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

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Subject: Communication of approval and important safety information for XELJANZ® (tofacitinib) for adult patients with moderately to severely active ulcerative colitis

Dear Healthcare Provider,

XELJANZ® (tofacitinib citrate), an inhibitor of Janus kinases (JAKs), is now approved by the Food and Drug Administration (FDA) for adult patients with moderately to severely active ulcerative colitis (UC).

The purpose of this letter is to inform you of the dosing for this new indication, as well as important safety information for XELJANZ®.

It is important to note that for UC, the recommended dose of XELJANZ® is 10 mg twice daily for at least 8 weeks; then 5 or 10 mg twice daily. Discontinue after 16 weeks of 10 mg twice daily, if adequate therapeutic benefit is not achieved. Use the lowest effective dose to maintain response.

Please see the accompanying Prescribing Information at www.xeljanz.com

XELJANZ® is currently approved for rheumatoid arthritis (RA), psoriatic arthritis PsA, and now for UC. XELJANZ® XR is approved only for use in RA and PsA and is not approved for use in UC. The 10 mg twice daily dose is approved only for use in UC, not in RA or PsA. The safety and efficacy of treatment with XELJANZ® has not been established in pediatric patients.

Limitations of Use

XELJANZ® is not recommended to be used in combination with biologic therapies for ulcerative colitis or with potent immunosuppressants such as azathioprine and cyclosporine.

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.

Patient Counseling

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

Serious Risks Associated with XELJANZ® (tofacitinib)

Dose-dependent adverse reactions seen in patients treated with 10 mg twice daily, in comparison to the 5 mg twice daily, include the following: herpes zoster infections, serious infections, and non-melanoma skin cancer (NMSC). Additional information on specific risks follows:

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, including herpes zoster, 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.

- Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with XELJANZ®. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ®.
- In the UC population, XELJANZ® treatment with 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily, including serious herpes zoster infections. Additionally, opportunistic herpes zoster infections including herpes zoster meningoencephalitis and ophthalmologic herpes zoster infections were seen in patients who were treated with XELJANZ® 10 mg twice daily.
- Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ®. 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.

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 NMSC or when considering continuing XELJANZ® in patients who develop a malignancy. Lymphoma and other malignancies have been reported in patients treated with XELJANZ®.
- During the UC controlled clinical studies (8-week induction and 52-week maintenance studies), which included 1220 patients, 0 cases of solid cancer or lymphoma were observed in XELJANZ® treated patients. In the long-term extension study, malignancies (including solid cancers and lymphomas) were observed more often in patients treated with XELJANZ® 10 mg twice daily.
- In a Phase 2B, controlled dose-ranging study in de-novo renal transplant patients, patients were randomized to XELJANZ® or to cyclosporine. XELJANZ®-treated patients received 15 mg BID for either 3 months or 6 months followed by dose decrease to 10 mg BID, which was continued through 12 months post-transplant. All subjects received induction therapy with basiliximab and high dose corticosteroids followed by concomitant maintenance therapy with mycophenolic acid (MPA) products and steroids. In the subsequent long-term extension study, the XELJANZ® dose was reduced to 5 mg BID by 18 months post-transplant while continuing MPA products with or without steroids. 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.
- In the UC population, treatment with XELJANZ® 10 mg twice daily was associated with greater risk of NMSC. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Use in Specific Populations

- 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. Advise females to inform their prescriber of a known or suspected pregnancy. Inform patients that Pfizer has a registry for pregnant women who have taken XELJANZ® during pregnancy. Advise patients to contact the registry at 1-877-311-8972 to enroll.

- Lactation: There are no data on the presence of tofacitinib in human milk, the effects on a breastfed infant, or the effects on milk production. Tofacitinib is present in the milk of lactating rats *(see Data)*. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adults treated with XELJANZ®, such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 18 hours after the last dose of XELJANZ® (approximately 6 elimination half-lives).
- Please refer to the product labeling for additional information regarding: Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Use in Diabetics, Renal Impairment, and Hepatic Impairment

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.
- In the controlled clinical trials, there were dose- dependent increases in LDL cholesterol, HDL cholesterol, total cholesterol and triglyceride levels seen in patients treated with XELJANZ®. There were no clinically relevant changes in LDL/HDL cholesterol ratios.

Medication Guide

Advise the patient to read the FDA-approved patient labeling (Medication Guide). The Medication Guide contains information that can be used to facilitate discussions about the known and potential risks of therapy.

Reporting Adverse Events

To report suspected adverse reactions 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

For more information, please call Pfizer Medical Information at 1-800-438-1985

Sincerely,

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Pfizer Inc.

Enclosure