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

November 10, 2014

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® (tofacitinib)

Dear Healthcare Provider,

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.

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 (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 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.
- 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 website (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

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 website (www.XELJANZREMS.com).

Sincerely,

Freda C. Lewis-Hall, MD
Executive Vice President and Chief Medical Officer
Pfizer Inc

Enclosure