



U.S. Food And Drug Administration Extends Action Date For XELJANZ® (Tofacitinib) Supplemental New Drug Application In Ulcerative Colitis By Three Months

Tuesday, December 12, 2017 - 11:52am

Pfizer Inc. (NYSE: PFE) announced today that the U.S. Food and Drug Administration (FDA) has extended the action date by three months for the supplemental New Drug Application (sNDA) for XELJANZ® (tofacitinib), an oral treatment under investigation for adult patients with moderately to severely active ulcerative colitis (UC).

The FDA determined that additional review time was necessary due to information recently submitted by Pfizer and as such constitutes a major amendment. The FDA has provided an anticipated Prescription Drug User Fee Act (PDUFA) date in June 2018.

If approved by the FDA, tofacitinib would be the first oral Janus kinase (JAK) inhibitor to be a therapeutic option for people living with moderately to severely active UC.

About Tofacitinib

Tofacitinib citrate is a Janus kinase (JAK) inhibitor. Applications for tofacitinib for the treatment of moderately to severely active UC are currently under review by the U.S. FDA and the European Medicines Agency (EMA). It is not currently approved for the treatment of UC.

As the developer of tofacitinib, Pfizer is a leader in JAK science and is committed to enhancing understanding of tofacitinib through robust clinical development programs in

the treatment of immune-mediated inflammatory conditions.

Please see full Prescribing Information for XELJANZ/XELJANZ XR available at: <http://labeling.pfizer.com/showlabeling.aspx?id=959>

INDICATION

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.

IMPORTANT SAFETY INFORMATION

BOXED WARNING: SERIOUS INFECTIONS AND MALIGNANCY

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, and other infections due to opportunistic pathogens.

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.

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.

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.

WARNINGS AND PRECAUTIONS

SERIOUS INFECTIONS

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. Consider the risks and benefits of treatment before initiating XELJANZ/XELJANZ XR in patients:

with chronic or recurrent infection; who have been exposed to tuberculosis (TB); with a history of a serious or an opportunistic infection; who have lived or traveled in areas of endemic TB or mycoses; or with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR. XELJANZ/XELJANZ XR should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis.

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.

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.

Tuberculosis

Evaluate and test patients for latent or active infection prior to and per applicable guidelines during administration of XELJANZ/XELJANZ XR. Consider anti-TB therapy prior

to administration of XELJANZ/XELJANZ XR in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection. Treat patients with latent TB with standard therapy before administering XELJANZ/XELJANZ XR.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), was observed in clinical studies with XELJANZ. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ/XELJANZ XR. The risk of herpes zoster is increased in patients treated with XELJANZ/XELJANZ XR and appears to be higher in patients treated with XELJANZ in Japan and Korea.

MALIGNANCY and LYMPHOPROLIFERATIVE DISORDERS

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.

In the 7 controlled rheumatoid arthritis clinical studies, 11 solid cancers and 1 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 trials 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.

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.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

GASTROINTESTINAL PERFORATIONS

Gastrointestinal perforations have been reported in XELJANZ rheumatoid arthritis clinical trials, although the role of JAK inhibition is not known. 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).

LABORATORY ABNORMALITIES

Lymphocyte Abnormalities

Treatment with XELJANZ was associated with initial lymphocytosis at 1 month of exposure followed by a gradual decrease in mean lymphocyte counts of approximately 10% during 12 months of therapy. Counts less than 500 cells/mm³ were associated with an increased incidence of treated and serious infections. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a count less than 500 cells/mm³. In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm³, treatment with XELJANZ/XELJANZ XR is not recommended. 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/mm³) compared to placebo. Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with an ANC less than 1000 cells/mm³. For patients who develop a persistent ANC of 500-1000 cells/mm³, interrupt XELJANZ/XELJANZ XR dosing until ANC is greater than or equal to 1000 cells/mm³. In patients who develop an ANC less than 500 cells/mm³, 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.

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. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded.

Lipid Elevations

Treatment with XELJANZ was associated with 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.

Assess lipid parameters approximately 4-8 weeks following initiation of XELJANZ/XELJANZ XR therapy, and manage patients according to clinical guidelines for the management of hyperlipidemia.

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. A varicella virus-naïve patient experienced dissemination of the vaccine strain of varicella zoster virus 16 days after vaccination with live attenuated virus vaccine which was 2 days after 5 mg twice daily treatment with tofacitinib. The patient recovered after discontinuation of tofacitinib and treatment with antiviral medication. Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ/XELJANZ XR therapy.

GENERAL

Specific to XELJANZ XR

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. The recommended dose in patients with moderate hepatic impairment or with moderate or severe renal impairment is XELJANZ 5 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 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 infections (4.5%, 3.3%), headache (4.3%, 2.1%), diarrhea (4.0%, 2.3%), and nasopharyngitis (3.8%, 2.8%).

USE IN PREGNANCY

There are no adequate and well-controlled studies in pregnant women and the estimated background risks of major birth defects and miscarriage for the indicated population is unknown. Based on animal studies, tofacitinib has the potential to affect a developing fetus. Women of reproductive potential should be advised to use effective contraception.

Pfizer Inc.: 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. In addition, to learn more, please visit us on 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 December 12, 2017. 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) and a potential new indication for the treatment of adult patients with moderately to severely active ulcerative colitis (the “potential indication”), including their potential benefits, 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, without limitation, the ability to meet anticipated trial commencement and completion dates and regulatory submission dates, as well as the possibility of unfavorable clinical trial results, including unfavorable new clinical data and additional analyses of existing clinical data; uncertainties regarding the commercial success of XELJANZ and XELJANZ XR; the risk that clinical trial data are subject to differing interpretations, and, even when we view data as sufficient to support the safety and/or effectiveness of a product candidate, regulatory authorities may not share our views and may require additional data or may deny approval altogether; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; whether and when any other applications for the potential indication or any other potential indications for XELJANZ or XELJANZ XR may be filed with regulatory authorities in any jurisdictions; whether and when the FDA and EMA may approve the applications for XELJANZ for the potential indication and whether and when regulatory authorities in any jurisdictions may approve any other applications that may be filed or pending for XELJANZ or XELJANZ XR, which will depend on the assessment by such regulatory authorities of the benefit-risk profile suggested by the totality of the efficacy and safety information submitted; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of XELJANZ and XELJANZ XR, including the potential indication for 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, 2016 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 and www.pfizer.com.

Media: Neha Wadhwa M: +1 212-733-2835 Neha.Wadhwa@pfizer.com or Investors: Chuck Triano O: +1 212-733-3901 Charles.E.Triano@pfizer.com