Pfizer Inc
235 East 42nd Street
New York, NY 10017

IMPORTANT PRESCRIBING INFORMATION

March 2021

Subject: IMPORTANT PRESCRIBING INFORMATION for XELJANZ® (tofacitinib) – 5 mg tablet and Oral Solution Formulation for New Indication of Active Polyarticular Course Juvenile Idiopathic Arthritis and Important Safety Information Including Current BOXED WARNINGS

Dear Health Care Provider,

XELJANZ/XELJANZ Oral Solution was recently approved for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older. This letter describes the dosing for this new indication, newly approved dosage forms and strengths and Instructions for Use, as well as important safety information including current **BOXED WARNINGS**. Updates to the Boxed Warnings related to thrombosis events and all-cause mortality were communicated in an Important Drug Warning Letter in August of 2019.

XELJANZ Oral Solution is available for use in pcJIA patients with a body weight of 10 kg and above. In pcJIA patients with a body weight of 40 kg and above, XELJANZ 5 mg tablets can also be used. Please see weight-based dosing recommendations for XELJANZ Oral Solution in the table below.

As a condition of the initial FDA approval of XELJANZ for the treatment of adult patients with moderately to severely active rheumatoid arthritis (dated 06 November 2012), the FDA required post-marketing studies to evaluate the efficacy and safety of tofacitinib in children and adolescents from 2 to less than 18 years of age with pcJIA (referencing section 505B(a) of the FDCA).

Limitations of Use: Use of XELJANZ/XELJANZ Oral Solution in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Dosing and Administration Information for pcJIA

Recommended Dosage in pcJIA

Recommended body weight-based dosing for XELJANZ/XELJANZ Oral Solution in patients with pcJIA is noted in the table below.

XELJANZ/XELJANZ (1 mg/mL) Oral Solution		
pcJIA patients	10 kg ≤ body weight <20 kg	3.2 mg (3.2 mL Oral Solution) twice daily
	20 kg ≤ body weight <40 kg	4 mg (4 mL Oral Solution) twice daily
	body weight ≥40 kg	5 mg (one 5 mg tablet *or* 5 mL Oral Solution) twice daily[a]

[a] *pcJIA patients treated with 5 mL XELJANZ Oral Solution may be switched to a XELJANZ 5 mg tablet.*

Dosage Forms and Strengths Approved for Use in Patients with pcJIA

XELJANZ 5 mg tablets are approved for use in pcJIA patients with body weight ≥ 40 kg. They are white, round, immediate-release film-coated tablets.

XELJANZ (1 mg/mL) Oral Solution is a new formulation approved for management of patients with pcJIA. It is a clear, colorless oral solution. (Please note that the Oral Solution is not approved for other Indications.)

The safety and effectiveness of XELJANZ XR (extended release tablets) in pediatric patients have not been established.

Oral Solution Instructions for Use

Administer XELJANZ Oral Solution using the included press-in bottle adapter and oral dosing syringe. Each bottle is packaged with one press-in bottle adapter and one 5 mL oral dosing syringe with 3.2 mL, 4 mL, and 5 mL gradations. The press-in bottle adapter and oral dosing syringe are not made with natural rubber latex.

Please advise patients/caregivers to read the Instructions for Use leaflet before taking XELJANZ Oral Solution and each time they get a refill. There may be new information. A copy of the Instructions for Use leaflet accompanies this letter.

Serious Risks with Use of XELJANZ/XELJANZ ORAL Solution

Please review the full Prescribing Information (enclosed) for complete details on the risks of XELJANZ/XELJANZ Oral Solution. Please review the **BOXED WARNINGS** below on **Serious Infections, Mortality, Malignancy** and **Thrombosis**. While there are no significant updates to the **BOXED WARNINGS** currently, it is important to review this information in detail prior to prescribing XELJANZ/XELJANZ Oral Solution for patients with pcJIA.

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY AND THROMBOSIS

SERIOUS INFECTIONS

Patients treated with XELJANZ/XELJANZ Oral Solution 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 Oral Solution 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 use of XELJANZ/XELJANZ Oral Solution and during therapy. Treatment for latent infection should be initiated prior to use of XELJANZ/XELJANZ Oral Solution.
- 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 Oral Solution 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 Oral Solution, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

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 the ad-hoc analysis of a large, post-marketing safety study.

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.

THROMBOSIS

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. Rheumatoid arthritis 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 the ad-hoc analysis of a large, post-marketing safety study had an observed increase in incidence of these events. Many of these events were serious and some resulted in death. Avoid XELJANZ/XELJANZ Oral Solution in patients at risk. Discontinue XELJANZ/XELJANZ Oral Solution and promptly evaluate patients with symptoms of thrombosis.

For patients with ulcerative colitis, use XELJANZ/XELJANZ XR at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

This letter is not a comprehensive description of the risks associated with the use of XELJANZ or XELJANZ Oral Solution. In general, the types of adverse drug reactions in patients with pcJIA were consistent with those seen in adult rheumatoid arthritis patients. Please see Important Safety Information below.

Prescriber Action

Discuss the risks associated with XELJANZ/XELJANZ Oral Solution therapy with patients/caregivers. Advise patients/caregivers to read the FDA-approved patient labeling (Medication Guide

and Instructions for Use). The Medication Guide contains information that can be used to facilitate discussions about the known and potential risks of therapy with XELJANZ/XELJANZ Oral Solution.

Serious Infections

- Avoid use of XELJANZ/XELJANZ Oral Solution in patients with an active infection, including localized infections, or with chronic or recurrent infection. If a serious infection develops, XELJANZ/XELJANZ Oral Solution should be interrupted until the infection is controlled.
- Prior to initiating XELJANZ/XELJANZ Oral Solution, tests for active and latent TB should be performed. If the test is positive, treatment for TB should be started prior to starting XELJANZ/XELJANZ Oral Solution. All patients should be monitored for active TB during treatment, including patients who tested negative for latent TB prior to initiating therapy.
- Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ/XELJANZ Oral Solution.
- Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ/XELJANZ Oral Solution. Avoid use of live vaccines concurrently with XELJANZ/XELJANZ Oral Solution.
- Advise patients/caregivers that XELJANZ/XELJANZ Oral Solution may lower the ability of the patient's immune system to fight infections. Advise patients/caregivers that patients should not start taking XELJANZ/XELJANZ Oral Solution if they have an active infection. Instruct patients/caregivers to contact their healthcare provider immediately during treatment if symptoms suggesting infection appear, in order to ensure rapid evaluation and appropriate treatment. Advise patients/caregivers that the risk of herpes zoster, some cases of which can be serious, is increased in patients treated with XELJANZ/XELJANZ Oral Solution.

Malignancies and Lymphoproliferative Disorder

- Inform patients/caregivers that XELJANZ/XELJANZ Oral Solution may increase the risk of certain cancers, and that lymphoma and other cancers have been observed in patients taking XELJANZ.
- Instruct patients/caregivers to inform their healthcare provider if the patient has ever had any type of cancer.

Thrombosis

Advise patients/caregivers that the patient should stop taking XELJANZ/XELJANZ Oral Solution and call their healthcare provider right away if they experience any symptoms of thrombosis (sudden shortness of breath, chest pain worsened with breathing, swelling of leg or arm, leg pain or tenderness, red or discolored skin in the affected leg or arm).

Hypersensitivity

Advise patients/caregivers that the patient should stop taking XELJANZ/XELJANZ Oral Solution and call their healthcare provider right away if they experience any symptoms of allergic reactions while taking XELJANZ/XELJANZ Oral Solution.

Pregnancy

Advise pregnant women and females of reproductive potential of the potential risk to a fetus when taking XELJANZ/XELJANZ Oral Solution. Advise females to inform their prescriber of a known or suspected pregnancy. Advise patients who have taken XELJANZ/XELJANZ Oral Solution during pregnancy to contact the OTIS Pregnancy Registry at 1-877-311-8972 to enroll.

Lactation

Advise women not to breastfeed during treatment with XELJANZ/XELJANZ Oral Solution and for at least 18 hours after the last dose of XELJANZ/XELJANZ Oral Solution.

Infertility

Advise females of reproductive potential that XELJANZ/XELJANZ Oral Solution may impair fertility. It is not known if this effect is reversible.

Gastrointestinal Perforations

- XELJANZ/XELJANZ Oral Solution 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).
- Advise patients/caregivers to tell their healthcare provider if the patient has had diverticulitis (inflammation in parts of the large intestine) or ulcers in their stomach or intestines. Some people taking XELJANZ/XELJANZ Oral Solution can get tears in their stomach or intestines. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
- Advise patients/caregivers to tell their healthcare provider right away if the patient has a fever and stomach-area pain that do not go away, and/or a change in their bowel habits.

Please refer to the Full Prescribing Information for additional information regarding: Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Use in Diabetics, Renal Impairment, and Hepatic Impairment.

Important Information on Laboratory Abnormalities

Inform patients/caregivers that XELJANZ/XELJANZ Oral Solution may affect certain lab test results, and that blood tests are required before and during treatment with XELJANZ/XELJANZ Oral Solution.

Dose Adjustment for Laboratory Abnormalities, Renal and Hepatic Impairment in pcJIA Patients

Dosage adjustments or discontinuation are required for pcJIA patients receiving CYP3A4 and/or CYP2C19 inhibitors, with severe renal impairment (including but not limited to those undergoing hemodialysis), or moderate hepatic impairment, or with lymphopenia, neutropenia, or anemia.

XELJANZ/XELJANZ (1 mg/mL) Oral Solution		
pcJIA patients	Patients receiving: • strong CYP3A4 inhibitors (e.g., ketoconazole), *or* • a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole)	If taking 3.2 mg twice daily, reduce to 3.2 mg once daily.
		If taking 4 mg twice daily, reduce to 4 mg once daily.
		If taking 5 mg twice daily, reduce to 5 mg once daily
	Patients with: • moderate or severe renal impairment *or* • moderate hepatic impairment[a]	If taking 3.2 mg twice daily, reduce to 3.2 mg once daily.
		If taking 4 mg twice daily, reduce to 4 mg once daily.
		If taking 5 mg twice daily, reduce to 5 mg once daily.
	For patients undergoing hemodialysis	Dose should be administered after the dialysis session on dialysis days. If a dose was taken before the dialysis procedure, supplemental doses are not recommended after dialysis.

XELJANZ/XELJANZ (1 mg/mL) Oral Solution *(Continued)*		
pcJIA patients	Patients with a lymphocyte count less than 500 cells/mm^3, confirmed by repeat testing	Discontinue dosing.
	Patients with ANC 500 to 1000 cells/mm^3	Interrupt dosing until ANC is greater than 1000 cell/mm^3.
	Patients with ANC less than 500 cells/mm^3	Discontinue dosing.
	Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL	Interrupt dosing until hemoglobin values have normalized.

[a]*Use in patients with severe hepatic impairment is not recommended.*

Additional Pharmacovigilance Activities

To further characterize the safety profile of XELJANZ/XELJANZ Oral Solution in patients with pcJIA (beyond the clinical development program) a post-marketing surveillance study of pcJIA patients treated with XELJANZ/XELJANZ Oral Solution in the US will be initiated within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. For more information on the CARRA Registry, please visit *https://carragroup.org/research-registry/projects/carra-registry* or *https://clinicaltrials.gov/ct2/show/NCT02418442?term=carra+registry&recrs=ab&draw=2&rank=1*.

Reporting Adverse Events

Healthcare providers, patients, and their caregivers are encouraged to report adverse events in patients taking XELJANZ/XELJANZ Oral Solution to Pfizer at 1-800-438-1985. You are also encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

This letter is not intended as a complete description of the benefits and risks of XELJANZ/XELJANZ Oral Solution. The full Prescribing Information, Medication Guide and XELJANZ Oral Solution Instructions for Use should be consulted for further information. It is available at: http://labeling.pfizer.com/ShowLabeling.aspx?id=959

We want you to be aware of the Instructions for Use of XELJANZ/XELJANZ Oral Solution for the treatment of active pcJIA in patients 2 years of age and older (a newly approved Indication) and remind you of important safety information including current **BOXED WARNINGS**. Please review the Prescribing Information, Medication Guide and Oral Solution Instructions for Use so you can consider this information if prescribing and when counseling your patients/caregivers on the use of XELJANZ/XELJANZ Oral Solution for pcJIA. If you have any questions or would like additional information, please call Pfizer Medical Information at 1-800-438-1985.

Sincerely,

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Pfizer Inc.