the drug outweigh its risks.

The goal of the XELJANZ REMS is:

- To inform healthcare providers about the serious risks associated with XELJANZ treatment.

In order for Pfizer to communicate certain risks about XELJANZ, Pfizer has worked with the FDA to develop a detailed communication plan to communicate the following important risks:

- serious and other important infections
- malignancies and lymphoproliferative disorders
- changes in laboratory parameters, such as decreases in lymphocytes, neutrophils, and hemoglobin levels, and increases in lipids.

To learn more about serious risks, read the full prescribing information, including the boxed warning and Medication Guide. Please discuss the Medication Guide with your patients.

Elements of the communication plan include the following:

- A Dear Healthcare Provider Letter
- A Dear Pharmacist Letter
- Dissemination of information about the known and potential serious risks associated with XELJANZ through certain professional societies' scientific meetings and journals
- Dissemination of information about the known and potential serious risks associated with XELJANZ through the XELJANZ REMS website

Continue to check back on this website; it will be updated to include additional information intended to assist in the proper communication of the serious risks associated with XELJANZ treatment.

Please read the following materials:

**Prescribing Information and Medication Guide**

**Communication to HCP through Scientific Journals**

**Healthcare Provider Letter**

**Pharmacist Letter**

**Important Safety Information**

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/s/  
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CAROL F HILL  
02/11/2015

SALLY M SEYMOUR  
02/11/2015

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**203214Orig1s008**

**RISK ASSESSMENT and RISK MITIGATION  
REVIEW(S)**

**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**

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

Date: December 17, 2014

Reviewer(s): Nyedra W. Booker, Pharm.D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK)

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

Acting Deputy Division Director: Reema Mehta, Pharm.D., M.P.H., DRISK

Subject: Evaluation of proposed modification to the approved Xeljanz REMS

Drug Name(s): Xeljanz (tofacitinib)

Dosage and Route: 5 mg oral tablets

Application Type/Number: NDA 203-214

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

OSE RCM #: 2014-2342

## 1 INTRODUCTION

This is a review of Division of Risk Management's (DRISK) evaluation of the proposed modification to the Xeljanz (tofacitinib) risk evaluation and mitigation strategy (REMS) submitted by PF Prism C.V. c/o Pfizer, Inc. on November 7, 2014.

The Sponsor submitted the proposed REMS modification in response to a REMS Modification Notification Letter, dated September 9, 2014 in which the Agency requested the Applicant remove patients from the goals of the REMS, remove the Medication Guide (MG) as an element of the REMS, and revise the REMS assessment plan accordingly. The requested modifications were based on the Agency's assessment of the 18-month REMS Assessment Report, dated May 5, 2014.

## 2 BACKGROUND

Xeljanz (tofacitinib) is a Janus kinases (JAKs) 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 dose of Xeljanz is 5 mg twice daily. The dose should be reduced to once daily for patients receiving CYP3A4 inhibitors, moderate to severe renal impairment, or in patients with moderate hepatic impairment. It is recommended that Xeljanz not be initiated in patients with an absolute lymphocyte count less than  $500\text{cells}/\text{mm}^3$ , an absolute neutrophil count (ANC) less than  $1000\text{ cells}/\text{mm}^3$ , or who have hemoglobin levels less than 9g/dL. Dose interruption is recommended for management of lymphopenia, neutropenia, and anemia.

Xeljanz is associated with the following serious risks:

- Serious infections (e.g., tuberculosis, invasive fungal infections, and bacterial, viral, and other infections due to opportunistic pathogens) that may lead to hospitalization or death. Most patients who develop these infections were taking concomitant immunosuppressants (e.g., methotrexate, corticosteroids).
- Malignancy, including lymphoma and other malignancies, have been observed. Additionally, Epstein Barr Virus- associated post-transplant lymphoproliferative disorder has been observed at an increase rate in renal transplant patients treated with Xeljanz and concomitant immunosuppressive medications.
- Laboratory abnormalities: increase in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol; lymphocyte abnormalities; neutropenia; and anemia.

Xeljanz was approved on November 6, 2012 with a REMS. The goal of the REMS is to inform healthcare providers and patients about the serious risks associated with Xeljanz and consists of the following:

- Medication Guide
- Communication Plan: Dear Healthcare Provider Letter, Dear Pharmacist Letter, Journal Information Pieces [Rheumatologists or Rheumatology Healthcare Providers (Appendix C), Infectious Disease Specialists (Appendix D), Family

Practitioners, General Practitioners, and Internal Medicine Specialists (Appendix E), Emergency Medicine Specialists (Appendix F), Pharmacists (Appendix G)]

- Timetable for Submission of Assessments: REMS Assessment Reports will be submitted at 18 months, 3 years, and 7 years from REMS approval.

### **3 REGULATORY HISTORY**

Xeljanz was initially approved on November 6, 2012 with a REMS.

On November 8, 2013, a modification to the Xeljanz REMS was approved. The modification included changes to the approved REMS and relevant REMS materials to reflect a change in NDA ownership (including revisions to indicate a new applicant name, address, and contact information).

On March 26, 2014, a modification to the Xeljanz REMS was approved. The modification included revisions to the Medication Guide, Dear Healthcare Provider Letter, Dear Pharmacist Letter, and Journal Information Pieces to incorporate information regarding viral hepatitis and the risk of non-melanoma skin cancer associated with Xeljanz.

On May 5, 2014, the 18-month REMS Assessment Report (1<sup>st</sup> assessment) was received.

On June 25, 2014, DRISK, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), and the Office of Compliance (OC) met to discuss the 18-month REMS Assessment Report. The team concluded that the result of patients, prescribers, and pharmacist surveys indicated reasonable knowledge of the REMS risks.

July 2, 2014: DRISK review of 18-month REMS Assessment Report completed.

On September 9, 2014, the Agency notified the Sponsor of the following required modifications to the approved Xeljanz REMS via a REMS Modification Notification Letter:

- Removal of the MG as an element of the approved REMS
- Modification of the REMS goal to remove “and patients”
- Removal of the Survey of Patient Knowledge and Understanding from the REMS supporting document

On November 7, PF Prism C.V. submitted the proposed modification requested by the Agency (Supplement 8). This submission is the subject of this review.

### **4 MATERIALS REVIEWED**

#### **4.1 SPONSOR’S SUBMISSIONS**

- PF Prism C.V. Proposed REMS Modification for NDA 203-214/S-008, dated November 7, 2014

## 4.2 OTHER MATERIALS INFORMING THE REVIEW

- REMS Modification Notification/REMS Assessment Plan Revision for NDA 203-214, dated September 9, 2014
- Wilkins Parker J. DRISK REMS Modification Review for NDA 203-214, dated August 20, 2014
- Cvetkovich, T. DRISK REMS Assessment Review for NDA 203-214, dated July 2, 2014

## 5 RATIONALE FOR PROPOSED REMS MODIFICATIONS

PF Prism C.V. submitted proposed modifications to the REMS on November 7, 2014 in response to a REMS Modification Notification letter dated September 9, 2014, requesting the following modifications: 1) remove the Medication Guide as a REMS element, 2) remove “and patients” from the REMS goal, and 3) remove the Survey of Patient Knowledge and Understanding from the REMS supporting document.

During review of the 18-month Xeljanz REMS assessment, the review team (DRISK, DPARP, OC) determined that patients had adequate knowledge to support elimination of the Medication Guide from the REMS. This was evidenced by patient surveys demonstrating sufficient patient understanding that regular laboratory testing is necessary while receiving Xeljanz. Further, patients understood the signs and symptoms that may indicate an infection, the need for TB testing, that the drug itself can cause a decreased immune response and increased risk of cancer, conditions that should be reported before initiating Xeljanz, and the signs and symptoms of a potential intestinal perforation that should be immediately reported to a physician.

Therefore, patients successfully demonstrated the level of knowledge that they were expected to know while on Xeljanz therapy and additional assessment of patient knowledge was not necessary.

## 6 RESULTS OF REVIEW OF PROPOSED REMS MODIFICATIONS

The proposed modifications to the REMS goals and elements (received November 7, 2014) are described below.

### 6.1 GOALS

The REMS goal was revised to remove “and patients” as described below:

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

*Reviewer Comment:* We agree with the Sponsor’s proposed changes.

## 6.2 REMS ELEMENTS

### 6.2.1 Medication Guide

The Medication Guide was removed from the REMS but will remain as a component of labeling.

*Reviewer Comment: We agree with the Sponsor's proposed changes.*

### 6.2.2 Communication Plan

Minor editorial changes were made to the REMS Document (e.g., ~~two~~ 2 years) and Dear Healthcare Provider Letters (e.g., Disorders).

*Reviewer Comment: We agree with the Sponsor's proposed changes.*

### 6.2.3 Timetable for Submission of Assessments

The timetable for submission of assessments of the REMS will remain the same as that approved on November 6, 2012.

## 6.3 SUPPORTING DOCUMENT

- The Survey of Patient Knowledge and Understanding was removed from the REMS supporting document.
- Minor editorial changes were made to align with changes to the REMS as described above.

*Reviewer Comment: We agree with the Sponsor's proposed changes.*

## 7 REMS ASSESSMENT PLAN

The REMS assessment plan has been revised to remove the Survey of Patient Knowledge and Understanding.

*Reviewer Comment: We agree with the Sponsor's proposed changes.*

## 8 DISCUSSION AND CONCLUSION

DRISK finds the proposed REMS modification for Xeljanz as submitted on November 7, 2014 acceptable. The revisions were proposed by the Sponsor in response to a REMS Modification Notification letter dated September 9, 2014. Therefore, the modified Xeljanz REMS is acceptable to DRISK.

## 9 RECOMMENDATIONS

DRISK recommends approval of the Xeljanz REMS Modification under S-008, received November 7, 2014, and appended to this review. The following revised Assessment plan should be included in the approval letter:

REMS Assessment Plan

- i. **A survey of physicians' knowledge and understanding of the serious risks of tofacitinib will be made.**

Pfizer will conduct surveys to assess physician comprehension of information presented in the Communication Plan at 18 months, by 3 years and 7 years from the date of approval of the REMS (please refer to [Appendix A](#) for the draft survey).

**ii. A survey of pharmacists' knowledge and understanding of the serious risks of tofacitinib will be made.**

Pfizer will conduct surveys to assess pharmacist comprehension of information presented in the Communication Plan at 18 months, by 3 years and 7 years from the date of approval of the REMS (please refer to [Appendix A](#) for the draft survey).

**iii. An assessment and conclusions regarding the success of the REMS in meeting the stated goals will be made.**

Pfizer will conduct a REMS assessment to evaluate the effectiveness of the REMS (please refer to [Appendix A for the protocol synopsis](#)). The assessment report will be submitted periodically according to the timeline specified in the [REMS](#) (at 18 months, 3 years and 7 years), including assessment of:

- The knowledge and understanding of prescribers and pharmacists of the risk of tofacitinib use described in the REMS through survey. The survey results will include reported awareness, receipt, and reading of REMS related materials (i.e., full prescribing information, Dear Healthcare Provider Letter, Dear Pharmacist Letter, and the summarized important drug warning) and survey-assessed knowledge of risks of tofacitinib.
- The implementation of the communication plan included in the [REMS](#), which will consist of the information listed in section **iv** below.

**iv. An assessment of the communication plan including**

- The source(s) of the list of healthcare professionals to whom the Dear Healthcare Provider Letter, Dear Pharmacist Letter are distributed
- Journal information pieces published, including date and journal name, volume, and issue
- The date of launch of the communication plan (Dear Healthcare Provider Letter, Dear Pharmacist Letter, website, and journal information pieces)
- The number of recipients of the Dear Healthcare Provider and Dear Pharmacist Letters
- Date(s) of distribution of the Dear Healthcare Provider and Dear Pharmacist Letters
- The number of returned and refused letters

## **10 ATTACHMENTS**

Attachment: XELJANZ REMS

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

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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NYEDRA W BOOKER  
12/17/2014

REEMA J MEHTA  
12/18/2014  
I concur.