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Pfizer Announces FDA Approval To Include Radiographic Data On Reduction Of Progression Of Structural Joint Damage For Adults With Moderately To Severely Active Rheumatoid Arthritis In Labeling For XELJANZ® (tofacitinib citrate)

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Pfizer Inc. (NYSE: PFE) announced today that the U.S. Food and Drug Administration (FDA) has approved a supplemental New Drug Application (sNDA) to update the current label of XELJANZ® (tofacitinib citrate) 5 mg tablets to include radiographic data from two Phase 3 studies, ORAL Scan (A3921044) and ORAL Start (A3921069). "XELJANZ is the first oral JAK inhibitor for moderately to severely active rheumatoid arthritis. The reduction of radiographic progression seen in ORAL Scan and ORAL Start represents a clinically meaningful outcome for patients," said Dr. Steven Romano, Global Medicines Development Lead for the Pfizer Global Innovative Pharmaceutical business.

XELJANZ is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate (MTX). XELJANZ may be used as a single agent or in combination with MTX or other non-biologic disease-modifying antirheumatic drugs (DMARDs). Use of XELJANZ in combination with biologic DMARDs or potent immunosuppressants, such as azathioprine and cyclosporine is not recommended. The recommended dose is 5 mg twice-daily (BID).

The U.S. Prescribing Information contains a boxed warning for serious infections and malignancies. Patients treated with XELJANZ 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 MTX or corticosteroids. Lymphoma and other malignancies have been observed in patients treated with XELJANZ.

The updated U.S. label now includes the radiographic response data from ORAL Scan (Study IV) at 6 months and ORAL Start (Study VI) at 6 and 12 months (see detailed study descriptions below the table). These studies evaluated the effect of XELJANZ on the progression of structural joint damage as measured by mean change from baseline in van der Heijde modified Total Sharp Score (mTSS) and its components, erosion score and joint

space narrowing (JSN) score. The proportion of patients with no radiographic progression (mTSS change from baseline less than or equal to 0) was also assessed.

Radiographic Changes at Months 6 and 12

	Study IV (ORAL Scan)		
	Placebo **N=139** **Mean (SD)[a]**	**XELJANZ 5 mg Twice Daily** **N=277** **Mean (SD)[a]**	**XELJANZ 5 mg Twice Daily** **Mean Difference from Placebo[b]** **(CI)**
mTSS[c]			
Baseline	33 (42)	31 (48)	-
Month 6	0.5 (2.0)	0.1 (1.7)	-0.3 (-0.7, 0.0)
	Study VI (ORAL Start)		
	MTX **N=166** **Mean (SD)[a]**	**XELJANZ 5 mg Twice Daily** **N=346** **Mean (SD)[a]**	**XELJANZ 5 mg Twice Daily** **Mean Difference from MTX[b]** **(CI)**
mTSS[c]			
Baseline	17 (29)	20 (40)	-
Month 6	0.8 (2.7)	0.2 (2.3)	-0.7 (-1.0, -0.3)
Month 12	1.3 (3.7)	0.4 (3.0)	-0.9 (-1.4, -0.4)

[a]SD = Standard Deviation
[b]Difference between least squares means XELJANZ minus placebo or MTX (95% CI = 95% confidence interval)
[C]Month 6 and Month 12 data are mean change from baseline.

In the placebo plus MTX group in ORAL Scan (Study IV), 74 percent of patients experienced no radiographic progression at Month 6 compared to 84 percent of patients treated with XELJANZ 5 mg BID plus MTX.

In the MTX group of ORAL Start (Study VI), 55 percent of patients experienced no radiographic progression at Month 6 compared to 73 percent of patients treated with XELJANZ 5 mg BID.

It is important to note that the U.S. label specifies that use of live vaccines should be avoided concurrently with XELJANZ. Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ therapy.

The ORAL Start study showed that XELJANZ 5 mg BID, as a single agent, was statistically significantly superior to MTX, providing a greater inhibition of progression of structural joint damage, as measured by mean change from baseline in mTSS at Month 6 (primary endpoint), and sustained at 12 months (refer to table above). The study was conducted in MTX-naïve patients with moderately to severely active RA who were randomized to receive XELJANZ 5 or 10 mg BID or to MTX dose-titrated over 8 weeks to 20 mg weekly. XELJANZ is not indicated for use in MTX-naïve patients. The safety experience of the patients in ORAL Start was consistent with the results of the five Phase 3 pivotal trials.

The risks and benefits of treatment should be considered prior to initiating XELJANZ in patients with chronic or recurrent infection; who have been exposed to tuberculosis; with a history of a serious or an opportunistic infection; who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to infection.

The ORAL Scan study demonstrated that XELJANZ 10 mg BID provided statistically significantly greater reduction of progression of structural joint damage as measured by mean change from baseline in mTSS compared to placebo at 6 months (primary endpoint – refer to table above). Results for the 5 mg BID dose exhibited similar effects on mean progression of structural damage but were not statistically significant (refer to table above). The ORAL Scan study was conducted in patients with moderately to severely active RA who had an inadequate response to MTX. Patients were randomized to receive XELJANZ 5 or 10 mg BID or placebo, and all treatments were added to background MTX. The controlled period for the study ended at 6 months. The 10 mg BID dose is not approved.

It is important to note that the U.S. label says viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), was observed in clinical studies with XELJANZ. XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis).

About XELJANZ

XELJANZ is a prescription medicine called a Janus kinase (JAK) inhibitor. XELJANZ is used to treat adults with moderately to severely active rheumatoid arthritis in which methotrexate did not work well.

· It is not known if XELJANZ is safe and effective in people with Hepatitis B or C.

· XELJANZ is not for people with severe liver problems.

- It is not known if XELJANZ is safe and effective in children.

Important Safety Information

· **XELJANZ can lower the ability of the immune system to fight infections. Some people have serious infections while taking XELJANZ, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections. Healthcare providers should test patients for TB before starting XELJANZ, and monitor them closely for signs and symptoms of TB and other infections during treatment. People should not start taking XELJANZ if they have any kind of infection unless their healthcare provider tells them it is okay.**

· **XELJANZ may increase the risk of certain cancers by changing the way the immune system works. Malignancies were observed in clinical studies of XELJANZ.**

· Some people who have taken XELJANZ with certain other medicines to prevent kidney transplant rejection have had a problem with certain white blood cells growing out of control (Epstein Barr virus-associated post-transplant lymphoproliferative disorder).

· Some people taking XELJANZ get tears in their stomach or intestines. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate. Patients should tell their healthcare provider right away if they have fever and stomach-area pain that does not go away, or a change in bowel habits.

· XELJANZ can cause changes in certain lab test results including low blood cell counts, increases in certain liver tests, and increases in cholesterol levels. Healthcare providers should do blood tests before starting patients on XELJANZ and while they are taking XELJANZ, to check for these side effects. Normal cholesterol levels are important to good heart health. Healthcare providers may stop XELJANZ treatment because of changes in blood cell counts or liver test results.

· Use of XELJANZ in patients with severe hepatic impairment is not recommended.

· Patients should tell their healthcare providers if they plan to become pregnant or are pregnant.

It is not known if XELJANZ will harm an unborn baby. To monitor the outcomes of pregnant women exposed to XELJANZ, a registry has been established. Physicians are encouraged to register patients and pregnant women are encouraged to register themselves by calling 1-877-311-8972.

· Patients should tell their healthcare providers if they plan to breastfeed or are breastfeeding. Patients and their healthcare provider should decide if they will take XELJANZ or breastfeed. They should not do both.

· In carriers of the hepatitis B or C virus (viruses that affect the liver), the virus may become active while using XELJANZ. Healthcare providers may do blood tests before and during treatment with XELJANZ.

· Common side effects include upper respiratory tract infections (common cold, sinus infections), headache, diarrhea, and nasal congestion, sore throat, and runny nose (nasopharyngitis).

Please click the direct link to the full prescribing information for XELJANZ, including boxed warning and Medication Guide: http://labeling.pfizer.com/ShowLabeling.aspx?id=959.

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Media Contact: Victoria Davis M: 347-558-3455 E: Victoria.Davis@pfizer.com Investor Contact: Chuck Triano O: 212-733-3901 E: Charles.E.Triano@pfizer.com