



# XELJANZ® (tofacitinib citrate) Receives Marketing Authorisation in the European Union for Active Psoriatic Arthritis

Thursday, June 28, 2018 - 09:49am

Pfizer Inc. (NYSE:PFE) announced today that the European Commission (EC) has approved XELJANZ® (tofacitinib citrate) 5 mg twice daily (BID) in combination with methotrexate (MTX) for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.<sup>1</sup> XELJANZ is the first and only oral Janus kinase (JAK) inhibitor to be approved in the European Union (EU) for the treatment of adults with active PsA. In 2017, XELJANZ in combination with MTX was approved in the EU for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs.<sup>2</sup>

“People living with psoriatic arthritis may experience a variety of symptoms, making the condition particularly difficult to diagnose and treat,” said Angela Lukin, Regional President, Inflammation and Immunology, Pfizer. “We are proud that we are now able to offer XELJANZ as an option to adult patients living with active psoriatic arthritis in the European Union.”

The EC approval was based on a submission package that included data from the Phase 3 Oral Psoriatic Arthritis Trials (OPAL) clinical development program in PsA, which consisted of two pivotal studies, OPAL Broaden and OPAL Beyond, as well as available data from an ongoing long-term extension trial, OPAL Balance.<sup>3,4,5</sup>

“Psoriatic arthritis, a chronic inflammatory condition which affects between 1.5 and 3 million people in Europe, causes joint pain and swelling that can eventually lead to

permanent joint damage if not diagnosed and treated sufficiently early on,” said Frank Behrens, Rheumatology at Goethe University and Fraunhofer IME-Translational Medicine & Pharmacology, Frankfurt, Germany. “This approval for XELJANZ is an important milestone for the psoriatic arthritis community, who are in need of an additional oral treatment option to help manage their condition.”

### About Psoriatic Arthritis

Psoriatic arthritis (PsA) is a chronic, autoimmune, inflammatory disease that may include manifestations in peripheral joints, tendons, ligaments or skin.<sup>6</sup> PsA may include a variety of symptoms such as joint pain and stiffness, swollen toes and/or fingers and reduced range of motion.<sup>6,7,8</sup>

### About XELJANZ® (tofacitinib citrate)

XELJANZ® (tofacitinib citrate) is the first and only Janus kinase (JAK) inhibitor approved by the FDA for three indications in adults: moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis (PsA) and moderately to severely active ulcerative colitis (UC). XELJANZ is now approved in more than 80 countries for the treatment of adult patients with moderate to severe RA, with additional applications pending globally for all three respective indications.

As the developer of XELJANZ, Pfizer is committed to advancing JAK science and enhancing understanding of XELJANZ through robust clinical development programs in the treatment of immune-mediated inflammatory conditions.

## INDICATIONS AND IMPORTANT XELJANZ® (tofacitinib) SAFETY INFORMATION FROM THE U.S. PRESCRIBING INFORMATION

### 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.

## 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. 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. NMSC 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).

## 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 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  $\geq 5\%$  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.

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

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.

DISCLOSURE NOTICE: The information contained in this release is as of June 28, 2018. 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 and a new indication in the EU for the treatment of adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy, 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, uncertainties regarding the commercial success of XELJANZ and XELJANZ XR, including for the new indication for XELJANZ; the uncertainties inherent in research and development, including the ability to meet anticipated clinical 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; 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 applications for the new indication or any other potential indications for XELJANZ or XELJANZ XR may be filed with regulatory authorities in any additional jurisdictions; whether and when regulatory authorities in any other jurisdictions may approve any applications that may be pending or filed for the new indication or for any other indications 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 and, if approved, whether they will be commercially successful; decisions by regulatory authorities regarding labeling and other matters that could affect the availability or commercial potential of XELJANZ and XELJANZ XR, including the new 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, 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).



---

1 Pfizer. Data on File. European Commission Approval Letter.

2 XELJANZ Summary of Product Characteristics. Available at:  
<https://www.medicines.org.uk/emc/product/2500/smpc>. Accessed June 28, 2018

3 Mease P, Hall S, FitzGerald O, et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. *New England Journal of Medicine*. 2017;377(16):1537-1550.

4 Gladman D, Rigby W, Azevedo V, et al. Tofacitinib in Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. *New England Journal of Medicine*. 2017;377(16):1525-1536.

5 Nash P, Coates LC, Kivitz AJ, Mease PJ, et al. Safety and Efficacy of Tofacitinib, an Oral Janus Kinase Inhibitor, in Patients with Active Psoriatic Arthritis: Interim Data from OPAL Balance, an Open Label, Long-Term Extension Study [ACR 2017. Abstract #64778]

6 Strauss, EJ. Orthopedic Manifestations and Management of Psoriatic Arthritis. *American Journal of Orthopedics*. 2008;37(3):138-47.

7 National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) National Institutes of Health. Psoriatic Arthritis Overview. <https://www.niams.nih.gov/health-topics/psoriatic-arthritis>. Accessed June 28, 2018.

8 Arthritis Foundation. Psoriatic Arthritis Symptoms. <http://www.arthritis.org/about-arthritis/types/psoriatic-arthritis/symptoms.php>. Accessed June 28, 2018.

Pfizer Inc. Media: Neha Wadhwa, 212-733-2835 [Neha.Wadhwa@pfizer.com](mailto:Neha.Wadhwa@pfizer.com) or Pfizer Europe Media: Dervila Keane, +353 86 2110834 [Dervila.M.Keane@pfizer.com](mailto:Dervila.M.Keane@pfizer.com) or Investor: Chuck Triano, 212-733-3901 [Charles.E.Triano@pfizer.com](mailto:Charles.E.Triano@pfizer.com)