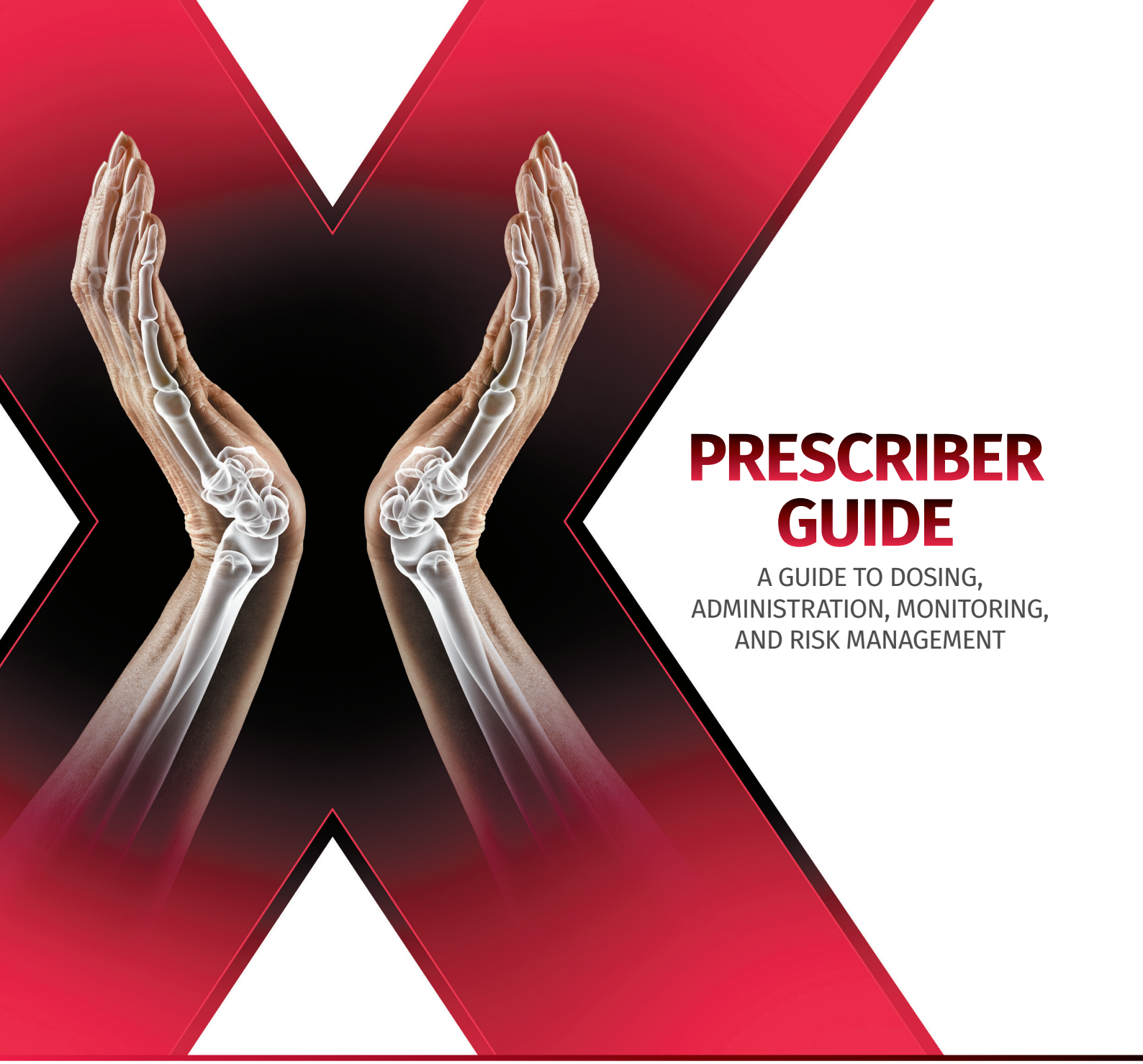

PRESCRIBER GUIDE

A GUIDE TO DOSING, ADMINISTRATION, MONITORING, AND RISK MANAGEMENT

XELJANZ®
(tofacitinib)

Version: 4.1
Date of approval: 28/01/2022

PRESCRIBER GUIDE

This Prescriber Guide intends to provide guidance on tofacitinib to the prescribing physicians with respect to therapeutic indications, dosing and administration including considerations for administration, instruction on monitoring laboratory parameters, precautions and warnings, patient counseling, reporting of adverse events, and a summary of the risk management plan.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Version: 4.1 Date of approval: 28/01/2022

A guide to dosing, administration, monitoring, and risk management

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. 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 (AS)

Tofacitinib 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.

Posology and method of administration

RA and PsA

The recommended posology for RA and PsA is 5 mg film-coated tablets, administered orally twice daily. This should not be exceeded.

Prolonged release formulation (RA and PsA)

For RA and PsA, the recommended dosage of the 11 mg prolonged release tablet is orally once daily, which should not be exceeded. Treatment with XELJANZ 5 mg film-coated tablets twice daily and XELJANZ 11 mg prolonged-release tablet once daily may be switched between each other on the day following the last dose of either tablet XELJANZ 11 mg prolonged release once daily has demonstrated pharmacokinetic equivalence to XELJANZ 5mg film coated tablets twice daily.

AS

The recommended dose of tofacitinib is 5 mg administered 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 film coated 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 film coated tablets twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg film coated 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 film coated tablets given orally twice daily.

Tofacitinib 10 mg film coated tablets twice daily for maintenance treatment is not recommended in patients with UC who have known venous thromboembolism (VTE) risk factors, unless there is no suitable alternative treatment available.

For patients with UC who are not at increased risk for VTE tofacitinib 10 mg film coated tablets orally twice daily may be considered if the patient experiences a decrease in response on tofacitinib 5 mg film coated 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 film coated 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 XEJLANZ, 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 film coated 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 film coated tablets twice daily therapy.

JIA

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 juvenile idiopathic arthritis 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 film-coated tablet) twice daily

Patients ≥40 kg treated with tofacitinib 5 mL oral solution twice daily may be switched to tofacitinib 5 mg film-coated 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.

XELJANZ dose should be reduced by half in patients receiving potent inhibitors of cytochrome (CYP) P450 3A4 (e.g., ketoconazole) and in patients receiving one or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g., fluconazole) as follows:

- XELJANZ dose should be reduced to 5 mg once daily in patients receiving 5 mg twice daily.
- XELJANZ dose should be reduced to 5 mg once daily in patients receiving 11 mg prolonged release once daily (indicated for RA and PsA)
- XELJANZ dose should be reduced to 5 mg twice daily in patients with UC receiving 10 mg twice daily.

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(s) or to any of the excipients listed in Summary of Product Characteristics (SmPC)
- Active tuberculosis (TB) or other severe infections such as sepsis or opportunistic infections
- Severe hepatic impairment
- Pregnancy and lactation

Prior to administering XELJANZ

- Discuss the risks with patients using the **patient alert card** and **XELJANZ treatment initiation checklist** (see enclosed checklist for more details).
- Considering the increased risk of serious infections, myocardial infarction, and malignancies with

tofacitinib in patients over 65 years of age, tofacitinib should only be used in these patients if no suitable treatment alternatives are available

- Use with caution in patients with VTE risk factors
- 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 including patients over 65 years of age, current or past smokers and 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 current or past 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^3)
  - Low absolute neutrophil count (<1000 cells/mm^3 in adult patients and <1200 cells/mm^3 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 alert card. An adequate supply will be provided to prescribers for distribution to patients (through Pfizer local country office distribution channels). Additional copies can be downloaded via the prescriber website (see section Risk Communication for more details). **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^3	Dose should be maintained
		Between 500 and 750 cells/mm^3 (confirmed by repeat testing	Dosing should be reduced or interrupted For patients receiving XELJANZ 5 mg twice daily, or 11 mg prolonged 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^3 (confirmed by repeat testing)	Dosing should be discontinued.
Neutrophils (ANC)	At baseline, after 4 to 8 weeks of treatment, and then every 3 months	ANC greater than 1000 cells/mm^3	Dose should be maintained
		ANC 500–1000 cells/mm^3	For persistent decreases in this range, reduce or interrupt dosing For patients receiving XELJANZ 5 mg twice daily, or 11 mg prolonged 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^3 resume treatment as clinically appropriate.
		ANC less than 500 cells/mm^3	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

Laboratory parameters	Routine Monitoring	Laboratory value	Recommended Actions
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

Considering the increased risk of serious infections, myocardial infarction, and malignancies with XELJANZ in patients over 65 years of age, 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.

In a post hoc exploratory analysis within this study, in patients with known VTE risk factors, occurrences of subsequent VTEs were observed more frequently in tofacitinib-treated patients that, at 12 months treatment, had D-dimer level ≥2× upper limit of normal (ULN) versus those with D-dimer level <2× ULN; this was not evident in TNF inhibitor-treated patients. Interpretation is limited by the low number of VTE events and restricted D-dimer test availability (only assessed at Baseline, Month 12, and at the end of the study). In patients who did not have a VTE during the

study, mean D-dimer levels were significantly reduced at Month 12 relative to Baseline across all treatment arms. However, D-dimer levels ≥2× ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D-Dimer testing in this study

XELJANZ should be used with caution 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 ≥ 2× 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 ≥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.

For further guidance on VTE risk factors, please visit the Euopean Society of Cardiology guidelines for diagnosis and management of acute pulmonary embolism: https://doi.org/10.1093/eurheartj/ehz405

XELJANZ 10 mg film coated tablets twice daily for maintenance treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available.

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.

Rheumatoid arthritis:

In a large, randomised post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular (CV) risk factor (Study ORAL Surveillance (A3921133)), VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors. The majority of these events were serious and some cases of PE resulted in death.

In an interim safety analysis, the incidence rates (95% CI) for PE for tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, and TNF inhibitors were 0.54 (0.32-0.87), 0.27 (0.12-0.52), and 0.09 (0.02-0.26) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for PE was 5.96 (1.75-20.33) and 2.99 (0.81-11.06) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily, respectively.

In a subgroup analysis in patients with VTE risk factors in the above-mentioned interim analysis of the study, the risk for PE was further increased. Compared with TNF inhibitors, the HR for PE was 9.14 (2.11-39.56) for tofacitinib 10 mg twice daily and 3.92 (0.83-18.48) for tofacitinib 5 mg twice daily.

The incidence rates (95% CI) for DVT for tofacitinib 10 mg twice daily, 5 mg twice daily, and TNF inhibitors were 0.38 (0.20 0.67), 0.30 (0.14 0.55), and 0.18 (0.07 0.39) patients with events per 100 patient years, respectively. Compared with TNF inhibitors, the HR for DVT with tofacitinib 10 mg twice daily was 2.13 (0.80 5.69), and for 5 mg twice daily the HR was 1.66 (0.60 4.57)

Completed randomised studies in RA

In studies of 6-, 12-, or 24-month duration (in which patients were not required to be 50 years or older or have at least one CV risk factors), the rate of PE in the 5 mg twice daily and 10 mg twice daily tofacitinib groups was 0.12 (95% CI 0.02 – 0.34) and 0.15 (0.03 – 0.44) patients with events per 100 patient-years, respectively. The rate of DVT in the 5 mg twice daily and 10 mg twice daily tofacitinib groups was 0.15 (95% CI 0.04 – 0.40) and 0.10 (0.01 – 0.36) patients with events per 100 patient-years, respectively.

Ulcerative colitis:

In the UC ongoing extension trial, cases of PE and DVT have been observed in patients using tofacitinib 10 mg twice daily and with underlying VTE risk factor(s).

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 due to the increased risk of serious infections observed in Study ORAL Surveillance.

Serious infections for prolonged-release tablet and film-coated tablet from non- interventional post approval safety study: Data from a non-interventional post approval safety study that evaluated tofacitinib in RA patients from a registry (US Corrona) showed that a numerically higher

IR of serious infection was observed for the PR 11 mg tablet administered once daily than the 5 mg film-coated tablet administered twice daily. Crude IRs (95% CI) (i.e., not adjusted for age or sex) from availability of both formulations at 12 months following initiation of treatment were 3.45 (1.93, 5.69) and 2.78 (1.74, 4.21) and at 36 months were 4.71 (3.08, 6.91) and 2.79 (2.01, 3.77) patients with events per 100 patient-years in the PR 11 mg tablet once daily and film-coated 5 mg tablet twice daily groups, respectively. The unadjusted HR was 1.30 (95% CI; 0.67, 2.50) at 12 months and 1.93 (95% CI; 1.15, 3.24) at 36 months for the PR 11 mg once daily dose compared to the film-coated 5 mg twice daily dose. Data is based on a small number of patients with events observed with relatively large confidence intervals and limited follow up time.

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.^{3}
- Patients with long standing RA who have previously received two or more biologic DMARDs.
- Patients with UC treated with 10 mg film coated 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, who are current or past smokers, and patients with other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.

Rhematoid arthritis

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 (Study ORAL Surveillance), an increase in non-fatal myocardial infarction was observed in patients treated with tofacitinib compared to TNF inhibitor.

Table 1: Incidence rate and hazard ratio for MACE and myocardial infarction

	Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily[a]	All Tofacitinib[b]	TNF inhibitor
MACE[c]				
IR (95% CI) per 100 PY	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.98 (0.79, 1.19)	0.73 (0.52, 1.01)
HR (95% CI) vs TNFi	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)	
Fatal MI[c]				
IR (95% CI) per 100 PY	0.00 (0.00, 0.07)	0.06 (0.01, 0.18)	0.03 (0.01, 0.09)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	0.00 (0.00, Inf)	1.03 (0.21, 5.11)	0.50 (0.10, 2.49)	
Non-fatal MI[c]				
IR (95% CI) per 100 PY	0.37 (0.22, 0.57)	0.33 (0.19, 0.53)	0.35 (0.24, 0.48)	0.16 (0.07, 0.31)
HR (95% CI) vs TNFi	2.32 (1.02, 5.30)	2.08 (0.89, 4.86)	2.20 (1.02, 4.75)	

[a]The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.
[b]Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
[c]Based on events occurring on treatment or within 60 days of treatment discontinuation.
Abbreviations: MACE = major adverse cardiovascular events, MI = myocardial infarction, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, Inf = infinity

The following predictive factors for development of MI (fatal and non-fatal) were identified using a multivariate Cox model with backward selection: age ≥ 65 years, male, current or past smoking, history of diabetes, and history of coronary artery disease (which includes myocardial infarction, coronary heart disease, stable angina pectoris, or coronary artery procedures)

In other completed randomised studies of 6-, 12-, or 24-month duration, the incidence rates (95% CI) for myocardial infarction in the 5 mg twice daily and 10 mg twice daily tofacitinib groups were 0.08 (0.01, 0.29) and 0.16 (0.03, 0.46) patients with events per 100 patient-years, respectively.

In the long-term safety all exposure population, incidence rates (95% CI) for myocardial infarction were 0.18 (0.10, 0.30) and 0.15 (0.09, 0.22) patients with events per 100 patient-years for 5 mg and 10 mg twice daily tofacitinib groups, respectively

Malignancies and lymphoproliferative disorder [Excluding Non-melanoma Skin Cancer (NMSC)]

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 excluding NMSC, particularly lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors.

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 over 65 years of age, patients who are current or past 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.

Rheumatoid arthritis

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 (Study ORAL Surveillance), an increase in malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed in patients treated with tofacitinib compared to TNF inhibitor.

Table 2: Incidence rate and hazard ratio for malignancies excluding NMSC[a]

	Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily[b]	All Tofacitinib[c]	TNF inhibitor
Malignancies excluding NMSC				
IR (95% CI) per 100 PY	1.13 (0.87, 1.45)	1.13 (0.86, 1.45)	1.13 (0.94, 1.35)	0.77 (0.55, 1.04)
HR (95% CI) vs TNFi	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)	
Lung cancer				
IR (95% CI) per 100 PY	0.23 (0.12, 0.40)	0.32 (0.18, 0.51)	0.28 (0.19, 0.39)	0.13 (0.05, 0.26)
HR (95% CI) vs TNFi	1.84 (0.74, 4.62)	2.50 (1.04, 6.02)	2.17 (0.95, 4.93)	
Lymphoma				
IR (95% CI) per 100 PY	0.07 (0.02, 0.18)	0.11 (0.04, 0.24)	0.09 (0.04, 0.17)	0.02 (0.00, 0.10)
HR (95% CI) vs TNFi	3.99 (0.45, 35.70)	6.24 (0.75, 51.86)	5.09 (0.65, 39.78)	

[a]Based on events occurring on treatment or after treatment discontinuation up to the end of the study
[b]The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.
[c]Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
Abbreviations: NMSC = non melanoma skin cancer, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years

The following predictive factors for development of malignancies excluding NMSC were identified using a Multivariate Cox model with backward selection: age ≥ 65 years and current or past smoking

In other completed randomised studies of 6-, 12-, or 24-month duration, the incidence rates (95% CI) for lung cancer in the 5 mg twice daily and 10 mg twice daily tofacitinib groups were 0.12 (0.02, 0.34) and 0.05 (0.00, 0.28) patients with events per 100 patient-years, respectively, and the incidence rates (95% CI) for lymphoma were 0.00 (0.00, 0.14) and 0.15 (0.03, 0.44), respectively.

In the long-term safety all exposure population, the incidence rates (95% CI) for lung cancer in the 5 mg twice daily and 10 mg twice daily tofacitinib groups were 0.13 (0.07, 0.23) and 0.12 (0.07, 0.19) patients with events per 100 patient-years, respectively, and the incidence rates (95% CI) for lymphoma were 0.01 (0.00, 0.06) and 0.07 (0.04, 0.13), respectively.

Non-melanoma skin cancer

NMSCs have 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.

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.

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, and malignancies with XELJANZ in patients over 65 years of age, 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 once daily when the indicated dose in the presence of normal renal function is 5 mg twice daily. or 11 mg prolonged release once daily (indicated in RA). 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 once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily. or 11 mg prolonged release once daily (indicated in RA). 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.

FOR MORE DETAILS ON PRESCRIBING XELJANZ, PLEASE REFER TO THE SUMMARY OF PRODUCT CHARACTERISTICS.

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 alert 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 alert card to each patient who is prescribed with XELJANZ.
- remind patients to use the patient alert card.
- discuss the risks with each patient and ensure patient understanding of the treatment potential risks.
- ensure patients to carry the patient alert 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.

To order more copies of the patient alert card, please call Pfizer's Local Representative, Vivian Corporation Ltd.: 00356 22588600 or visit the website: www.tofacitinib-rmp.com.mt

Reporting of Adverse Events

Reporting of Adverse Events

If you become aware of any suspected adverse reactions in association with use of XELJANZ, please report the event promptly to

ADR Reporting

www.medicinesauthority.gov.mt/adrportal

Malta Medicines Authority
Sir Temi Żammit Buildings,
Malta Life Sciences Park,
San Ġwann,
SĠN 3000,
Malta Website: www.medicinesauthority.gov.mt/adrportal
e-mail: postlicensing.medicinesauthority@gov.mt

Also for Medical information please contact Vivian Corporation at

+356 2258 8600

pv@viviancorp.com

OR

Pfizer Hellas S.A. Medical Information at +30 210 67 85 800.

Risk Management Plan (RMP)

A risk management system, described in the risk management plan (RMP), is a set of pharmacovigilance activities and interventions required by the European Medicine Agency (EMA) to ensure that the benefits of the medicinal product outweigh its risks.

The XELJANZ RMP is developed:

- to identify, characterise, prevent or minimise risks relating to XELJANZ including the assessment of the effectiveness of those activities and interventions.

Risk Communication

In order to communicate certain risks about XELJANZ, Pfizer has worked with the EMA to develop a detailed communication plan to communicate the risks described in the summary of product characteristics, including the following items:

- patient alert card
- prescriber guide
- prescriber treatment initiation checklist
- prescriber treatment maintenance checklist

Two treatment checklists: initiation checklist and maintenance checklists, are developed for you to be used prior to and during XELJANZ treatment. They intend to remind you of the risks associated with use of XELJANZ and the recommended tests before and during the XELJANZ treatment.

Prescriber website for Xeljanz (tofacitinib) ▼

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Version: 4.1 Date of approval: 28/01/2022

All the educational materials including patient alert card and treatment initiation/maintenance checklist are available at www.tofacitinib-rmp.com.mt.

Please visit this website for more details.

Ongoing Risk Assessment

RA

In order to continue to characterise the risks relating to XELJANZ in treatment of RA, Pfizer has committed to to study risks within 4 established European RA registries including one in UK (i.e., BSRBR), one in Germany (i.e., RABBIT), one in Sweden (i.e., ARTIS), and one in Spain (i.e., BIOBADASER).

The purpose of the registry surveillance studies is to collect additional longitudinal safety data from the clinical practice setting regarding the use of XELJANZ in patients with rheumatoid arthritis.

Physicians from those countries can learn more about these registries via the following contact information:

- BSRBR:
  https://bsrbr.org/
- RABBIT – Rheumatoide Arthritis:
  Beobachtung der Biologika-Therapie:
  https://biologika-register.de
- ARTIS
  https://srq.nu/en/artis-health-professional
- BIOBADASER:
  https://biobadaser.ser.es/default.aspx

UC

In order to continue to characterize the risks relating to XELJANZ in treatment of UC, Pfizer has committed to participating in a prospective, non-interventional active surveillance study using European UC registries, including one in Sweden (Swedish National Quality Registry for Inflammatory Bowel Disease [SWIBREG] and one European wide (United Registries for Clinical Assessment and Research [UR-CARE]).

The purpose of this active study is to further understand and characterise the safety profile of XELJANZ within the clinical practice setting in patients with UC. This will include a sub-analysis of the safety profile in patients treated with XELJANZ 10 mg twice daily maintenance therapy.

Physicians from those countries can learn more about these registries via the following contact information:

- SWIBREG
  http://www.swibreg.se/
- UR-CARE
  https://www.ecco-ibd.eu/science/ur-care.html

JIA

In order to continue to characterize the risks relating to XELJANZ in treatment of JIA, Pfizer has committed to study the risks within 4 established European registries, including two in Germany (the German Biologics in Pediatric Rheumatology Registry or BiKeR and the Juvenile Arthritis Methotrexate/Biologics long-term Observation or JuMBO registry), one in Sweden (Swedish JIA Clinical Registry) and one in UK (JIA Biologics Register).

The purpose of the registry surveillance studies is to collect additional longitudinal safety data from the clinical practice setting regarding the use of XELJANZ in patients with polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis

Physicians from those countries can learn more about these registries via the following contact information:

- BiKeR
  www.biker-register.de
- UK JIA Biologics Register
  https://sites.manchester.ac.uk/bcrdbspar/

Also for Medical information please contact Vivian Corporation at

+356 2258 8600

pv@viviancorp.com

OR

Pfizer Hellas S.A. Medical Information at +30 210 67 85 800.

Pfizer

XELJANZ®
(tofacitinib)