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

IMPORTANT DRUG WARNING

February 28, 2019

Subject: Communication of new safety information for XELJANZ® (tofacitinib)

Dear Healthcare Provider,

On February 19, Pfizer announced it has taken steps to transition rheumatoid arthritis (RA) 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 was taken as the result of notification from the tofacitinib Rheumatology Data Safety Monitoring Board (DSMB) of an increase in the frequency of pulmonary embolism and overall mortality in patients in the trial who were taking the 10 mg twice daily dose of tofacitinib. This RA 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. All patients entered the study on stable doses of background methotrexate. Similar results to RA 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 (FAERS) database. The 10 mg twice daily dose of tofacitinib is not approved for RA.

The 10 mg twice daily dose is approved in the United States only in the dosing regimen for adult patients with moderate to severe ulcerative colitis (UC). As indicated in the U.S. Prescribing Information (USPI), in a UC long term extension study, four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one fatality in a patient with advanced cancer.

On February 25, the FDA issued an announcement and a Drug Safety Communication regarding the study. In its announcement, FDA noted:

> The FDA is actively examining the data from the trial and working directly with Pfizer to better understand the safety signal, its impact on patients, and how tofacitinib should be used. The agency will take appropriate action, as warranted, to ensure patients enrolled in this and other trials are protected and that health care professionals and clinical trial researchers understand the risks associated with this use. We are communicating now, given the serious nature of the safety issue, to ensure that patients taking tofacitinib are aware that the FDA still believes the benefits of taking tofacitinib for its approved uses continue to outweigh the risks. Patients taking tofacitinib for its approved uses should continue to take their medication as directed by their health care professional. Today's safety alert underscores the importance of monitoring and addressing safety questions that arise in the post-market setting.

In its Drug Safety Communication, FDA noted:

> Health care professionals should follow the recommendations in the tofacitinib prescribing information for the specific condition they are treating. Monitor patients for the signs and symptoms of pulmonary embolism and advise them to seek medical attention immediately if they experience them.

FDA's announcement and Drug Safety Communication are attached for your reference.

Patient safety is of the utmost importance to Pfizer and the company continually monitors the safety of its medicines. As such we continue to work with FDA on this safety signal. We wanted you to be aware of these emerging data from this RA study and its 10 mg twice daily dose group so that you can consider this when counseling your patients on the use of Xeljanz. For more information, please see the Xeljanz Prescribing Information at www.xeljanz.com or call Pfizer Medical Information at 1-800-438-1985.

Sincerely,

Tamas Koncz, MD, MSc, PhD
Chief Medical Officer, Inflammation and Immunology
Pfizer Inc.

Enclosures

INDICATIONS and RECOMMENDED DOSING

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.

Recommended Dosing for RA: Xeljanz 5mg twice daily or Xeljanz XR 11 mg once daily. See dosing adjustments in full Prescribing Information at www.xeljanz.com. Xeljanz 10 mg twice daily is not an approved dose for RA.

Psoriatic Arthritis (PsA)

- 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.

Recommended Dosing for PsA: Xeljanz 5mg twice daily or Xeljanz XR 11 mg once daily in combination with non biologic disease modifying antirheumatic drugs (DMARDs) in psoriatic arthritis. See dosing adjustments in full Prescribing Information at www.xeljanz.com. Xeljanz 10mg twice daily is not an approved dose for PsA.

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.

Recommended Dosing for UC: 10 mg twice daily for at least 8 weeks; followed by 5 or 10 mg twice daily, depending on therapeutic response. Use the lowest effective dose to maintain response. Discontinue XELJANZ after 16 weeks of treatment with 10 mg twice daily, if adequate therapeutic benefit is not achieved. See dosing adjustments in full Prescribing Information at www.xeljanz.com. Xeljanz XR 11 mg once daily is not an approved dose for UC.

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 post-marketing 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 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^3. In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3, 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^3) compared to placebo. Avoid initiation of XELJANZ/XELJANZ XR 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/XELJANZ XR 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/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 non-deformable 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 ≥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 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.

NEWS PROVIDED BY
U.S. Food and Drug Administration (https://prn.to/2EkhOA7)
Feb 25, 2019, 16:10 ET

FDA responds to safety signal reported in required postmarketing trial for Xeljanz

SILVER SPRING, Md., Feb. 25, 2019 /PRNewswire/

"Today the FDA is warning about a safety signal that emerged in a required postmarketing trial of the drug Xeljanz (tofacitinib) in patients with rheumatoid arthritis. This particular trial was initiated to further evaluate the safety of tofacitinib at two doses (5 mg twice daily or 10 mg dose twice daily) versus a control group of another treatment, and was specifically designed to assess the risk of cardiovascular events, cancer and opportunistic infections. Data review by the study's Data Safety Monitoring Board identified a safety signal of pulmonary embolism and increased overall mortality in patients in the trial who were taking the 10 mg dose of tofacitinib twice daily. The trial's sponsor Pfizer, at the recommendation of the FDA took immediate action to protect patient safety and transitioned patients in the ongoing trial from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily, which is the FDA-approved dose for adult patients with moderate to severe rheumatoid arthritis," said Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research Director. "The FDA is actively examining the data from the trial and working directly with Pfizer to better understand the safety signal, its impact on patients, and how tofacitinib should be used. The agency will take appropriate action, as warranted, to ensure patients enrolled in this and other trials are protected and that health care professionals and clinical trial researchers understand the risks associated with this use. We are communicating now, given the serious nature of the safety issue, to ensure that patients taking tofacitinib are aware that the FDA still believes the benefits of taking tofacitinib for its approved uses continue to outweigh the risks. Patients taking tofacitinib for its approved uses should continue to take their medication as directed by their health care professional. Today's safety alert underscores the importance of monitoring and addressing safety questions that arise in the postmarket setting."

Today, the FDA released a Drug Safety Communication alerting health care professionals and patients about a safety signal seen in a postmarketing trial in patients with rheumatoid arthritis (RA) who were taking tofacitinib 10 mg twice daily. The FDA required the drug manufacturer, Pfizer, to conduct the trial when it approved tofacitinib in 2012. This ongoing trial is evaluating the safety of tofacitinib at two doses (the approved 5 mg twice daily and a higher dose of 10 mg twice daily) versus a tumor necrosis factor inhibitor (TNFi) control group. Data review by the Data Safety Monitoring Board identified a safety signal of pulmonary embolism and increased overall mortality in the 10 mg twice daily treatment group. Pfizer has transitioned patients in the ongoing trial from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily, which is the FDA-approved dose for adult patients with moderate to severe rheumatoid arthritis. The 10 mg twice daily dose of tofacitinib is not an FDA-approved dose for rheumatoid arthritis but is approved in the dosing regimen for patients with ulcerative colitis. The postmarketing trial was designed to assess the risk of cardiovascular (CV) events, opportunistic infections and malignancy, and 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.

Postmarketing studies play a critical role in the FDA's efforts to ensure the safety of FDA-approved drugs and products. They can allow for further evaluation of potential safety issues or enable a better characterization of risk factors for known concerns. These studies provide vital information about the safety of the FDA approved treatment so the FDA can help ensure that the benefits to the intended patients outweigh the risks. The FDA provides guidance and oversight of companies to ensure the studies are completed safely and in a timely manner. When significant safety issues do arise, the FDA works quickly to prevent further injury or deaths.

Xeljanz is approved for the treatment of certain adults with moderate to severe rheumatoid arthritis, active psoriatic arthritis, and moderate to severe ulcerative colitis. Patients treated with Xeljanz are at increased risk for developing serious infections that may lead to hospitalization or death. The most common serious infections reported with Xeljanz included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis and appendicitis.

Safety Announcement (https://bit.ly/2tJFoRY)

Safety trial finds risk of blood clots in the lungs and death with higher dose of tofacitinib (Xeljanz, Xeljanz XR) in rheumatoid arthritis patients; FDA to investigate

[2-25-2019] The U.S. Food and Drug Administration (FDA) is alerting the public that a safety clinical trial found an increased risk of blood clots in the lungs and death when a 10 mg twice daily dose of tofacitinib (Xeljanz, Xeljanz XR) was used in patients with rheumatoid arthritis (RA). FDA has not approved this 10 mg twice daily dose for RA; this dose is only approved in the dosing regimen for patients with ulcerative colitis.

In this ongoing safety trial required by FDA when it approved tofacitinib for RA, the drug manufacturer, Pfizer, is transitioning patients who were on the high 10 mg twice daily dose to the lower, currently approved dose of 5 mg twice daily. This trial will continue and is expected to be completed by the end of 2019. We are working with the manufacturer to evaluate other currently available safety information for tofacitinib and will update the public with any new information based on our ongoing review.

Health care professionals should follow the recommendations in the tofacitinib prescribing information (https://bit.ly/2EIFFiO) for the specific condition they are treating. Monitor patients for the signs and symptoms of pulmonary embolism, and advise them to seek medical attention immediately if they experience them.

Patients should not stop or change your dose of tofacitinib without first talking to your health care professional, as doing so may worsen your condition. Patients taking tofacitinib should seek medical attention immediately if you experience symptoms of a blood clot in your lungs or other unusual symptoms such as:

- Sudden shortness of breath or difficulty breathing
- Chest pain or pain in your back
- Coughing up blood
- Excessive sweating
- Clammy or bluish colored skin

Tofacitinib works by decreasing the activity of the immune system. It was first approved in 2012 to treat adult patients with RA who did not respond well to the medicine methotrexate. In RA, the body attacks its own joints, causing pain, swelling, and loss of function. In 2017, we approved the medicine to treat patients with a second condition, psoriatic arthritis, who did not respond well to methotrexate or other similar medicines called nonbiologic disease-modifying antirheumatic drugs (DMARDs). Psoriatic arthritis is a condition that also causes joint pain and swelling. In 2018, we approved tofacitinib to treat a condition called ulcerative colitis, which is a chronic, inflammatory bowel disease affecting the colon.

When FDA first approved tofacitinib, we required a clinical trial among patients with RA to evaluate the risk of heart-related events, cancer, and opportunistic infections with the medicine at two doses (10 mg twice daily and 5 mg twice daily) in combination with methotrexate in comparison to another drug called a tumor necrosis factor (TNF) inhibitor. RA patients in the trial were required to be at least 50 years old and have at least one cardiovascular risk factor. During the most recent analysis of the trial, an external data safety monitoring committee found an increased occurrence of blood clots in the lungs and death in patients treated with tofacitinib 10 mg twice daily compared to patients treated with tofacitinib 5 mg twice daily or a TNF inhibitor.

To help FDA track safety issues with medicines, we urge health care professionals and patients to report side effects involving tofacitinib or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

Contact FDA

For More Info 855-543-DRUG (3784) and press 4 druginfo@fda.hhs.gov.

Report a Serious Problem to MedWatch Complete and submit the report Online (https://bit.ly/1KGErtT). Download form (https://bit.ly/2mlhQ20) or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form or submit by fax to 1-800-FDA-0178.