A practical guide to **XELJANZ** and **XELJANZ XR**

XELJANZ in RA, PsA, active JIA, AS and UC
XELJANZ XR in RA

Pr XELJANZ® (tofacitinib citrate)

Pr XELJANZ® XR (tofacitinib citrate)

RHEUMATOID ARTHRITIS

PrXELJANZ®/PrXELJANZ® XR (tofacitinib), in combination with methotrexate (MTX), is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA) in adult patients with moderately to severely active RA who have had an inadequate response to MTX and to one or more disease-modifying anti-rheumatic drugs (DMARDs). In cases of intolerance to MTX and other DMARDs, physicians may consider the use of XELJANZ/XELJANZ XR (tofacitinib) as monotherapy.

PSORIATIC ARTHRITIS

PrXELJANZ® (tofacitinib), in combination with methotrexate (MTX) or another conventional synthetic disease-modifying anti-rheumatic drug (DMARD), is indicated for reducing the signs and symptoms of psoriatic arthritis (PsA) in adult patients with active PsA when the response to previous DMARD therapy has been inadequate.

ACTIVE JUVENILE IDIOPATHIC ARTHRITIS

PrXELJANZ® (tofacitinib) is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA; rheumatoid factor positive [RF+] or negative [RF-] polyarthritis, extended oligoarthritis, and systemic JIA without systemic manifestations), and juvenile psoriatic arthritis (jPsA) in children weighing ≥40 kg, who have responded inadequately or are intolerant to tumour necrosis factor (TNF) inhibitors or when use of those therapies is inadvisable.

ANKYLOSING SPONDYLITIS

PrXELJANZ® (tofacitinib) is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to a biologic DMARD or when use of those therapies is inadvisable.

ULCERATIVE COLITIS

PrXELJANZ® (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) with an inadequate response, loss of response or intolerance to either conventional UC therapy or a TNFα inhibitor.

XELJANZ should not be used in combination with other Janus kinase (JAK) inhibitors, immunomodulating biologics (e.g., biologic DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

AS = Ankylosing spondylitis; JIA = Active Juvenile Idiopathic Arthritis; PsA = Psoriatic arthritis; RA = Rheumatoid arthritis; TNFa = Tumour necrosis factor alpha; UC = Ulcerative colitis

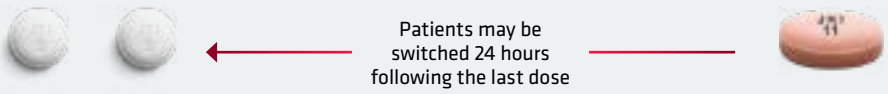
Convenient oral dosing options: XELJANZ twice daily in RA, PsA, active JIA and AS, as well as XELJANZ XR once daily in RA[1]

Recommended dose in RA

XELJANZ 5 mg BID

XELJANZ XR 11 mg QD

Switching between XELJANZ and XELJANZ XR where appropriate in RA



XELJANZ/XELJANZ XR is given orally with or without food. Swallow XELJANZ XR tablets whole and intact. Do not crush, split or chew.

Recommended dose in PsA, active JIA and AS

XELJANZ 5 mg BID

XELJANZ XR is not indicated for PsA, active JIA or AS.

An oral solution formulation that was used in the JIA clinical trials for patients weighing <40 kg is not marketed in Canada.

Combination therapy limitations of use

	RA	PsA	Active JIA
Combination therapy	XELJANZ/XELJANZ XR is used in combination with MTX.	XELJANZ is used in combination with MTX or another csDMARD. XELJANZ XR is not indicated for PsA.	XELJANZ may be used in combination with MTX. XELJANZ XR is not indicated for JIA.

XELJANZ should not be used in combination with other JAK inhibitors, immunomodulating biologics (e.g., biologic DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

Monotherapy	**In cases of intolerance to MTX and other DMARDs**, monotherapy may be considered.	XELJANZ is not indicated as monotherapy for PsA.	XELJANZ may be used as monotherapy.

	AS
Combination therapy	XELJANZ should not be used in combination with other JAK inhibitors, immunomodulating biologics (e.g., biologic DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine. XELJANZ XR is not indicated for AS.

For complete dosing information, please refer to the XELJANZ/XELJANZ XR Product Monograph.

BID = Twice daily; csDMARD = Conventional synthetic disease-modifying anti-rheumatic drug; DMARD = Disease-modifying anti-rheumatic drug; JAK = Janus kinase; MTX = Methotrexate; QD = Once daily

Convenient oral dosing option: XELJANZ twice daily in UC[1]

Recommended doses in UC

WEEK 0 — **WEEK 8 (at least)**

Induction phase	Maintenance phase
10 mg BID	**5 mg BID**
	
• Induction therapy should be discontinued in patients who show no evidence of adequate therapeutic benefit by Week 16	• Depending on therapeutic response during the induction phase, 10 mg BID may also be used for maintenance therapy in some patients • To minimize adverse effects, the lowest effective dose possible should be used for maintenance therapy • For the treatment of UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response

XELJANZ is given orally with or without food.

Combination therapy limitations of use

	UC
Combination therapy	XELJANZ should not be used in combination with other JAK inhibitors, immunomodulating biologics (e.g., biologic DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine. XELJANZ XR is not indicated for UC.

For complete dosing information, please refer to the XELJANZ/XELJANZ XR Product Monograph.

BID = Twice daily; DMARD = Disease-modifying anti-rheumatic drug; JAK = Janus kinase

Monitoring recommendations for XELJANZ and XELJANZ XR[1]

		Following 4–8 weeks after initiation			
	Baseline	4–8 weeks after initiation	Every 3 months	Every 6 months	Periodically
Lipids	■	■		■	
Lymphocytes	■	■	■		
Neutrophils	■	■	■		
Hemoglobin	■	■	■		
Vital signs*	■				■
Tuberculosis testing	■				■
Renal function	■				
Liver enzymes	■	Evaluate according to routine patient management			

Adapted from the XELJANZ/XELJANZ XR Product Monograph[1]

Routine monitoring of liver enzymes and prompt investigation of the cause of the liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

* Pulse rate and blood pressure

Dosing considerations[1]

Geriatrics (>65 years)	No dosage adjustment required.
Body weight (40–140 kg)	
Pediatrics (<18 years)	XELJANZ 5 mg **BID** for JIA patients weighing ≥40 kg. XELJANZ XR should not be used in this patient population. An oral solution formulation that was used in the JIA clinical trials for patients weighing <40 kg is not marketed in Canada.
Renal impairment	**Mild:** No dose adjustment required. Use XELJANZ with caution in patients with **moderate** (CLcr ≥30 and <60 mL/min) and **severe** (CLcr ≥15 and <30 mL/min) renal impairment, including patients with ESRD but not limited to those undergoing hemodialysis. • For those undergoing hemodialysis, a dose should be administered after the dialysis session on dialysis day. If a dose was taken before the procedure, supplemental doses are not recommended after. • Patients with severe renal insufficiency should remain on reduced dose even after hemodialysis. The recommended dose of XELJANZ is • 5 mg **BID** when the indicated dose in the presence of normal renal function is 10 mg BID. • 5 mg **QD** when the indicated dose in the presence of normal renal function is 5 mg BID. XELJANZ XR is not recommended in patients with moderate and severe renal impairment, including patients with ESRD undergoing hemodialysis. Consider XELJANZ 5 mg in these patients.
Hepatic impairment	**Mild:** No dose adjustment required. **Moderate:** The recommended dose of XELJANZ is: • 5 mg **BID** when the indicated dose in the presence of normal hepatic function is 10 mg BID • 5 mg **QD** when the indicated dose in the presence of normal hepatic function is 5 mg BID Use XELJANZ with caution in this population. XELJANZ XR should not be used. **Severe:** XELJANZ/XELJANZ XR is contraindicated.
Active infections (including chronic or localized infections)	XELJANZ/XELJANZ XR should not be administered.
Serious infections	Avoid treatment with XELJANZ/XELJANZ XR until infection is controlled.
Lymphocyte count <0.5 x 10^9 cells/L	Should not be initiated and if developed in patients taking XELJANZ/XELJANZ XR, should be discontinued.
Absolute neutrophil count (ANC) <1 x 10^9 cells/L	Avoid initiation in patients with ANC <1 x 10^9 cells/L. For patients who develop a persistent ANC of 0.5 to 1 x 10^9 cells/L, interrupt until ANC is >1 x 10^9 cells/L. In patients who develop an ANC <0.5 x 10^9 cells/L, discontinue treatment.
Hemoglobin level <90 g/L	XELJANZ/XELJANZ XR should not be initiated in patients with low hemoglobin values (i.e., <90 g/L). Treatment with XELJANZ/XELJANZ XR should be interrupted in patients who develop hemoglobin levels <80 g/L or whose hemoglobin level drops >20 g/L on treatment.
Pregnant women	XELJANZ/XELJANZ XR is contraindicated during pregnancy. Women of reproductive potential should be advised to use effective contraception during XELJANZ/XELJANZ XR treatment and for 4 to 6 weeks after the last dose.
Nursing women	XELJANZ/XELJANZ XR is contraindicated.
Patients at risk of thrombosis (including pulmonary embolism, deep venous thrombosis, and arterial thrombosis) **and patients with symptoms of thrombosis**	Avoid XELJANZ/XELJANZ XR in patients that may be at increased risk of thrombosis. Discontinue XELJANZ/XELJANZ XR and promptly evaluate patients with symptoms of thrombosis. For the treatment of UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

Adapted from the XELJANZ/XELJANZ XR Product Monograph[1]

BID = Twice daily; CLcr = Creatinine clearance; DMARD = Disease-modifying anti-rheumatic drug;
ESRD = End-stage renal disease; QD = Once daily

Hematological dosing recommendations[1]

Dose adjustment for lymphopenia	
Lab value of lymphocytes	**Recommendation**
Absolute lymphocyte count ≥0.5 x 10^9 cells/L	Maintain dose
Absolute lymphocyte count <0.5 x 10^9 cells/L (confirmed by repeated testing)	Discontinue XELJANZ/XELJANZ XR

Dose adjustment for neutropenia	
Lab value of neutrophils	**Recommendation**
ANC >1 x 10^9 cells/L	Maintain dose
ANC 0.5–1 x 10^9 cells/L	For persistent decreases in this range, interrupt or reduce administration with XELJANZ/XELJANZ XR until ANC is >1 x 10^9 cells/L • For patients receiving XELJANZ 5 mg BID, interrupt administration of XELJANZ until ANC reaches >1 x 10^9 cells/L, resume XELJANZ 5 mg BID **RA patients:** • When ANC reaches >1 x 10^9 cells/L, resume XELJANZ XR 11 mg QD **UC patients:** • For patients receiving XELJANZ 10 mg BID, reduce dose to 5 mg BID; When ANC reaches >1 x 10^9 cells/L, increase to XELJANZ 10 mg BID based on clinical response
ANC <0.5 x 10^9 cells/L (confirmed by repeated testing)	Discontinue XELJANZ/XELJANZ XR

Dose adjustment for anemia	
Lab value of hemoglobin	**Recommendation**
<20 g/L decrease and ≥90 g/L	Maintain dose
≥20 g/L decrease or <80 g/L (confirmed by repeated testing)	Interrupt administration of XELJANZ/XELJANZ XR until hemoglobin values have normalized (>80 g/L)

Adapted from the XELJANZ/XELJANZ XR Product Monograph[1]

Neutrophils and lymphocytes

In RA clinical trials, confirmed neutrophil decreases in ANC <1 x 10^9 cells/L occurred in 0.08% of patients in the XELJANZ 5 mg BID group during 12 months of exposure. There were no confirmed neutrophil decreases in ANC <0.5 x 10^9 cells/L observed in any treatment group.

In RA clinical trials, confirmed decreases in absolute lymphocyte counts <0.5 x 10^9 cells/L occurred in 0.2% of patients for the XELJANZ 5 mg BID group during 12 months of exposure.

In an RA Phase 2/3 open-label, uncontrolled, long-term extension follow-up trial (up to 114 months), cases of neutropenia have been reported in 4.0% of patients (0.97 events/100 patient-years) treated with XELJANZ 5 mg BID and 0.4% had confirmed decreases in ANC <1 x 10^9 cells/L.

In an RA Phase 2/3 open-label, uncontrolled, long-term extension follow-up trial (up to 114 months), cases of lymphopenia have been reported in 4.5% (1.07 events/100 patient-years) of patients treated with XELJANZ 5 mg BID and 1.1% had confirmed decreases in absolute lymphocyte counts <0.5 x 10^9 cells/L.

In the controlled clinical trials in PsA, AS and JIA, changes in hematologic findings observed with XELJANZ treatment were similar to the changes observed in Phase 3 clinical trials in RA.

In UC clinical studies, changes in neutrophils observed with XELJANZ treatment were similar to the changes observed in RA clinical studies.

In a 52-week maintenance UC study, a single absolute lymphocyte count <0.5 x 10^9 cells/L was reported in 2.6% of patients in the XELJANZ 10 mg BID group and was not reported in patients in the XELJANZ 5 mg BID group and the placebo group. No patients in any treatment group had confirmation of a lymphocyte count <0.5 x 10^9 cells/L based on two sequential tests.

Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts <0.5 x 10^9 cells/L were associated with an increased incidence of treated and serious infections.

Drug interactions[1]

Drugs that **do not** require a dose adjustment when co-administered with XELJANZ/XELJANZ XR: methotrexate (MTX), CYP3A4 substrates (e.g., midazolam), oral contraceptives (ethinyl estradiol and levonorgestrel), a substrate of organic cationic transporter and multidrug and toxic compound extrusion (metformin).

In vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations exceeding 80 times the steady state C_{max} of a 5 and 10 mg BID dose in patients treated with tofacitinib (the recommended XELJANZ dose in RA or PsA is 5 mg BID).

In vitro, tofacitinib is a substrate for multidrug resistance (MDR) 1, but not for breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP) 1B1/1B3, or organic cationic transporter (OCT) 1/2. In vitro data indicate that the potential for tofacitinib to inhibit transporters such as P-glycoprotein, MDR1, organic anionic transporter (OAT) P1B1/1B3, OCT2, OAT1/3, cationic transporters or multidrug resistance-associated protein (MRP) at therapeutic concentrations is also low.

Caution should be observed if XELJANZ/XELJANZ XR is used concomitantly with other drugs that lower heart rate and/or prolong the PR interval, such as antiarrhythmics, beta blockers, alpha$_2$-adrenoceptor agonists, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1-phosphate receptor modulators, and some HIV protease inhibitors.

BID = Twice daily

Drug, food and herb interactions[1]

Category	Example	Clinical comment
Potent inhibitors of cytochrome CYP3A4	**Ketoconazole**	When co-administered, the recommended dose of XELJANZ is: • 5 mg **BID** when the indicated dose is 10 mg BID • 5 mg **QD** when the indicated dose is 5 mg BID Combined use with XELJANZ XR is not recommended.
One or more medications that result in moderate inhibition of CYP3A4 and potent inhibition of CYP2C19	**Fluconazole**	
Potent immunosuppressive drugs	**Tacrolimus and cyclosporine**	Combined use with XELJANZ/XELJANZ XR is not recommended.
Potent inducers of CYP3A4	**Rifampin**	Combined use with XELJANZ/XELJANZ XR is not recommended. Co-administration of XELJANZ/XELJANZ XR with potent inducers of CYP3A4 may result in loss of or reduced clinical response/efficacy.
Foods that affect CYP450 3A-mediated metabolism	**Grapefruit juice**	Co-administration with XELJANZ/XELJANZ XR should be avoided.
Herbs that induce CYP3A4	**St. John's wort**	Co-administration with XELJANZ/XELJANZ XR may result in loss of or reduced clinical response.

Adapted from the XELJANZ/XELJANZ XR Product Monograph[1]

BID = Twice daily; QD = Once daily

Specific safety considerations[1]

Lipids

Treatment with XELJANZ was associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.

In controlled RA clinical studies, mean LDL and HDL cholesterol increased by 14% and 16% from baseline, respectively, in the XELJANZ 5 mg BID arm. Mean LDL/HDL ratios were essentially unchanged in patients treated with XELJANZ. In the RA long-term safety population, elevations in the lipid parameters remained consistent with what was seen in the controlled clinical studies.

In controlled RA clinical trials, elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) generally reached maximal effects at 6 weeks following initiation of XELJANZ. Lipid-lowering medication was initiated by 4.4% of patients treated with XELJANZ 5 mg BID during five controlled RA clinical trials.

Increases of total cholesterol, LDL cholesterol, and HDL cholesterol were also reported in a post-authorization safety study. Mean percent increases in LDL and HDL at 12 months were 13.80% and 11.71% in the XELJANZ 5 mg BID arm, and 17.04% and 13.63% in the XELJANZ 10 mg BID arm, respectively.

In controlled clinical trials in PsA, AS and JIA, changes in clinical chemistry findings observed with XELJANZ treatment were similar to the changes observed in Phase 3 clinical trials in RA.

Assessment of lipid parameters should be performed at baseline and approximately 4–8 weeks following initiation of XELJANZ/XELJANZ XR therapy, and every 6 months thereafter. Patients should be managed according to local clinical guidelines for the management of hyperlipidemia.

Liver enzymes

Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo.

Evaluate liver enzymes before initiating XELJANZ and thereafter according to routine patient management.

Prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury (DILI). If increases in alanine transaminase (ALT) or aspartate transaminase (AST) are observed and DILI is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until the diagnosis is excluded.

Most of the liver enzyme abnormalities in RA and PsA patients occurred in studies with background DMARD (primarily MTX) therapy.

One case of DILI was reported in an RA patient treated with tofacitinib 10 mg BID (not a recommended dose in RA) for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT with values greater than 3x ULN associated concurrently with total bilirubin value greater than 2x ULN, which required hospitalization and a liver biopsy.

Elevations of ALT and AST were reported more frequently in patients taking XELJANZ compared with patients taking TNFi in a post-authorization safety study. In RA patients taking XELJANZ 5 mg BID, the ALT and AST elevations greater than 3x ULN were observed in 6.01% and 3.21% of patients, respectively. In RA patients taking XELJANZ 10 mg BID (not a recommended dose), the ALT and AST elevations greater than 3x ULN were observed in 6.51% and 4.57% of patients, respectively.

In UC patients, XELJANZ treatment with 5 and 10 mg BID was also associated with an increased incidence of liver enzyme elevation compared to placebo, with a trend for higher incidence with 10 mg BID as compared to 5 mg BID.

There were three pediatric patients in Study JIA-1 receiving 5 mg tofacitinib BID who experienced elevated hepatic enzymes that decreased upon discontinuation and were adjudicated as possible or probable DILI.

The impact of XELJANZ/XELJANZ XR on chronic viral hepatitis reactivation is unknown. XELJANZ/XELJANZ XR has not been studied in patients with positive hepatitis B virus or hepatitis C virus serology, and should therefore not be used in these populations.

XELJANZ/XELJANZ XR is contraindicated in patients with severe hepatic impairment. Dose adjustment of XELJANZ is recommended for patients with moderate hepatic impairment.

Asian patients

XELJANZ/XELJANZ XR should be used with caution in Asian patients:

- Asian patients have an increased risk of herpes zoster and opportunistic infections and treatment with XELJANZ was associated with increased rates of infections in Asian patients compared to other races
- Increased risk of interstitial lung disease
- An increased incidence of some adverse events such as elevated transaminases (ALT, AST) and decreased white blood cells (WBCs) have been observed

Musculoskeletal

Treatment with XELJANZ was associated with increases in creatine kinase (CK). Maximum effects were generally observed within 6 months.

Rhabdomyolysis was reported in one patient treated with XELJANZ.

CK levels should be checked in patients with symptoms of muscle weakness and/or muscle pain to evaluate for evidence of rhabdomyolysis.

Increases in CK were reported more frequently in patients treated with XELJANZ 10 mg as compared to those treated with 5 mg BID.

Pediatrics

The safety and efficacy of XELJANZ in pediatric patients for indications other than JIA have not been established. Safety and efficacy of XELJANZ XR in children <18 years of age has not yet been established.

An oral solution formulation used in the JIA clinical trials for patients weighing <40 kg is not marketed in Canada.

Geriatrics

The frequency of adverse events including serious infections, all-cause mortality, cardiovascular events, malignancies, non-melanoma skin cancer, gastrointestinal perforations, interstitial lung disease, venous thromboembolism, and arterial thromboembolism in XELJANZ-treated subjects 65 years of age and older was higher than among those under the age of 65.

Reproductive health

Based on findings in animal studies, XELJANZ/XELJANZ XR may cause decreased fertility when administered to females and may cause fetal harm when administered to a pregnant woman.

Serious infections

Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

BID = Twice daily; DMARD = Disease-modifying anti-rheumatic drug; MTX = Methotrexate; ULN = Upper limit of normal

Specific safety considerations[1]

The most common serious infections reported with XELJANZ included pneumonia, urinary tract infection, cellulitis, herpes zoster, bronchitis, septic shock, diverticulitis, gastroenteritis, appendicitis and sepsis.

Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcus, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infections, listeriosis and aspergillosis were reported with XELJANZ.

Some patients have presented with disseminated rather than localized disease, and patients were often taking concomitant immunomodulating agents such as MTX or corticosteroids. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

Reported infections with XELJANZ/XELJANZ XR also include bacterial, viral, and other infections due to opportunistic pathogens.

A dose-dependent increase in serious infections was observed in patients treated with XELJANZ compared to TNF inhibitors in a post-authorization safety study. Some of these serious infections resulted in death. Opportunistic infections were also reported in the study.

Caution is recommended when administering XELJANZ/XELJANZ XR in the following patients:

- geriatric and diabetic patients, as they have a higher incidence of infections in general
- patients with a history of chronic lung disease, as they may be more prone to infections

Events of interstitial lung disease (some of which had a fatal outcome) have been reported in RA patients treated with XELJANZ in clinical trials and in the post-marketing setting.

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection.

Patients treated with XELJANZ 10 mg BID are at higher risk of serious infections, and herpes zoster infections compared to those treated with 5 mg BID. The incidence rate per 100 person-years (PYs) for herpes zoster opportunistic infections in the UC 52-week maintenance study was higher in patients treated with XELJANZ 10 mg BID (6.64) as compared to XELJANZ 5 mg BID (2.05) or placebo (0.97).

The risk of opportunistic infections is higher in Asian geographic regions.

XELJANZ/XELJANZ XR should not be administered in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating XELJANZ/XELJANZ XR in patients:

- with chronic or recurrent infections
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or travelled 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/XELJANZ XR. XELJANZ/XELJANZ XR should 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/XELJANZ XR 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.

If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled.

Tuberculosis:

Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections including active tuberculosis, which may present with pulmonary or extrapulmonary disease.

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

- who have been exposed to tuberculosis or
- who have resided or travelled in areas of endemic tuberculosis or endemic mycoses

Patients should be evaluated and tested for latent or active tuberculosis (TB) infection prior to administration of XELJANZ/XELJANZ XR and periodically (e.g., annually) while taking XELJANZ/XELJANZ XR.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis during and after treatment with XELJANZ/XELJANZ XR, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

XELJANZ/XELJANZ XR should not be given to patients with active TB.

Antituberculosis therapy should also be considered prior to administration of XELJANZ/XELJANZ XR in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but have risk factors for tuberculosis infection.

Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering XELJANZ/XELJANZ XR.

Malignancies

Lymphoma and other malignancies have been observed in patients treated with XELJANZ including but not limited to: lymphomas, lung cancer, breast cancer, colorectal cancer, gastric cancer, melanoma, prostate cancer, pancreatic cancer and renal cell carcinoma. 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.

Patients with RA, particularly those with highly active disease, may be at a higher risk (several fold) than the general population for the development of lymphoma.

An increase in malignancies, including lung cancer, were observed in RA patients 50 years or older with at least one additional cardiovascular (CV) risk factor who were taking tofacitinib compared with TNF inhibitors.

Caution should be applied when using XELJANZ/XELJANZ XR in geriatric patients, patients who are current or past smokers, and patients with other malignancy risk factors.

Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy.

Non-melanoma skin cancers (NMSCs)

NMSCs have been reported in patients treated with XELJANZ.

NMSC is a dose-related adverse reaction, with a greater risk in patients treated with 10 mg BID of XELJANZ than in patients treated with 5 mg BID. An increase in overall NMSCs, including cutaneous squamous cell carcinomas was observed in patients treated with XELJANZ compared to TNF inhibitors in a post-authorization safety study.

BID = Twice daily; MTX = Methotrexate; TNF = Tumour necrosis factor

Specific safety considerations[1]

Caution should be used when treating geriatric patients and patients with a prior history of NMSC, where a higher incident of NMSC was observed. Periodic skin examination is recommended.

In a UC 52-week maintenance study, NMSC was reported in 3 patients (1.5%) treated with 10 mg BID, as compared with no reported events in patients treated with 5 mg BID and 1 patient (0.5%) treated with placebo. In a long-term open-label extension study, NMSC was reported in 6 patients in the 10 mg BID group and 2 patients in the 5 mg BID group.

Cardiovascular

Thrombosis:

Thrombosis, including pulmonary embolism, deep venous thrombosis and arterial thrombosis, was observed at an increased incidence in RA patients treated with XELJANZ in a post-authorization safety study.

In this post-authorization safety study, patients treated with XELJANZ 10 mg BID had a higher rate of all-cause mortality, including sudden CV death, and thrombosis compared to those treated with XELJANZ 5 mg BID or TNF blockers. Many of these events were serious and some resulted in death.

A dosage of XELJANZ 10 mg BID or XELJANZ XR 22 mg QD is not recommended for the treatment of RA or PsA.

In a long-term extension study in patients with UC, four cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg BID, including one death in a patient with advanced cancer.

For the treatment of UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

XELJANZ/XELJANZ XR should be avoided in patients that may be at increased risk of thrombosis.

Discontinue XELJANZ/XELJANZ XR and promptly evaluate patients with symptoms of thrombosis.

Major Adverse Cardiovascular Events:

Major adverse cardiovascular events (MACE), including events of myocardial infarction, were observed in patients who were treated with XELJANZ 5 mg BID, XELJANZ 10 mg BID or TNF inhibitors in a post-authorization safety study. An increase in non-fatal myocardial infarctions was observed in patients treated with tofacitinib compared to TNF inhibitors. MACE, including events of myocardial infarction, were more common in geriatric patients and in patients who were current or past smokers. Caution should be used in treating geriatric patients, patients who are current or past smokers, and patients with other CV risk factors.

Heart rate decrease and PR interval prolongation:

XELJANZ caused a decrease in heart rate and a prolongation of the PR interval.

Caution should be observed in patients with a low heart rate at baseline (<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure.

Concomitant medications that result in a decrease in heart rate and/or PR interval prolongation should be avoided to the extent possible during treatment with XELJANZ/XELJANZ XR.

Immunizations

No data are available on the secondary transmission of injections by live vaccines to patients receiving XELJANZ/XELJANZ XR.

BID = Twice daily; CV = Cardiovascular; QD = Once daily; TNF = Tumour necrosis factor

All patients should be brought up to date with all immunizations in agreement with current immunization guidelines prior to starting XELJANZ/XELJANZ XR. Concurrent use with live vaccines is not recommended. The interval between live vaccinations and initiation of XELJANZ/XELJANZ XR therapy should be in accordance with current vaccination guidelines regarding immunomodulatory agents.

Live zoster vaccine should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus. Vaccination should occur at least 2 weeks but preferably 4 weeks before initiating XELJANZ/XELJANZ XR.

Interstitial lung disease

Events of interstitial lung disease (ILD) have been reported in RA clinical trials with XELJANZ, although the role of JAK inhibition in these events is not known. All patients who developed ILD were taking concomitant methotrexate, corticosteroids and/or sulfasalazine, which have been associated with ILD.

Events of interstitial lung disease (some of which had a fatal outcome) have been reported in RA patients treated with XELJANZ in clinical trials and in the post-marketing setting.

Endocrine and Metabolism

Hypoglycaemia in patients treated for diabetes:

There have been reports of hypoglycaemia following initiation of tofacitinib in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycaemia occurs.

Retinal venous thrombosis

Retinal venous thrombosis (RVT) has been reported in patients treated with tofacitinib. Patients should be advised to promptly seek medical care if they experience symptoms suggestive of RVT.

Fractures

Fractures of multiple types, including osteoporotic fractures, have been observed in patients treated with XELJANZ/XELJANZ XR in clinical studies and the post-marketing setting. Caution should be applied when using XELJANZ/XELJANZ XR in patients with known risk factors for fractures such as geriatric patients, female patients, and patients using corticosteroids.

Gastrointestinal perforations

Events of gastrointestinal perforation have been reported with XELJANZ in rheumatoid arthritis patients, although the role of JAK inhibition in these events is not known. Many patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. The relative contribution of these concomitant medications versus XELJANZ to the development of gastrointestinal perforations is not known.

XELJANZ/XELJANZ XR should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., use of concomitant NSAIDs and/or corticosteroids, patients with a history of diverticulitis).

Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

BID = Twice daily; QD = Once daily; TNF = Tumor necrosis factor

Specific safety considerations[1]

Reporting of adverse events

Healthcare professionals can report any adverse events associated with the use of XELJANZ/XELJANZ XR to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

Any suspected adverse reactions may also be reported to Pfizer Medical Information by calling 1-800-463-6001.

When reporting adverse events, please provide as much information as possible, including information about medical history, any concomitant medication, onset and treatment dates.

Contraindications:

XELJANZ/XELJANZ XR is contraindicated:

- In patients with known hypersensitivity to tofacitinib or ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- In patients with severe hepatic impairment.
- During pregnancy and breastfeeding.

Most serious warnings and precautions:

Serious Infections: Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled. Reported infections include: active tuberculosis (may be presented with pulmonary or extrapulmonary disease; patients should be tested for latent tuberculosis before and during use), invasive fungal infections (may be presented with disseminated disease), bacterial, viral, and other infections due to opportunistic pathogens.

Treatment with XELJANZ/XELJANZ XR should not be initiated in patients with active infections including chronic or localized infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

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. An increase in malignancies, including lung cancer, were observed in rheumatoid arthritis patients 50 years or older with at least one additional cardiovascular (CV) risk factor who were taking tofacitinib compared with TNF inhibitors. Caution should be applied when using XELJANZ/XELJANZ XR in geriatric patients, patients who are current or past smokers, and patients with other malignancy risk factors.

Thrombosis: Rheumatoid arthritis (RA) patients with at least one cardiovascular (CV) risk factor had a higher rate of all-cause mortality and thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, with XELJANZ 10 mg twice daily (not a recommended dose in RA) compared to those treated with 5 mg twice daily or TNF blockers. Many of these adverse events were serious and some resulted in death. Avoid XELJANZ/XELJANZ XR in patients at risk of thrombosis. Discontinue XELJANZ/XELJANZ XR and promptly evaluate patients with symptoms of thrombosis. For patients with ulcerative colitis (UC), use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

Major Adverse Cardiovascular Events: Major adverse cardiovascular events, including non-fatal myocardial infarction, were observed more frequently with tofacitinib compared to TNF inhibitors in rheumatoid arthritis patients who were 50 years or older with at least one additional CV risk factors. Caution should be applied when using XELJANZ/XELJANZ XR in geriatric patients, patients who are current or past smokers, and patients with other CV risk factors.

Other relevant warnings and precautions:

- Combined use of XELJANZ/XELJANZ XR with potent immunosuppressive drugs has not been studied and is not recommended.
- Effective contraception should be used during XELJANZ/XELJANZ XR treatment and for 4–6 weeks after the last dose.
- Based on animal studies, XELJANZ/ XELJANZ XR may cause decreased fertility when administered to females and may cause fetal harm when administered to a pregnant woman.
- Discontinue XELJANZ/XELJANZ XR promptly if a hypersensitivity reaction is suspected and evaluate its potential cause or causes.
- Risk of viral reactivation, including herpes zoster.
- All patients should be brought up to date with all immunizations in agreement with current immunization guidelines prior to starting XELJANZ/XELJANZ XR. Concurrent use with live vaccines is not recommended.
- Live zoster vaccine should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus. Vaccination should occur at least 2 weeks but preferably 4 weeks before initiating XELJANZ/XELJANZ XR.
- Risk of malignancies, including lung cancer and lymphomas, and nonmelanoma skin cancer. Caution should be used in treating geriatric patients, patients who are current or past smokers, and patients with other malignancy risk factors.
- Risk of lymphopenia, neutropenia, anemia, and lipid elevations.
- Consideration should be given to lymphocyte counts when assessing individual patient risk of infection because the risk of infection may be higher with increasing degrees of lymphopenia.
- In patients with moderate hepatic impairment, the recommended dose of XELJANZ is half the total daily dose indicated for patients with normal hepatic function. XELJANZ XR should not be used in this population. XELJANZ/XELJANZ XR is contraindicated in patients with severe hepatic impairment and should not be used in patients with positive hepatitis B virus or hepatitis C virus serology.
- In patients with moderate and severe renal impairment, including patients with end-stage renal disease (ESRD) but not limited to those undergoing hemodialysis, the recommended dose of XELJANZ is half the total daily dose indicated for patients with normal renal function.
- Increased incidence of liver enzyme elevations.
- Use caution when administering XELJANZ XR to patients with pre-existing severe gastrointestinal narrowing.
- Use with caution in patients with a risk or history of interstitial lung disease (ILD).
- XELJANZ XR is not indicated for pediatric use.
- Caution should be used when treating geriatric patients and patients with diabetes because of an increased risk of serious infections.
- Hypoglycaemia in patients treated for diabetes.
- Caution should be used in patients with a history of chronic lung disease as they may be more prone to infections.
- Use with caution in Asian patients because of an increased risk of events compared to other races including: herpes zoster, opportunistic infections and ILD.
- Risk of gastrointestinal perforation. Use with caution in patients who may be at increased risk for gastrointestinal perforation.
- Increases in creatine kinase.
- Decrease in heart rate and a prolongation of the PR interval. Caution should be observed in patients with a low heart rate at baseline (<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure.
- Avoid XELJANZ/XELJANZ XR in patients that may be at increased risk of thrombosis. Discontinue XELJANZ/XELJANZ XR and promptly evaluate patients with symptoms of thrombosis.
- An increase in non-fatal myocardial infarctions was observed in patients treated with tofacitinib compared to TNF inhibitors. Caution should be used in treating geriatric patients, patients who are current or past smokers, and patients with other CV risk factors.
- Caution should be applied when using XELJANZ/XELJANZ XR in patients with known risk factors for fractures such as geriatric patients, female patients, and patients using corticosteroids.
- Retinal venous thrombosis (RVT) has been reported in patients treated with tofacitinib. Patients should be advised to promptly seek medical care if they experience symptoms suggestive of RVT.

For more information:

Please consult the Product Monograph at https://www.pfizer.ca/en/our-products/xeljanz-tofacitinib and an Important Safety Information Advisory available at https://recalls-rappels.canada.ca/en/alert-recall/janus-kinase-inhibitors-and-risk-major-adverse-cardiovascular-events-thrombosis for important information relating to adverse reactions, interactions, and dosing information, which have not been discussed in this piece. The Product Monograph is also available by calling 1-800-463-6001.

Reference: 1. Pfizer Canada ULC. XELJANZ/XELJANZ XR Product Monograph. April 5, 2024

Convenient oral dosing options:

XELJANZ twice daily in RA, PsA, active JIA, AS and UC
XELJANZ XR once daily in RA[1]

Patient Support Program

PfizerFlex

Experienced, Dedicated Team

Comprehensive support to help your patients manage their XELJANZ or XELJANZ XR treatment including:

- **Enrolment designed to be simple and rapid**
- A dedicated **program coordinator**
- **Reimbursement navigation** and financial assistance
- **Education** and adherence support

The PfizerFlex Support Program can provide quick access to XELJANZ or XELJANZ XR.

Enrol your patients by calling **1-855-935-3539**.

Direct your patients to visit **PfizerFlex.ca** for information on support services offered by the program.

To learn more, talk to your Pfizer representative.

VISIT THE XELJANZPRO.CA WEBSITE

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PP-XEL-CAN-1057-EN

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REVIEWED BY PAAB

XELJANZ (tofacitinib citrate)

XELJANZ XR (tofacitinib citrate)