



# Pfizer Announces Modification To Ongoing Tofacitinib FDA Post-Marketing Requirement Study In Patients With Rheumatoid Arthritis

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NEW YORK, N.Y., February 19, 2019 – Pfizer Inc. (NYSE:PFE) announced today the company has taken steps to transition rheumatoid arthritis study patients who were on tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily in the Food and Drug Administration (FDA) post-marketing requirement study A3921133. This action is being taken as the result of notification from the tofacitinib Rheumatology Data Safety Monitoring Board (DSMB) of a safety signal regarding the tofacitinib 10 mg twice daily treatment arm. The 5 mg twice daily dose is the FDA approved dose for adult patients with moderate to severe rheumatoid arthritis.

Study A3921133 is an ongoing, open-label, endpoint-driven study to evaluate the safety of tofacitinib at two doses versus a tumor necrosis factor inhibitor (TNFi) control group. This study was designed to assess the risk of cardiovascular (CV) events and therefore in contrast to previous tofacitinib studies, patients were required to be at least 50 years of age and have at least one CV risk factor to be eligible for participation in this study. All patients entered the study on stable doses of background methotrexate.

Pfizer uses external, independent, blinded endpoint adjudication committees to review safety events in a standardized manner and an independent, external data safety monitoring board (DSMB) to monitor Pfizer uses external, independent, blinded endpoint adjudication committees to review safety events in a standardized manner and an independent, external data safety monitoring board (DSMB) to monitor

The study is fully enrolled and will continue through to completion. The DSMB stated it firmly believes that the risk-benefit profile of tofacitinib 5 mg twice daily in comparison to the TNFi group remains appropriately balanced in this study. We will work with the FDA and other regulatory agencies to review the full results upon completion of this study. Furthermore, the DSMB stated that other, ongoing studies of tofacitinib in RA, juvenile idiopathic arthritis, psoriatic arthritis, and ankylosing spondylitis should continue unchanged.

Patient safety is of the utmost importance to Pfizer and the company continually monitors the safety of its medicines. Similar results to study A3921133 have not been identified in Pfizer analyses of other tofacitinib RA clinical trials or routine monitoring of post-marketing safety data, including our statistical analyses of the FDA Adverse Event Reporting System database.

Xeljanz (tofacitinib) is FDA approved for the treatment of adults with moderate to severe rheumatoid arthritis, active psoriatic arthritis, and moderate to severe ulcerative colitis. Patients and physicians with questions should contact Pfizer medical information at <https://www.pfizer.com/products/product-contact-information>.

**ABOUT XELJANZ (tofacitinib)** XELJANZ is the first and only Janus kinase (JAK) inhibitor approved by the FDA for adult patients with moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis (PsA) and moderately to severely active ulcerative colitis (UC). As the developer of tofacitinib, Pfizer is committed to advancing the science of JAK inhibition and enhancing understanding of tofacitinib through robust clinical development programs in the treatment of immune-mediated inflammatory conditions. Please see full Prescribing Information, including BOXED WARNING for XELJANZ/XELJANZ XR available at: <http://labeling.pfizer.com/ShowLabeling.aspx?id=959>.

## **INDICATIONS Rheumatoid Arthritis**

XELJANZ/XELJANZ XR (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis 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). 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.

## **Psoriatic Arthritis**

XELJANZ/XELJANZ XR (tofacitinib) is indicated for the treatment of adult patients with

active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs). 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 (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). Limitations of Use: Use of XELJANZ in combination with biologic therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

**IMPORTANT SAFETY INFORMATION SERIOUS INFECTIONS Patients treated with XELJANZ/XELJANZ XR 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/XELJANZ XR 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/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR 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/XELJANZ XR in patients with an active, serious infection, including localized infections, or with chronic or recurrent infection.

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/XELJANZ XR 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/XELJANZ XR, 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.

**MALIGNANCIES Lymphoma and other malignancies have been observed in patients treated with XELJANZ. 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 risks and benefits of XELJANZ/XELJANZ XR 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/XELJANZ XR in patients who develop a malignancy.

Malignancies (including solid cancers and lymphomas) were observed more often in patients treated with XELJANZ 10 mg twice daily dosing in the UC long-term extension study.

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. 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.

**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 discernable 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/XELJANZ XR 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/XELJANZ XR 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/XELJANZ XR treatment in patients with a count less than 500 cells/mm<sup>3</sup>. In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm<sup>3</sup>, treatment with XELJANZ/XELJANZ XR 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<sup>3</sup>) compared to placebo. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with an ANC less than 1000 cells/mm<sup>3</sup>. For patients who develop a persistent ANC of 500-1000 cells/mm<sup>3</sup>, interrupt XELJANZ/XELJANZ XR dosing until ANC is greater than or equal to 1000 cells/mm<sup>3</sup>. In patients who develop an ANC less than 500 cells/mm<sup>3</sup>, treatment with XELJANZ/XELJANZ XR 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/XELJANZ XR treatment in patients with a hemoglobin level less than 9 g/dL. Treatment with XELJANZ/XELJANZ XR 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/XELJANZ XR 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/XELJANZ XR therapy.

**VACCINATIONS** Avoid use of live vaccines concurrently with XELJANZ/XELJANZ XR. 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/XELJANZ XR 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 nondeformable extended release formulation.

**HEPATIC and RENAL IMPAIRMENT** Use of XELJANZ/XELJANZ XR 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, 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.

**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 rheumatoid arthritis (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 psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in RA patients.

Adverse reactions reported in  $\geq 5\%$  of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and  $\geq 1\%$  greater than reported in patients receiving placebo in either the induction or maintenance clinical trials for ulcerative colitis 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/XELJANZ XR 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.

**Working together for a healthier world** ® At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products. Our global portfolio includes medicines and vaccines as well as many of the world's best-known consumer health care products. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at [www.pfizer.com](http://www.pfizer.com). In addition, to learn more, please visit us on [www.pfizer.com](http://www.pfizer.com) and follow us on Twitter at @Pfizer and @Pfizer\_News, LinkedIn, YouTube and like us on Facebook at [Facebook.com/Pfizer](https://www.facebook.com/Pfizer).

DISCLOSURE NOTICE: The information contained in this release is as of February 19, 2019. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments. This release contains forward-looking information about XELJANZ (tofacitinib) that involves

substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; risks associated with interim data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; uncertainties regarding the commercial impact of this most recent DSMB analysis of this ongoing clinical trial A3921133; whether and when any applications that may be pending or filed for any potential indications for XELJANZ in any jurisdictions may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy, and, if approved, whether they will be commercially successful; decisions by regulatory authorities impacting labeling, safety, manufacturing processes and/or other matters that could affect the availability or commercial potential of XELJANZ; and competitive developments. A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2017 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at [www.sec.gov](http://www.sec.gov) and [www.pfizer.com](http://www.pfizer.com). # # # # # Media Contact: Neha Wadhwa M: +1 212-733-2835 E: [Neha.Wadhwa@pfizer.com](mailto:Neha.Wadhwa@pfizer.com) Investor Contact: Charles Triano O: +1 212-733-3901 E: [Charles.E.Triano@pfizer.com](mailto:Charles.E.Triano@pfizer.com)