Malignancy and Lymphoproliferative Disorders

Consider the risks and benefits of XELJANZ 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 in patients who develop a malignancy.
NMSC has been reported in patients treated with XELJANZ. The risk of NMSC may be higher in patients treated with XELJANZ 10 mg twice daily than in patients treated with 5 mg twice daily.
Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Vaccinations

Prior to initiating XELJANZ it is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines. Avoid use of live vaccines concurrently with XELJANZ.

ADDITIONAL INFORMATION AND REPORTING OF SUSPECTED ADVERSE REACTIONS

For additional information please refer to the Prescribing Information approved by the Ministry of Health.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Adverse events can be reported directly to the Ministry of Health using the adverse events digital form which is available on the home page of the Ministry of Health website: www.health.gov.il or by this link:
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il
Adverse events can also be reported to Pfizer by email: isr.aereporting@pfizer.com

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XELJANZ®
(tofacitinib citrate)

XELJANZ® Prescriber Guide

XELJANZ (tofacitinib) is indicated for the treatment of adult patients with:

- Moderately to severely active rheumatoid arthritis, as monotherapy or in combination with DMARDs
- Active Psoriatic Arthritis
- Moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

XELJANZ should be avoided in combination with biologics and potent immunosuppressants because of the possibility of increased immunosuppression and increased risk of infection.

Recommended Dosage of XELJANZ in Patients with UC

Adult patients	10 mg twice daily for at least 8 weeks; followed by 5 or 10 mg twice daily, depending on therapeutic response. Use the lowest effective dose to maintain response. Discontinue XELJANZ after 16 weeks of treatment with 10 mg twice daily, if adequate therapeutic benefit is not achieved.
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 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, reduce to 5 mg once daily.
Patients with: • moderate or severe renal impairment • moderate hepatic impairment*	If taking 10 mg twice daily, reduce to 5 mg twice 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 in patients after dialysis.
Patients with lymphocyte count less than 500 cells/mm^3, confirmed by repeat testing Patients with ANC less than 500 cells/mm^3	Discontinue dosing.
Patients with ANC 500 to 1000 cells/mm^3	If taking 10 mg twice daily, reduce to 5 mg twice daily. When ANC is greater than 1000, increase to 10 mg twice daily based on clinical response. If taking 5 mg twice daily, interrupt dosing. When ANC is greater than 1000, resume 5 mg twice daily.
Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL	Interrupt dosing until hemoglobin values have normalized.

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

Important Administration Instructions

- Do not initiate XELJANZ in patients with an absolute lymphocyte count less than 500 cells/mm^3, an absolute neutrophil count less than 1000 cells/mm^3 or a hemoglobin level less than 9 g/dL.
- Dose interruption is recommended for management of lymphopenia, neutropenia, and anemia.
- Interrupt use of XELJANZ if a patient develops a serious infection until the infection is controlled.
- Xeljanz is given with or without food.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving XELJANZ. XELJANZ treatment with 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Avoid use of XELJANZ in patients with an active, serious infection, including localized infections. 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.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient; appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.
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 infections.

Tuberculosis - Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of XELJANZ.

Viral Reactivation - Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ In patients treated with XELJANZ, the incidence of herpes zoster appears to be increased in:

- Japanese and Korean patients.
- Patients with an absolute lymphocyte count (ALC) less than 1000 cells/mm^3.
- Patients with long standing RA who have previously received two or more biologic DMARDs.
- Patients treated with 10 mg twice daily.