IMPORTANT DRUG WARNING

Pfizer Inc
235 East 42nd Street
New York, NY 10017

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Subject: IMPORTANT DRUG WARNING Modification to BOXED WARNING: Serious Risks Regarding Mortality, Malignancy, Major Adverse Cardiovascular Events, and Thrombosis with Use of XELJANZ/XELJANZ XR/XELJANZ Oral Solution (tofacitinib), and Revision to Rheumatoid Arthritis, Psoriatic Arthritis, Polyarticular Course Juvenile Idiopathic Arthritis Indications

Dear Health Care Provider,

The purpose of this letter is to inform you of important safety information for XELJANZ/XELJANZ XR/XELJANZ Oral Solution (tofacitinib), which is approved for adults with moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis (PsA), moderately to severely active ulcerative colitis (UC), and polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older. (Please see complete Indications, including Limitations of Use, in the full prescribing information.)

Based on final results from the completed post-marketing required safety clinical trial ORAL Surveillance (A3921133; NCT02092467), the Prescribing Information and Medication Guide for XELJANZ/XELJANZ XR/XELJANZ Oral Solution have been revised to inform increased all-cause mortality, malignancies, MACE, and thrombosis in patients treated with XELJANZ/XELJANZ XR/XELJANZ Oral Solution compared to patients treated with tumor necrosis factor (TNF) blockers, and to inform a revision to the INDICATION AND USAGE in patients with RA, PsA, and pcJIA.

The Prescribing Information has been updated as follows:

- **BOXED WARNING**: MACE was added, and revisions were made to Mortality, Malignancies, and Thrombosis; please see below for **BOXED WARNING**
- Indications and Usage (Section 1): Revisions were made to require patients to have inadequate response or intolerance to one or more TNF blockers for RA, PsA and pcJIA
- Warnings and Precautions (Section 5): MACE was added (Section 5.4), and revisions were made to Mortality (Section 5.2), Malignancy and Lymphoproliferative Disorders (Section 5.3), and Thrombosis (Section 5.5)
- Clinical Studies (Section 14): Safety Study was added (Section 14.5) on ORAL Surveillance with results from each of the co-primary endpoints and other endpoints

Serious Risks with Use of XELJANZ/XELJANZ XR/XELJANZ Oral Solution

These include Serious Infections, Mortality, Malignancy, Major Adverse Cardiovascular Events, and Thrombosis.

BOXED WARNING has been updated to include Major Adverse Cardiovascular Events and revised for Mortality, Malignancies, and Thrombosis, as follows:

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day. A XELJANZ/XELJANZ Oral Solution 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

MALIGNANCIES

Malignancies, including lymphomas and solid tumors, have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. In RA patients, a higher rate of malignancies (excluding NMSC) was observed in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day compared with TNF blockers.

Lymphomas and lung cancers were observed at a higher rate in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day in RA patients compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

MAJOR ADVERSE CARDIOVASCULAR EVENTS

RA patients 50 years of age and older with at least one additional cardiovascular risk factor, treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily, had a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue XELJANZ/XELJANZ XR/XELJANZ Oral Solution in patients that have experienced a myocardial infarction or stroke.

THROMBOSIS

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death. RA patients 50 years of age and older with at least one cardiovascular risk factor treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid XELJANZ/XELJANZ XR/XELJANZ Oral Solution in patients at risk. Discontinue XELJANZ/XELJANZ XR/XELJANZ Oral Solution and promptly evaluate patients with symptoms of thrombosis.

Warnings and Precautions have been similarly updated.

INDICATIONS AND USAGE for RA, PsA, and pcJIA have been revised, to inform that XELJANZ is indicated as follows:

- Rheumatoid Arthritis: XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers. *Limitations of Use:* Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

- Psoriatic Arthritis: XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers. *Limitations of Use:* Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

- Polyarticular Course Juvenile Idiopathic Arthritis: XELJANZ/XELJANZ Oral Solution is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blockers. *Limitations of Use:* Use of XELJANZ/XELJANZ Oral Solution in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Prescriber Action

- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with XELJANZ/XELJANZ XR/XELJANZ Oral Solution, particularly in patients who are current or past smokers, those with other cardiovascular risk factors, those who develop a malignancy while on treatment, and those with a known malignancy other than a successfully treated nonmelanoma skin cancer.

- Reserve XELJANZ/XELJANZ XR/XELJANZ Oral Solution for the treatment of RA, PsA, and pcJIA to patients who have an inadequate response or who are intolerant to one or more TNF blockers. See the revised Indications as stated above.

- Counsel patients about the benefits and risks of XELJANZ/XELJANZ XR/XELJANZ Oral Solution. Encourage patients to read the Medication Guide they receive with each prescription, which explains the safety risks and provides other important information.

- Inform patients that XELJANZ/XELJANZ XR/XELJANZ Oral Solution may increase their risk of certain cancers, and that lymphoma and other cancers have been observed in patients taking XELJANZ. Instruct patients to inform their healthcare provider if they have ever had any type of cancer.

- Inform patients that XELJANZ/XELJANZ XR/XELJANZ Oral Solution may increase their risk of MACE defined as myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue XELJANZ/XELJANZ XR/XELJANZ Oral Solution in patients that have experienced a myocardial infarction or stroke.

- Avoid XELJANZ/XELJANZ XR/XELJANZ Oral Solution in patients that may be at increased risk of thrombosis. Discontinue and promptly evaluate patients with symptoms of thrombosis. Advise patients to stop taking XELJANZ/XELJANZ XR/XELJANZ Oral Solution and to call their healthcare provider right away if they experience any symptoms of thrombosis (sudden shortness of breath, chest pain worsened with breathing, swelling of leg or arm, leg pain or tenderness, red or discolored skin in the affected leg or arm).

Reporting Adverse Events

Healthcare providers and patients are encouraged to report adverse events in patients taking XELJANZ/XELJANZ XR/XELJANZ Oral Solution to Pfizer at 1-800-438-1985. You are also encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

This letter is not intended as a complete description of the benefits and risks of XELJANZ/XELJANZ XR/XELJANZ Oral Solution. The full Prescribing Information and Medication Guide should be consulted for further information. It is available at: http://XeljanzPI.com.

Patient safety is of the utmost importance to Pfizer and the company continually monitors the safety of its medicines. We wanted you to be aware of these updates to the Prescribing Information and Medication Guide so that you can consider them when counseling your patients on the use of XELJANZ/XELJANZ XR/XELJANZ Oral Solution.

If you have any questions or would like additional information, please call Pfizer Medical Information at 1-800-438-1985.

Sincerely,

Tamas Koncz, MD, MSc, PhD
Chief Medical Officer

Inflammation and Immunology
Pfizer Inc.

INDICATIONS AND USAGE

Rheumatoid Arthritis

XELJANZ/XELJANZ XR (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more TNF blockers. Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic disease-modifying antirheumatic drugs (DMARDs) or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Psoriatic Arthritis

XELJANZ/XELJANZ XR (tofacitinib) is indicated for the treatment of adult patients with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to one or more TNF blockers. Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ulcerative Colitis

XELJANZ/XELJANZ XR (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or intolerance to one or more TNF blockers. Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Polyarticular Course Juvenile Idiopathic Arthritis

XELJANZ/XELJANZ Oral Solution (tofacitinib) is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blockers. Limitations of Use: Use of XELJANZ/XELJANZ Oral Solution in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with XELJANZ* are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants, such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ use.**

- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**

- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Avoid use of XELJANZ in patients with an active, serious infection, including localized infections.

In the UC population, XELJANZ 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with XELJANZ 10 mg twice daily.

The risks and benefits of treatment with XELJANZ should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection, or those who have lived or traveled in areas of endemic TB or mycoses. Viral reactivation including herpes virus and hepatitis B reactivation have been reported. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infection.

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular (CV) risk factor comparing XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden CV death, was observed with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day. A XELJANZ 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA. For UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

MALIGNANCIES

Malignancies, including lymphomas and solid tumors, have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. In RA patients, a higher rate of malignancies (excluding NMSC) was observed in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day compared with TNF blockers.

Lymphoma and lung cancers were observed at a higher rate in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day in RA patients compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with XELJANZ, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy while on treatment, and patients who are current or past smokers. A XELJANZ 10 mg twice daily (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

Other malignancies were observed in clinical studies and the postmarketing setting including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer. NMSCs have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. In the UC population, treatment with XELJANZ 10 mg twice daily was associated with greater risk of NMSC.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

RA patients 50 years of age and older with at least one CV risk factor, treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily, had a higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue XELJANZ in patients that have experienced a myocardial infarction or stroke.

Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with XELJANZ, particularly in patients who are current or past smokers and patients with other CV risk factors. Inform patients about the symptoms of serious CV events. A XELJANZ 10 mg twice a day (or a XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

THROMBOSIS

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death. RA patients 50 years of age and older with at least one CV risk factor treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid XELJANZ in patients at risk. Discontinue XELJANZ and promptly evaluate patients with symptoms of thrombosis.

A XELJANZ 10 mg twice daily (or XELJANZ XR 22 mg once daily) dosage is not recommended for the treatment of RA or PsA. In a long-term extension study in UC, five cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one death in a patient with advanced cancer. For UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal perforations have been reported in XELJANZ clinical trials, although the role of JAK inhibition is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). There was no discernible difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids. XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs).

HYPERSENSITIVITY

Angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients receiving XELJANZ and some events were serious. If a serious hypersensitivity reaction occurs, promptly discontinue tofacitinib while evaluating the potential cause or causes of the reaction.

LABORATORY ABNORMALITIES

Lymphocyte Abnormalities: Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts. Avoid initiation of XELJANZ treatment in patients with a count less than 500 cells/mm^3. In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3, treatment with XELJANZ is not recommended. Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Monitor lymphocyte counts at baseline and every 3 months thereafter.

Neutropenia: Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo. Avoid initiation of XELJANZ treatment in patients with an ANC less than 1000 cells/mm^3. For patients who develop a persistent ANC of 500-1000 cells/mm^3, interrupt XELJANZ dosing until ANC is greater than or equal to 1000 cells/mm^3. In patients who develop an ANC less than 500 cells/mm^3, treatment with XELJANZ is not recommended. Monitor neutrophil counts at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Anemia: Avoid initiation of XELJANZ treatment in patients with a hemoglobin level less than 9 g/dL. Treatment with XELJANZ should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment. Monitor hemoglobin at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Liver Enzyme Elevations: Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy. If drug-induced liver injury is suspected, the administration of XELJANZ should be interrupted until this diagnosis has been excluded. Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury.

Lipid Elevations: Treatment with XELJANZ was associated with dose-dependent increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. There were no clinically relevant changes in LDL/HDL cholesterol ratios. Manage patients with hyperlipidemia according to clinical guidelines. Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of XELJANZ therapy.

VACCINATIONS

Avoid use of live vaccines concurrently with XELJANZ. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents. Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ therapy.

PATIENTS WITH GASTROINTESTINAL NARROWING

Caution should be used when administering XELJANZ XR to patients with pre-existing severe gastrointestinal narrowing. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable extended-release formulation.

HEPATIC and RENAL IMPAIRMENT

Use of XELJANZ in patients with severe hepatic impairment is not recommended. For patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily, reduce to XELJANZ 5 mg once daily. For UC patients with moderate hepatic impairment or with moderate or severe renal impairment taking XELJANZ 10 mg twice daily, reduce to XELJANZ 5 mg twice daily. If taking XELJANZ XR 22 mg once daily, reduce to XELJANZ XR 11 mg once daily.

ADVERSE REACTIONS

The most common serious adverse reactions were serious infections. The most commonly reported adverse reactions during the first 3 months in controlled clinical trials in patients with RA with XELJANZ 5 mg twice daily and placebo, respectively, (occurring in greater than or equal to 2% of patients treated with XELJANZ with or without DMARDs) were upper respiratory tract infection, nasopharyngitis, diarrhea, headache, and hypertension. The safety profile observed in patients with active PsA treated with XELJANZ was consistent with the safety profile observed in RA patients.

Adverse reactions reported in ≥5% of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and ≥1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials for UC were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

USE IN PREGNANCY

Available data with XELJANZ use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy. In animal studies, tofacitinib at 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings. The relevance of these findings to women of childbearing potential is uncertain. Consider pregnancy planning and prevention for females of reproductive potential.

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*Unless otherwise stated, "XELJANZ" in the Important Safety Information refers to XELJANZ, XELJANZ XR, and XELJANZ Oral Solution.