

# XELJANZ<sup>®</sup>

## Prescriber Guide

### Therapeutic indications

#### **Rheumatoid arthritis**

XELJANZ, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

XELJANZ can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

#### **Psoriatic arthritis**

XELJANZ in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy.

#### **Ankylosing spondylitis**

XELJANZ is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

#### **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, lost response, or were intolerant to either conventional therapy or a biologic agent.

#### **Juvenile idiopathic arthritis (JIA)**

XELJANZ is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (jPsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs.

Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

## Posology and method of administration

### RA, PsA and AS

The recommended posology for RA, PsA and AS is 5 mg tablets, administered orally twice daily, or one 11 mg extended-release tablet which should not be exceeded.

### Switching between XELJANZ tablets and XELJANZ extended-release tablets

Treatment with XELJANZ 5 mg tablets twice daily and XELJANZ 11 mg extended-release tablet once daily may be switched between each other on the day following the last dose of either tablet. XELJANZ 11 mg extended-release once daily has demonstrated pharmacokinetic equivalence to XELJANZ 5 mg tablets twice daily.

### UC

#### Induction treatment for UC (weeks 0 through week 8, with extension to week 16 as necessary)

The recommended dose for UC is 10 mg tablets given orally twice daily for induction for 8 weeks. For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg tablets twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg tablets twice daily for maintenance. XELJANZ induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

#### Maintenance treatment for UC (post induction period)

The recommended dose for maintenance treatment is tofacitinib 5 mg tablets given orally twice daily.

Avoid XELJANZ in patients at increased risk for thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis.

Tofacitinib 10 mg tablets twice daily for maintenance treatment is not recommended in patients with UC who have known major adverse cardiovascular events (MACE) and malignancy risk factors, unless there is no suitable alternative treatment available.

For patients with UC who are not at increased risk for VTE, MACE and malignancy, tofacitinib 10 mg tablets orally twice daily may be considered if the patient experiences a decrease in response on tofacitinib 5 mg tablets twice daily and failed to respond to alternative treatment options for ulcerative colitis such as tumour necrosis factor inhibitor (TNF inhibitor) treatment. Tofacitinib 10 mg tablets twice daily for maintenance treatment should be used for the shortest duration possible. The lowest effective dose needed to maintain response should be used.

In patients who have responded to treatment with XELJANZ, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

### Retreatment in UC

If therapy is interrupted, restarting treatment with XELJANZ may be considered. If there has been a loss of response, reinduction with XELJANZ 10 mg tablets twice daily may be considered. The treatment interruption period in clinical studies extended up to 1 year. Efficacy may be regained by 8 weeks of 10 mg tablets twice daily therapy.

### Polyarticular JIA and juvenile PsA (patients 2 years of age and older)

Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

The recommended dose in patients 2 years of age and older is based upon the following weight categories:

**Table 1:** Tofacitinib dose for patients with polyarticular JIA and juvenile PsA two years of age and older

Body weight (kg)	Dose regimen
10 - < 20	3.2 mg (3.2 mL of oral solution) twice daily
20 - < 40	4 mg (4 mL of oral solution) twice daily
≥ 40	5 mg (5 mL of oral solution or 5 mg tablet) twice daily

Patients ≥ 40 kg treated with tofacitinib 5 mL oral solution twice daily may be switched to tofacitinib 5 mg tablets twice daily. Patients < 40 kg cannot be switched from tofacitinib oral solution.

XELJANZ treatment of RA, PsA, AS, UC and JIA patients should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of these respective conditions.

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

### Dose discontinuation in AS

Available data suggest that clinical improvement in AS is observed within 16 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

## Considerations for administration

### Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in the local Prescribing Information.
- Active tuberculosis (TB) or other severe infections such as sepsis or opportunistic infections.
- Severe hepatic impairment.
- Pregnancy and lactation.

## Use in Special Populations

### Elderly

No dose adjustment is required in patients aged 65 years and older. There are limited data in patients aged 75 years and older.

Considering the increased risk of serious infections, myocardial infarction, malignancies and all cause mortality with XELJANZ in patients over 65 years of age and older, XELJANZ should only be used in these patients if no suitable treatment alternatives are available.

### Patients with renal impairment

- No dose adjustment is required in patients with mild (creatinine clearance 50-80 mL/min) or moderate renal impairment (creatinine clearance 30-49 mL/min).
- Severe renal impairment (creatinine clearance <30 mL/min): Dose should be reduced to 5 mg (or weight-based equivalent of XELJANZ oral solution) once daily when the indicated dose in the presence of normal renal function is 5 mg (or weight-based equivalent of XELJANZ oral solution) twice daily or 11 mg extended release once daily. Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily in patients with UC. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis.

### Patients with hepatic impairment

- No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A).
- Moderate hepatic impairment (Child Pugh B): Dose should be reduced to 5 mg (or weight-based equivalent of XELJANZ oral solution) once daily when the indicated dose in the presence of normal hepatic function is 5 mg (or weight-based equivalent of XELJANZ oral solution) twice daily or 11 mg extended release once daily. Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily in patients with UC.
- XELJANZ should not be used in patients with severe hepatic impairment (Child Pugh C).

### Pediatric patients

The safety and efficacy of XELJANZ in children less than 2 years of age with pJIA and jPsA has not been established. No data are available.

The safety and efficacy of tofacitinib in children less than 18 years of age with other indications (e.g., ulcerative colitis) has not been established. No data are available.

Only in paediatric patients: Available data suggest that clinical improvement is observed within 18 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

### Pregnancy and lactation

- Use of XELJANZ during pregnancy is contraindicated.
- Use of XELJANZ during breastfeeding is contraindicated.

### Women of childbearing potential

- Women of childbearing potential should be advised to use effective contraception during treatment with XELJANZ and for at least 4 weeks after the last dose.

## Prior to administering XELJANZ

- Discuss the risks with patients using the patient safety information card.

### **Tofacitinib should only be used if no suitable treatment alternatives are available in patients:**

- 65 years of age and older;
- patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);
- patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

- **Considering the increased risk of serious infections, myocardial infarction, malignancies and all cause mortality with tofacitinib in patients over 65 years of age and older, tofacitinib should only be used in these patients if no suitable treatment alternatives are available.**
- Avoid XELJANZ in patients at increased risk for thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis.
- Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known MACE and malignancy risk factors, unless there is no suitable alternative treatment available.
- Consider the risk and benefits of XELJANZ treatment carefully in patients who are at higher risk of developing serious infections including patients:
  - with recurrent infections
  - who have been exposed to TB
  - with a history of a serious or an opportunistic infection
  - who have resided or travelled in areas of endemic TB or endemic mycoses
  - who have underlying conditions that may predispose them to infection, such as diabetes mellitus.
- Evaluate and test the patient for latent or active TB infection. Patients with latent TB should be treated with standard antimycobacterial therapy before administering XELJANZ.

- All patients, particularly pJIA and jPsA patients, should be brought up to date with all immunisations in agreement with current immunisation guidelines. Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. The risk of herpes zoster appears to be higher in Japanese and Korean patients treated with XELJANZ.
- Screening for viral hepatitis should be performed in accordance with clinical guidelines.
- Assess the patient's cardiovascular risk factors, in patients over 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors.
  - Only use tofacitinib if no suitable treatment alternatives are available.
- Assess the patient's malignancy risk factors including patients over 65 years of age and older current or past long-time smokers, and other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer).
  - Only use tofacitinib if no suitable treatment alternatives are available.
- Check patients' laboratory parameters including lymphocytes, neutrophils, haemoglobin, lipids, and hepatic enzymes. Initiating treatment is not recommended in patients with:
  - Low absolute lymphocyte count (<750 cells/mm<sup>3</sup>)
  - Low absolute neutrophil count (<1000 cells/mm<sup>3</sup> in adult patients and <1200 cells/mm<sup>3</sup> in paediatric patients)
  - Low haemoglobin (<9 g/dL in adult patients and <10 g/dL in paediatric patients)

**Patients treated with XELJANZ should be given a patient safety information card. Patients should be advised to keep this card with them for at least 2 months after taking the last dose of XELJANZ.**

**Monitoring of laboratory parameters:**

Laboratory parameters	Routine Monitoring	Laboratory value	Recommended Actions
Lymphocytes (ALC)	At baseline, then every 3 months	Greater than or equal to 750 cells/mm <sup>3</sup>	Dose should be maintained
		Between 500 and 750 cells/mm <sup>3</sup> (confirmed by repeat testing)	Dosing should be reduced or interrupted  For patients receiving XELJANZ 5 mg twice daily or 11 mg extended release once daily, dosing should be interrupted.  For patients with UC receiving XELJANZ 10 mg twice daily, dosing should be reduced to XELJANZ 5 mg twice daily.  When ALC is greater than 750, resume treatment as clinically appropriate.
		Less than 500 cells/mm <sup>3</sup> (confirmed by repeat testing)	Dosing should be discontinued.

Laboratory parameters	Routine Monitoring	Laboratory value	Recommended Actions
Neutrophils (ANC)	At baseline, after 4 to 8 weeks of treatment, and then every 3 months	ANC greater than 1000 cells/mm <sup>3</sup>	Dose should be maintained
		ANC 500–1000 cells/mm <sup>3</sup> (confirmed by repeat testing)	For persistent decreases in this range, reduce or interrupt dosing  For patients receiving XELJANZ 5 mg twice daily or 11 mg extended release once daily, dosing should be interrupted.  For patients with UC receiving XELJANZ 10 mg twice daily, dosing should be reduced to XELJANZ 5 mg twice daily.  When ANC is greater than 1000 cells/mm <sup>3</sup> resume treatment as clinically appropriate.
		ANC less than 500 cells/mm <sup>3</sup> (confirmed by repeat testing)	Dosing should be discontinued
Haemoglobin	At baseline, after 4 to 8 weeks of treatment, and then every 3 months	Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Dose should be maintained
		Greater than 2 g/dL decrease or less than 8.0 g/dL (confirmed by repeat testing)	Interrupt dosing until haemoglobin values have normalised
Lipids	After 8 weeks following initiation of therapy	NA	Managed according to clinical guidelines for the management of hyperlipidaemia
Liver enzymes	Routine monitoring	NA	Following initiation, 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

ALC=absolute lymphocyte count; ANC=absolute neutrophil count; NA=not applicable

## Special warnings and precautions for use

### Combination with other therapies

XELJANZ has not been studied and its use should be avoided in patients in combination with biologics such as TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, and selective co-stimulation modulators and potent immunosuppressants such as azathioprine, 6-mercaptopurine, cyclosporine and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

There is a higher incidence of adverse events for the combination of XELJANZ plus MTX versus XELJANZ as monotherapy in RA clinical trials.

### Use in patients over 65 years of age and older

Considering the increased risk of serious infections, myocardial infarction, malignancies and all cause mortality with XELJANZ in patients 65 years of age and older, XELJANZ should only be used in these patients if no suitable treatment alternatives are available.

## Venous thromboembolism (VTE)

Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), have been observed in patients taking XELJANZ. In a randomised post-authorisation safety study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, a dose dependent increased risk for VTE was observed with XELJANZ compared to TNF inhibitors. The majority of these events were serious and some cases of PE resulted in death.

XELJANZ should be avoided in patients with known risk factors for VTE, regardless of indication and dosage.

For patients with RA with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is  $\geq 2 \times$  ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib

VTE risk factors include:

- Previous VTE
- Patients undergoing major surgery
- Immobilisation
- Myocardial infarction (within previous 3 months)
- Heart failure
- Use of combined hormonal contraceptives or hormone replacement therapy
- Inherited coagulation disorder
- Malignancy

Additional VTE risk factors such as age, obesity (BMI  $\geq 30$ ), diabetes, hypertension, smoking status should also be considered. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.

XELJANZ 10 mg tablets twice daily for maintenance treatment should be avoided in patients with UC who have known VTE risk factors.

Patients should be advised on potential symptoms of VTE and to seek immediate medical attention if they experience these symptoms. Promptly evaluate patients with signs and symptoms of VTE and discontinue XELJANZ in patients with suspected VTE, regardless of dose or indication.

## Serious infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving tofacitinib.

The most common serious infections reported with XELJANZ were pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal

candidiasis, multidermatomal herpes zoster, cytomegalovirus, BK virus infections and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localised disease, and patients were often taking concomitant immunomodulating agents such as MTX or corticosteroids which, in addition to rheumatoid arthritis or psoriatic arthritis, may predispose them to infections. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis). The risk of opportunistic infections is higher in Asian geographic regions.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. Treatment must be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. 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 recommended when XELJANZ treatment is used in the following patients:

- Elderly and diabetic patients given there is a higher incidence of infections in general
- Patients with a history of chronic lung disease as they may be more prone to infections.
- Patients with lymphopenia

In patients over 65 years of age, XELJANZ should only be used if no suitable treatment alternatives are available.

## Tuberculosis

The risks and benefits of treatment should be considered prior to initiating XELJANZ in patients:

- Who have been exposed to TB
- Who have resided or travelled in areas of endemic TB or endemic mycoses

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. 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<sup>3</sup>.
- Patients with long standing RA who have previously received two or more biologic DMARDs.
- Patients with UC treated with 10 mg tablets twice daily.

### **Major adverse cardiovascular events (including myocardial infarction)**

Major adverse cardiovascular events (MACE) have been observed in patients taking XELJANZ.

In a randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with XELJANZ compared to TNF inhibitors.

In patients over 65 years of age and older, who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.

Patients should be advised how to recognise potential symptoms of MI and to promptly seek emergency medical attention if they experience these.

### **Malignancies and lymphoproliferative disorder**

Tofacitinib may affect host defences against malignancies.

In a randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies, particularly NMSC, lung cancer and lymphoma, were observed with tofacitinib compared to TNF inhibitors.

NMSC, lung cancers and lymphomas in patients treated with tofacitinib have also been observed in other clinical studies and in the postmarketing setting.

Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.

Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer.

### **Interstitial lung disease**

Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with XELJANZ in RA clinical trials and in the post-marketing setting although the role of Janus kinase (JAK) inhibition in these events is not known. Asian RA patients are known to be at higher risk of interstitial lung disease, thus caution should be exercised in treating these patients.

### **Gastrointestinal perforations**

Events of gastrointestinal perforation have been reported in clinical trials although the role of Janus-kinase inhibition in these events is not known.

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 and patients with

concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory medicinal products). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

### **Vaccination**

- Prior to initiating XELJANZ it is recommended that all patients, particularly pJIA and jPsA patients be brought up to date with all immunisations in agreement with current immunisation guidelines.
- It is recommended that live vaccines not be given concurrently with XELJANZ. The decision to use live vaccines prior to XELJANZ treatment should take into account the pre-existing immunosuppression in a given patient.
- Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular consideration should be given to patients with longstanding rheumatoid arthritis who have received two or more prior biological DMARDs. If live zoster vaccine is administered; it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus (VZV). If the history of chickenpox is considered doubtful or unreliable it is recommended to test for antibodies against VZV.
- Vaccination with live vaccines should occur at least 2 weeks but preferably 4 weeks prior to initiation of XELJANZ or in accordance with current vaccination guidelines regarding immunomodulatory medicinal products.

**FOR MORE DETAILS ON PRESCRIBING XELJANZ, PLEASE REFER TO THE LOCAL PRESCRIBING INFORMATION.**

### **Patient Counseling**

**It is important for you to discuss the risks associated with use of XELJANZ with your patients, and in applicable instances, with their caregivers.**

A patient safety information card has been developed to help patients understand the risks associated with XELJANZ and remind them to seek immediate medical attention if they experience any listed signs and symptoms.

It is important for physicians to:

- Provide the patient safety information card to each patient who is prescribed with XELJANZ.
- Remind patients to use the patient safety information card.
- Discuss the risks with each patient and ensure patient understanding of the treatment potential risks.
- Ensure patients to carry the patient safety information card with them, particularly when they visit doctors' office and/or the emergency room.

You should remind patients to seek immediate medical attention if they experience any of the following signs and symptoms.

- Sudden shortness of breath or difficulty breathing, chest pain or pain in upper back, swelling of the leg or arm, leg pain or tenderness, or redness or discoloration in the leg or arm while taking XELJANZ, as these may be signs of a clot in the lungs or veins.
- Experience possible symptoms of allergic reactions such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue or throat, itching or skin rash when taking XELJANZ, or soon after taking XELJANZ.
- Develop symptoms of an infection, such as fever, persistent cough, weight loss, or excessive tiredness.
- Develop symptoms of herpes zoster, such as painful rash or blisters.
- Have been in close contact with a person with TB.
- Develop severe chest pain or tightness (that may spread to arms, jaw, neck and back), shortness of breath, cold sweat, light headedness or sudden dizziness as these may be signs of a heart attack.
- Notice any new growth on the skin or any changes in existing moles or spots.
- Develop symptoms of interstitial lung diseases, such as shortness of breath.
- Develop abdominal signs and symptoms such as stomach pain, abdominal pain, blood in stool, or any change in bowel habits with fever.
- Develop yellow skin, nausea, or vomiting.
- Are due to receive any vaccine. Patients should not receive certain types of vaccines while taking XELJANZ.
- Become pregnant or plan on becoming pregnant.

## 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 reporting portal which is available on the home page of the Ministry of Health website:

**www.health.gov.il** or by this link: **<https://sideeffects.health.gov.il>**

Adverse events can also be reported to Pfizer by email: **[isr.aereporting@pfizer.com](mailto:isr.aereporting@pfizer.com)**

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