XELJANZ®▼ (tofacitinib citrate)
PRESCRIBER TREATMENT INITIATION CHECKLIST
(FOR USE WHEN FIRST STARTING PATIENTS ON XELJANZ TREATMENT)

Patient: _____ Date: _____

Introduction
This treatment initiation checklist intends to remind you of the risks associated with the use of tofacitinib and the recommended tests BEFORE FIRST ADMINISTERING tofacitinib. The checklist should be used in conjunction with the XELJANZ Summary of Product Characteristics (SmPC). Tofacitinib should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of the conditions (listed below) for which it is indicated.

RHEUMATOID ARTHRITIS (RA)
XELJANZ (tofacitinib citrate) is an inhibitor of Janus kinases (JAKs) that was granted a marketing authorisation in the EU (22 March 2017) for use in combination with methotrexate (MTX) in adult patients with moderate to severe active RA who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate. The recommended dose is 5 mg film-coated tablets given twice daily or 11 mg prolonged-release tablets given once daily, which should not be exceeded.

PSORIATIC ARTHRITIS (PsA)
Tofacitinib has also received marketing authorisation in the EU for use in combination with MTX in adult patients with active PsA who have had an inadequate response or who have been intolerant to a prior DMARD therapy. The recommended dose is 5 mg film-coated tablets given twice daily or 11 mg prolonged release tablets given once daily, which should not be exceeded.

ULCERATIVE COLITIS (UC)
Tofacitinib has also received marketing authorisation in the EU for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

Induction treatment for UC (weeks 0 through week 8, with extension to week 16 as necessary)
The recommended dose for UC is 10 mg 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 twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. Tofacitinib 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 given orally twice daily.

The 10 mg twice daily maintenance dose is not recommended in patients with 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 given orally twice daily may be considered if the patient experiences a decrease in response on tofacitinib 5 mg 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 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 tofacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Retreatment in UC: if therapy is interrupted, restarting treatment with tofacitinib can be considered. If there has been a loss of response, reinduction with tofacitinib 10 mg 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 twice daily therapy.

JUVENILE IDIOPATHIC ARTHRITIS (JIA)
Tofacitinib has also received marketing authorisation in the EU 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.

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

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.

ANKYLOSING SPONDYLITIS (AS)
Tofacitinib has also received marketing authorisation in the EU for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy. The recommended dose is 5 mg film-coated tablets given twice daily.

SPECIAL WARNINGS & PRECAUTIONS
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 (MI) and malignancies (excluding non-melanoma skin cancer), particularly lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors.

Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT) have been observed in patients taking tofacitinib. A dose-dependent increased risk for VTE was observed in the randomised post-authorisation safety study of tofacitinib, compared to TNF inhibitors.

Events of serious infections, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy (including lymphoma and lung cancer), non-melanoma skin cancer, gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities have been also reported in patients treated with tofacitinib in clinical studies.

Patients should be closely monitored for any signs and symptoms, and laboratory abnormalities for early identification of these risks.

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

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PRIOR TO ADMINISTRATION OF TOFACITINIB TO PATIENTS, PLEASE CHECK THE FOLLOWING:

IS THE PATIENT OVER 65 YEARS OF AGE? Yes ☐ No ☐

If Yes:
Have you considered alternative treatment considering the increased risk of serious infections, myocardial infarction and malignancies with tofacitinib? ☐ ☐

Note the following:

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

IS THE PATIENT OVER 65 YEARS OF AGE, A CURRENT OR PAST SMOKER, OR DO THEY HAVE OTHER CARDIOVASCULAR RISK FACTORS? Yes ☐ No ☐

If Yes:
Are there any suitable treatment alternatives available for the patient? ☐ ☐

Note the following:

- Given the increased risk of major adverse cardiovascular events (MACE), tofacitinib should only be used in these patients if no suitable treatment alternatives are available

HAVE YOU DISCUSSED WITH THE PATIENT HOW TO RECOGNISE SYMPTOMS OF MI AND TO PROMPTLY SEEK MEDICAL ATTENTION IF THEY EXPERIENCE THESE? Yes ☐ No ☐

Note the following:

- The patient should be informed to seek medical attention if they develop sudden severe chest pain or tightness (that may spread to arms, jaw, neck and back), shortness of breath, cold sweat, light headedness or sudden dizziness

IS THE PATIENT OVER 65 YEARS OF AGE, A CURRENT OR PAST SMOKER OR DO THEY HAVE OTHER MALIGNANCY RISK FACTORS (E.G. CURRENT OR HISTORY OF MALIGNANCY OTHER THAN A SUCCESSFULLY TREATED NON-MELANOMA SKIN CANCER)? Yes ☐ No ☐

If Yes:
Are there any suitable treatment alternatives available for the patient? ☐ ☐

Note the following:

- Given the increased risk of malignancy, tofacitinib should only be used if no suitable treatment alternatives are available

DOES THE PATIENT HAVE ANY RISK FACTORS FOR VTE? Yes ☐ No ☐

Note the following:

- VTE risk factors include (but are not limited to):
  - Previous VTE
  - Patients undergoing major surgery
  - Immobilisation
  - Myocardial infarction (within previous 3 months)
  - Heart failure
  - Use of combined hormonal contraceptives or hormonal replacement therapy
  - Inherited coagulation disorder
  - Malignancy
- Additional VTE risk factors that should be considered include:
  - Age
  - Obesity (Body Mass Index [BMI] ≥30)
  - Diabetes
  - Hypertension
  - Smoking status
- Tofacitinib 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

HAVE YOU DISCUSSED WITH THE PATIENT HOW TO RECOGNISE SYMPTOMS OF VTE AND TO PROMPTLY SEEK MEDICAL ATTENTION IF THEY EXPERIENCE THESE? Yes ☐ No ☐

Note the following:

- The patient should be informed to seek medical attention if they develop 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
- Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication

DOES THIS PATIENT HAVE ANY EVIDENCE OF HEPATIC IMPAIRMENT (CHILD-PUGH A, B OR C)? Yes ☐ No ☐

Note the following:

- Severe hepatic impairment (Child-Pugh C): Tofacitinib should not be used
- Moderate hepatic impairment (Child-Pugh B):
  - RA, PsA and AS: Tofacitinib dose should be reduced to 5 mg once daily
  - UC: 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. 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
  - JIA: Tofacitinib dose should be reduced to 5 mg once daily or weight-based equivalent once daily when the indicated dose in the presence of normal hepatic function is 5 mg (or weight-based equivalent) twice daily
- Mild hepatic impairment (Child-Pugh A): No dose adjustment is required

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DOES THIS PATIENT HAVE ANY EVIDENCE OF RENAL IMPAIRMENT (BASED ON CREATININE CLEARANCE)? Yes ☐ No ☐

Note the following:

- Severe renal impairment (creatinine clearance <30 mL/min):
  - RA, PsA and AS: Tofacitinib dose should be reduced to 5 mg once daily
  - UC: 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. 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.
  - JIA: Tofacitinib dose should be reduced to 5 mg once daily or weight-based equivalent once daily when the indicated dose in the presence of normal renal function is 5mg (or weight-based equivalent) twice daily.
  - Patients with severe renal impairment should remain on a reduced dose even after haemodialysis
- Mild (creatinine clearance 50–80mL/min) or moderate renal impairment (creatinine clearance 30–49 mL/min):
  No dose adjustment is required

IS THIS PATIENT CURRENTLY PREGNANT OR DOES THIS PATIENT INTEND TO BECOME PREGNANT? Yes ☐ No ☐

Have you informed female patients that:

- Use of tofacitinib during pregnancy is contraindicated? ☐ ☐
- Women of childbearing potential should use effective contraception during treatment with tofacitinib and for at least 4 weeks after the last dose? ☐ ☐

IS THIS PATIENT BREASTFEEDING OR DOES THIS PATIENT INTEND TO BREASTFEED? Yes ☐ No ☐

- Have you informed female patients that use of tofacitinib during breastfeeding is contraindicated? ☐ ☐

IS THIS PATIENT CURRENTLY TAKING ANY BIOLOGICS OR ANY POTENT IMMUNOSUPPRESSANTS? Yes ☐ No ☐

Note the following:

- Tofacitinib should be avoided in combination with biologics such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, selective co-stimulation modulators and potent immunosuppressants such as azathioprine, cyclosporine, 6-mercaptopurine, and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection

IS THIS PATIENT CURRENTLY TAKING ANY POTENT INHIBITORS OF CYTOCHROME P450 (CYP) 3A4 (E.G., KETOCONAZOLE) OR TAKING ONE OR MORE CONCOMITANT MEDICINAL PRODUCTS THAT RESULT IN BOTH MODERATE INHIBITION OF CYP3A4 AS WELL AS POTENT INHIBITION OF CYP2C19 (E.G., FLUCONAZOLE)? Yes ☐ No ☐

Note the following:

- If yes, tofacitinib total daily dose should be reduced by half
- Tofacitinib dose should be reduced to 5 mg once daily in patients receiving 5 mg twice daily or patients receiving 11 mg prolonged released tablet once daily
- Tofacitinib dose should be reduced to 5 mg twice daily in patients receiving 10 mg twice daily

IS THIS PATIENT CURRENTLY TAKING ANY POTENT CYP INDUCERS (E.G., RIFAMPICIN)? Yes ☐ No ☐

Note the following:

- Coadministration of tofacitinib with potent CYP inducers (e.g., rifampicin) may result in a loss of or reduced clinical response. Coadministration of potent inducers of CYP3A4 with tofacitinib is not recommended

DOES THIS PATIENT HAVE ANY ACTIVE INFECTIONS INCLUDING LOCALISED INFECTIONS? Yes ☐ No ☐

Note the following:

- Tofacitinib should not be initiated in patients with active TB, serious infections, such as sepsis, or opportunistic infections
- The risks and benefits of treatment should be considered prior to initiating tofacitinib in 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 (e.g., history of chronic lung disease, diabetes or taking corticosteroids)

HAS THIS PATIENT BEEN EVALUATED AND TESTED FOR LATENT OR ACTIVE TB? Yes ☐ No ☐

Note the following:

- Patients should be evaluated and tested for latent or active TB prior to and per applicable guidelines during administration of tofacitinib
- Patients with latent TB should be treated with standard antimycobacterial therapy before administering tofacitinib

HAS ANTI-TB THERAPY BEEN CONSIDERED, PARTICULARLY IF THIS PATIENT HAS A HISTORY OF LATENT OR ACTIVE TB? N/A ☐ Yes ☐ No ☐

Note the following:

- Antituberculosis therapy should be considered prior to administration of tofacitinib in patients who test negative for TB but who have a history of latent or active TB and where an adequate course of treatment cannot be confirmed, or those who test negative but who have risk factors for TB infection
- Consultation with a healthcare professional with expertise in the treatment of TB is recommended to aid in the decision about whether initiating antituberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy

HAVE YOU INFORMED PATIENTS THAT VIRAL REACTIVATION HAS BEEN OBSERVED IN PATIENTS TAKING TOFACITINIB?	Yes ☐	No ☐

Note the following:

- Patients treated with tofacitinib who are Japanese or Korean, or patients with longstanding RA who have previously received two or more biological DMARDs, or patients with an ALC less than (<1.00 cells x10^9/L), or patients treated with 10 mg twice daily may have an increased risk of herpes zoster

HAS THIS PATIENT BEEN EVALUATED AND SCREENED FOR VIRAL HEPATITIS IN ACCORDANCE WITH PUBLISHED GUIDELINES?	Yes ☐	No ☐

Note the following:

- The impact of tofacitinib on chronic viral hepatitis reactivation is unknown
- Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with tofacitinib

DOES THIS PATIENT HAVE A HISTORY OF DIVERTICULITIS?	Yes ☐	No ☐

Note the following:

- Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis, patients with concomitant use of corticosteroids and/or non-steroidal anti-inflammatory drugs [NSAIDs])

HAVE THIS PATIENT'S LYMPHOCYTES, NEUTROPHILS, AND HAEMOGLOBIN BEEN MEASURED?	Yes ☐	No ☐

Note the following:

- Initiating treatment is not recommended in patients with:
  - Low absolute lymphocyte count (ALC) (<0.75 cells x10^9/L in adult patients and paediatric patients)
  - Low absolute neutrophil count (ANC) (<1.00 cells x10^9/L in adult patients or <1.20 cells x10^9/L in paediatric patients)
  - Low haemoglobin (<9 g/dL in adult patients or <10 g/dL in paediatric patients)
- Lymphocytes should be measured at baseline and every 3 months thereafter. Neutrophils should be measured at baseline, then after 4 to 8 weeks of treatment, and then every 3 months thereafter. Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter

DOES THE PATIENT HAVE ELEVATED ALANINE AMINOTRANSFERASE (ALT) OR ASPARTATE AMINOTRANSFERASE (AST)?	Yes ☐	No ☐

Note the following:

- Caution should be exercised when considering initiation of tofacitinib treatment in patients with elevated ALT or AST
- 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

HAVE ALL THE PATIENT'S IMMUNISATIONS BEEN BROUGHT UP TO DATE IN AGREEMENT WITH CURRENT IMMUNISATION GUIDELINES?	Yes ☐	No ☐

Note the following:

- Prior to initiating tofacitinib 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 tofacitinib. The decision to use live vaccines prior to 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 who 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 tofacitinib or in accordance with current vaccination guidelines regarding immunomodulatory medicinal products such as tofacitinib

Discussion with your patients

HAVE YOU DISCUSSED THE OVERALL BENEFITS AND RISKS OF TOFACITINIB WITH YOUR PATIENT?	Yes ☐	No ☐
HAVE YOU GIVEN THE PATIENT ALERT CARD TO YOUR PATIENT?	Yes ☐	No ☐
HAVE YOU DISCUSSED THE USE OF THE PATIENT ALERT CARD WITH YOUR PATIENT?	Yes ☐	No ☐

▼ 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 via HPRA Pharmacovigilance. Website: www.hpra.ie. Any suspected adverse reactions may also be reported to Pfizer Medical Information on 1800 633 363.