

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203214Orig1s000**

**REMS**

## **REMS**

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

**Pfizer Inc  
235 East 42nd St  
NY, NY 10017**

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

#### **GOAL**

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

#### **REMS ELEMENTS:**

##### **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. The Medication Guide is enclosed in [Appendix I](#).

##### **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 hyperlipidaemia,
- 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 three 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. This 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 three years through both traditional mailing and electronic mailing. This 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 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).
  - Quarterly, for three years following product approval, presentation as a printed information piece in *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*. 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 (XX-XX-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

November 2012

### 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.

#### **Limitations of Use**

XELJANZ should not 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.

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.

#### **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.

- XELJANZ should not be initiated 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.

### ***Malignancies and Lymphoproliferative Disorder***

- 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.

### ***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 full 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

November 2012

### IMPORTANT DRUG WARNING

Dear Pharmacist,

The purpose of this letter is to inform you of important safety information for XELJANZ® (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® for conditions other than RA have not yet been established.

#### **Limitations of Use**

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

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.

#### **Serious Risks of XELJANZ® (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.
- XELJANZ should not be initiated 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.

### ***Malignancies and Lymphoproliferative Disorder***

- 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.

### ***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 full 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® (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® for conditions other than RA have not yet been established.

#### **Limitations of Use**

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

#### **Serious Risks of XELJANZ® (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. XELJANZ should not be initiated 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 Disorder:** 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.

**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 Full 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® (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® for conditions other than RA have not yet been established.

#### Limitations of Use

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

#### Serious Risks of XELJANZ® (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. XELJANZ should not be initiated 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 Disorder:** 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.

**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 Full 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® (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® for conditions other than RA have not yet been established.

#### **Limitations of Use**

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

#### **Serious Risks of XELJANZ® (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. XELJANZ should not be initiated 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 Disorder:** 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.

**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 Full 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® (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® for conditions other than RA have not yet been established.

#### **Limitations of Use**

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

#### **Serious Risks of XELJANZ® (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. XELJANZ should not be initiated 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 Disorder:** 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.

**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 Full 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® (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® for conditions other than RA have not yet been established.

#### Limitations of Use

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

#### Serious Risks of XELJANZ® (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. XELJANZ should not be initiated 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 Disorder:** 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.

**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 Full 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 to ensure that the benefits of the drug outweigh its risks.

The goal of the XELJANZ REMS is:

- To inform healthcare providers and patients 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 other 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 prescribing information and medication guide and discuss it 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 risks of XELJANZ.



## Appendix I: Medication Guide

### MEDICATION GUIDE

#### **XELJANZ (ZEL' JANS') (tofacitinib)**

Read this Medication Guide before you start taking XELJANZ and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

**What is the most important information I should know about XELJANZ?  
XELJANZ may cause serious side effects including:**

#### **1. Serious infections.**

XELJANZ is a medicine that affects your immune system. XELJANZ can lower the ability of your immune system to fight infections. Some people have serious infections while taking XELJANZ, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

- Your healthcare provider should test you for TB before starting XELJANZ.
- Your healthcare provider should monitor you closely for signs and symptoms of TB infection during treatment with XELJANZ.

You should not start taking XELJANZ if you have any kind of infection unless your healthcare provider tells you it is okay.

Before starting XELJANZ, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection such as:
  - fever, sweating, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinating more often than normal
  - feeling very tired
- are being treated for an infection
- get a lot of infections or have infections that keep coming back
- have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis,

coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use XELJANZ. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.

- have or have had hepatitis B or C

After starting XELJANZ, call your healthcare provider right away if you have any symptoms of an infection. XELJANZ can make you more likely to get infections or make worse any infection that you have.

## **2. Cancer and immune system problems.**

XELJANZ may increase your risk of certain cancers by changing the way your immune system works.

- Lymphoma and other cancers can happen in patients taking XELJANZ. Tell your healthcare provider if you have ever had any type of cancer.
- Some people who have taken XELJANZ with certain other medicines to prevent kidney transplant rejection have had a problem with certain white blood cells growing out of control (Epstein Barr Virus-associated post transplant lymphoproliferative disorder).

## **3. Tears (perforation) in the stomach or intestines.**

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking XELJANZ get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

**4. Changes in certain laboratory test results.** Your healthcare provider should do blood tests before you start receiving XELJANZ and while you take XELJANZ to check for the following side effects:

- **changes in lymphocyte counts.** Lymphocytes are white blood cells that help the body fight off infections.
- **low neutrophil counts.** Neutrophils are white blood cells that help the body fight off infections.
- **low red blood cell count.** This may mean that you have anemia, which may make you feel weak and tired.

Your healthcare provider should routinely check certain liver tests.

You should not receive XELJANZ if your lymphocyte count, neutrophil count, or red blood cell count is too low or your liver tests are too high.

Your healthcare provider may stop your XELJANZ treatment for a period of time if needed because of changes in these blood test results.

You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving XELJANZ, and as needed after that. Normal cholesterol levels are important to good heart health.

See “What are the possible side effects of XELJANZ?” for more information about side effects.

### **What is XELJANZ?**

XELJANZ is a prescription medicine called a Janus kinase (JAK) inhibitor. XELJANZ is used to treat adults with moderately to severely active rheumatoid arthritis in which methotrexate did not work well.

It is not known if XELJANZ is safe and effective in people with Hepatitis B or C.

XELJANZ is not for people with severe liver problems.

It is not known if XELJANZ is safe and effective in children.

### **What should I tell my healthcare provider before taking XELJANZ?**

#### **XELJANZ may not be right for you. Before taking XELJANZ, tell your healthcare provider if you:**

- have an infection. See “What is the most important information I should know about XELJANZ?”
- have liver problems
- have kidney problems
- have any stomach area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines
- have had a reaction to tofacitinib or any of the ingredients in XELJANZ
- have recently received or are scheduled to receive a vaccine. People who take XELJANZ should not receive live vaccines. People taking XELJANZ can receive non-live vaccines.
- have any other medical conditions
- plan to become pregnant or are pregnant. It is not known if XELJANZ will harm an unborn baby.

Pregnancy Registry: Pfizer has a registry for pregnant women who take XELJANZ. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking XELJANZ, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.

- plan to breastfeed or are breastfeeding. You and your healthcare provider should decide if you will take XELJANZ or breastfeed. You should not do both.

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. XELJANZ and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- any other medicines to treat your rheumatoid arthritis. You should not take tocilizumab (Actemra<sup>®</sup>), etanercept (Enbrel<sup>®</sup>), adalimumab (Humira<sup>®</sup>), infliximab (Remicade<sup>®</sup>), rituximab (Rituxan<sup>®</sup>), abatacept (Orencia<sup>®</sup>), anakinra (Kineret<sup>®</sup>), certolizumab (Cimzia<sup>®</sup>), golimumab (Simponi<sup>®</sup>), azathioprine, cyclosporine, or other immunosuppressive drugs while you are taking XELJANZ. Taking XELJANZ with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

### **How should I take XELJANZ?**

- Take XELJANZ as your healthcare provider tells you to take it.
- Take XELJANZ 2 times a day with or without food.
- If you take too much XELJANZ, call your healthcare provider or go the nearest hospital emergency room right away.

### **What are possible side effects of XELJANZ?**

#### **XELJANZ may cause serious side effects, including:**

- See “What is the most important information I should know about XELJANZ?”
- **Hepatitis B or C activation infection** in people who carry the virus in their blood. If you are a carrier of the hepatitis B or C virus (viruses that affect the liver), the virus may become active while you use XELJANZ. Your healthcare provider may do blood tests before you start treatment with XELJANZ and while you are using XELJANZ. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B or C infection:

- feel very tired
- skin or eyes look yellow
- little or no appetite
- vomiting
- clay-colored bowel movements
- fevers
- chills
- stomach discomfort
- muscle aches
- dark urine
- skin rash

Common side effects of XELJANZ include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- diarrhea
- nasal congestion, sore throat, and runny nose (nasopharyngitis)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XELJANZ. For more information, ask your healthcare provider or pharmacist.

**Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.**

**You may also report side effects to Pfizer at 1-800-438-1985.**

### **How should I store XELJANZ?**

Store XELJANZ at 68°F to 77°F (room temperature).

Safely throw away medicine that is out of date or no longer needed.

**Keep XELJANZ and all medicines out of the reach of children.**

**General information about the safe and effective use of XELJANZ.**

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XELJANZ for a condition for which it was not prescribed. Do not give XELJANZ to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about XELJANZ. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about XELJANZ that is written for health professionals.

### **What are the ingredients in XELJANZ?**

**Active ingredient:** tofacitinib citrate

**Inactive ingredients:** microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, HPMC 2910/Hypromellose 6cP, titanium dioxide, macrogol/PEG3350, and triacetin.

**This Medication Guide has been approved by the U.S. Food and Drug Administration.**



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/s/  
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11/06/2012