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Pfizer Announces CHMP Opinion for XELJANZ® (tofacitinib) in the European Union Related to Ongoing Review of the Product

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NEW YORK, N.Y., November 15, 2019 – Pfizer Inc. (NYSE: PFE) announced today that the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a final opinion following the re-evaluation of the benefit/risk of the three approved indications of XELJANZ in the European Union (Article 20 procedure). This re-evaluation was initiated following Pfizer's initial announcement regarding the increased occurrence of pulmonary embolism (PE) and an increase in overall mortality with XELJANZ 10mg twice daily found in an ongoing postmarketing requirement study (A3921133) in rheumatoid arthritis (RA) patients 50 years of age or older with at least one cardiovascular risk factor.

The CHMP opinion will now be forwarded to the European Commission which will issue, by the end of January 2020, a final legally binding decision applicable in all EU Member States.

The EMA has recommended that XELJANZ should be used with caution in patients at high risk of blood clots. In addition, maintenance doses of 10 mg twice daily are not recommended in patients with ulcerative colitis (UC) who are at high risk of blood clots unless there is no suitable alternative treatment. 5 mg twice daily should not be exceeded for RA or psoriatic arthritis (PsA). Patients should be advised of the risk of venous thromboembolism and should seek immediate medical treatment if symptoms develop during treatment. Further, the EMA is recommending that, due to increased risk of infections, patients older than 65 years of age should be treated with XELJANZ only when there is no suitable alternative treatment.

The recommendations in this final CHMP opinion replace the provisional measures put in place at the start of the review in May 2019 which contraindicated the 10 mg twice daily dose of XELJANZ for patients at high risk of blood clots in the lungs. The CHMP is recommending removal of that contraindication. The changes come into force when the European Commission issues its decision.

"Pfizer remains confident in the benefit/risk profile of XELJANZ as an important treatment option for appropriate adult patients living with moderate to severe active rheumatoid arthritis, active psoriatic arthritis and moderately to severely active ulcerative colitis in the EU and globally where approved," said Tamas Koncz, M.D., Chief Medical Officer, Inflammation and Immunology, Pfizer. "The recommendations in the CHMP opinion provide important guidance to clinicians in the EU to help them determine which patients may benefit from XELJANZ in its three approved indications, while evaluating the relevant risks."

About Ongoing Study A3921133 Findings
The EMA public health communication reviewed interim data from study A3921133.

In Study A3921133 PE and mortality were observed at a statistically differently higher incidence rate (IR; patients with events per 100 patient-years) in patients treated with tofacitinib 10 mg twice daily (IR and 95% confidence interval (CI): 0.54 (0.32, 0.87) and 0.89 (0.59, 1.29), respectively) compared to tumor necrosis factor (TNF) inhibitors (IR and 95% CI: 0.09 (0.02, 0.26) and 0.27 (0.12, 0.51), respectively). While the incidence rates in patients treated with tofacitinib 5 mg twice daily (IR and 95% CI: 0.27 (0.12, 0.52) and 0.57 (0.34, 0.89) for PE and mortality, respectively) were higher compared to patients treated with TNF inhibitors, the differences were not statistically different.

It is important to note that XELJANZ 10 mg twice daily is only indicated for UC and is not indicated for RA or PsA.

About XELJANZ® (tofacitinib)
XELJANZ® (tofacitinib) is approved in the U.S. for adult patients in three indications: moderately to severely active rheumatoid arthritis (RA) after methotrexate failure, active psoriatic arthritis (PsA) after disease modifying antirheumatic drug (DMARD) failure and moderately to severely active ulcerative colitis (UC) after tumor necrosis factor (TNF) inhibitor failure. XELJANZ has been studied in more than 50 clinical trials worldwide, including more than 20 trials in RA patients, and prescribed to over 208,000 adult patients (the majority of whom were RA patients) worldwide in the last seven years. [1,2,3]

As the developer of tofacitinib, 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.

FDA APPROVED 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 diseasemodifying 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.

It is important to note that a dosage of Xeljanz 10 mg twice daily is not recommended for the treatment of rheumatoid arthritis or psoriatic arthritis.

Ulcerative Colitis

- XELJANZ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or who are intolerant to TNF blockers.

- Limitations of Use: Use of XELJANZ in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

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.

MORTALITY

Rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular (CV) risk factor treated with XELJANZ 10 mg twice a day had a higher rate of all-cause mortality, including sudden CV death, compared to those treated with XELJANZ 5 mg given twice daily or TNF blockers in a large, ongoing, postmarketing safety study.

XELJANZ 10mg twice daily or XELJANZ XR 22mg once daily is not recommended for the treatment of RA or PsA. For UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

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.

THROMBOSIS

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, has been observed at an increased incidence in RA patients who were 50 years of age and older with at least one CV risk factor treated with XELJANZ 10 mg twice daily compared to XELJANZ 5 mg twice daily or TNF blockers in a large, ongoing postmarketing safety study. Many of these events were serious and some resulted in death. Avoid XELJANZ/XELJANZ XR in patients at risk. Discontinue XELJANZ/XELJANZ XR and promptly evaluate patients with symptoms of thrombosis. For patients with UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response. XELJANZ 10 mg twice daily or XELJANZ XR 22 mg once daily is not recommended for the treatment of RA or PsA. In a long-term extension study in UC, four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice a day, including one death in a patient with advanced 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 UC 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 Prescribing Information, including BOXED WARNING for XELJANZ/XELJANZ XR available at:

http://labeling.pfizer.com/ShowLabeling.aspx?id=959.

Pfizer Inc.: Breakthroughs that change patients' lives®

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, including innovative medicines and vaccines. 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 November 15, 2019. 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) 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 the ability to meet anticipated clinical endpoints, commencement and/or completion dates for our clinical trials, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; risks associated with interim data; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from our clinical studies; uncertainties regarding the commercial success of XELJANZ and XELJANZ XR; uncertainties regarding the commercial impact of the update to the U.S. prescribing information for XELJANZ and XELJANZ XR; uncertainties regarding the commercial impact of the CHMP final opinion and the final decision to be issued by the European Commission, which may vary from the CHMP final opinion, as well as any potential actions by other regulatory authorities, based on analysis of clinical trial A3921133 or other data, which will depend, in part, on labeling determinations; whether and when any applications that may be pending or filed for any potential indications for XELJANZ or XELJANZ XR in any jurisdictions may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy, and, if approved, whether they will be commercially successful; decisions by regulatory authorities impacting labeling, safety, manufacturing processes and/or other matters that could affect the availability or commercial potential of XELJANZ and XELJANZ XR; 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, 2018 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. # # # # # 1 Pfizer Data on File. XELJANZ Worldwide Registration Status. 2 ClinicalTrials.gov. Tofacitinib RA Studies. https://clinicaltrials.gov/ct2/results?term=tofacitinib%2C+rheumatoid+arthrit is%2C+ORAL&type=&rslt=&recr=&age_v=&gndr=&cond=Rheumatoid+Arthritis&intr=&tit les=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&l ocn=&rcv_s=&rcv_e=&lup_s=&lup_e=. Accessed August 1, 2019. 3 Pfizer. Data on File. Tofa Counts. April 2019 Media Contact: Steve Danehy November 15, 2019 M: +1 212-733-1538 E: Steve.Danehy@pfizer.com Pfizer Europe Media Contact: Dervila Keane M: +353 86 2110834 E: Dervila.M.Keane@pfizer.com Investor Contact: Chuck Triano O: +1 212-733-3901 E: Charles.E.Triano@pfizer.com