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Pfizer Announces FDA Approval of XELJANZ® (tofacitinib) and XELJANZ® XR for the Treatment of Active Psoriatic Arthritis

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XELJANZ/XELJANZ XR, the First Oral JAK Inhibitor in the U.S. for Adults with Moderate to Severe Rheumatoid Arthritis, is now Approved for Adults with Active Psoriatic Arthritis

Pfizer Inc. (NYSE:PFE) announced today that the United States Food and Drug Administration (FDA) has approved XELJANZ® 5 mg twice daily (BID) and XELJANZ® XR (tofacitinib) extended release 11 mg once daily (QD) for the treatment of adult patients with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs). XELJANZ/XELJANZ XR is the first and only Janus kinase (JAK) inhibitor approved by the FDA for both moderate to severe rheumatoid arthritis (RA) and active PsA.

“Psoriatic arthritis is a complex and progressive disease with an unpredictable course,” said Angela Hwang, Global President, Inflammation and Immunology, Pfizer. “The approval of XELJANZ is an important step forward for patients seeking new treatments and is a testament to Pfizer’s unwavering commitment to advancing patient care.”

The recommended dose of XELJANZ/XELJANZ XR is in combination with nonbiologic DMARDs, and use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

The FDA approval of XELJANZ for the treatment of adult patients with active PsA was based on data from the Phase 3 **O**ral **P**soriatic **A**rthritis Tria**l** (OPAL) clinical development program, 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. The findings from OPAL Broaden and OPAL Beyond were published in October 2017 in the *New England Journal of Medicine*.

Both pivotal studies met their two primary efficacy endpoints, demonstrating statistically significant improvements in American College of Rheumatology 20 (ACR20) response and change from baseline in the Health Assessment Questionnaire–Disability Index (HAQ-DI) score at three months in patients receiving XELJANZ 5 mg BID treatment in combination with a nonbiologic DMARD, compared to those treated with placebo. In OPAL Broaden, 50% of patients taking XELJANZ 5 mg BID achieved an ACR20 response, compared to 33% of patients taking placebo (p?0.05), at three months. In OPAL Beyond, 50% of patients achieved an ACR20 response with XELJANZ 5 mg BID, compared to 24% of patients taking placebo (p?0.05), at three months. In both studies, statistically significant improvements in ACR20 response was also seen with XELJANZ 5 mg BID compared to placebo at week 2, a secondary endpoint and the first post-baseline

assessment (OPAL Broaden: 22% and 6% [p=0.0003], respectively; OPAL Beyond: 27% and 13% [p=0.0046], respectively).

“As a practicing rheumatologist, I’ve seen the significant physical impact psoriatic arthritis has on people living with the disease, and many patients are looking for additional therapeutic options,” said Philip Mease, M.D., Swedish Medical Center, University of Washington and study investigator. “I’m pleased that XELJANZ is now available for use in the treatment of this chronic condition.”

The safety profile observed in patients with active psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in rheumatoid arthritis patients. The most common adverse events observed occurring in greater than 3% of patients on XELJANZ 5 mg BID were nasopharyngitis, upper respiratory tract infection, headache and diarrhea. Please see Important Safety Information below.

“Psoriatic arthritis is a serious and debilitating chronic illness that should be diagnosed and treated early,” said Randy Beranek, president and CEO, National Psoriasis Foundation. “As an organization that advocates for people living with psoriatic arthritis, we welcome the availability of new therapies for treating this disease.”

About the OPAL Clinical Development Program

OPAL Broaden was a 12-month study in adult patients with active PsA who had an inadequate response to nonbiologic DMARDs and who were tumor necrosis factor inhibitor (TNFi) naïve. The study included an active control arm of adalimumab 40 mg administered subcutaneously every two weeks; however, the study was not powered for non-inferiority or superiority comparisons between tofacitinib and adalimumab. OPAL Beyond was a six-month study of adult patients with active PsA who had an inadequate response to a TNFi. All patients had active PsA for at least six months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least three tender/painful joints and at least three swollen joints, and active plaque psoriasis. In both studies, all patients were required to receive a stable background dose of a single nonbiologic DMARD.

About Psoriatic Arthritis

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

About XELJANZ/XELJANZ XR (tofacitinib)

XELJANZ/XELJANZ XR is the first and only Janus kinase (JAK) inhibitor approved by the FDA for moderate to severe rheumatoid arthritis (RA) and is now approved for adults with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs). As the developer of XELJANZ, 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 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.

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, including herpes zoster, 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 (eg, 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 the 2 controlled Phase 3 clinical trials in patients with active psoriatic arthritis, there were 3 malignancies (excluding NMSC) in 474 patients receiving XELJANZ plus nonbiologic DMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus nonbiologic DMARD group (3 months exposure) and 0 malignancies in 106 patients in the adalimumab plus nonbiologic DMARD group (12 months exposure). No lymphomas were reported. Malignancies have also been observed in the long-term extension study in psoriatic 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 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 5mg 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.

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.

DISCLOSURE NOTICE: The information contained in this release is as of December 14, 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 and XELJANZ XR and a new indication 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, 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, including in the new indication; 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 new indication or any other potential indications for XELJANZ or XELJANZ XR may be filed with regulatory authorities in any jurisdictions; 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 new indication; 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.

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