TOFACI (TOFACITINIB) PRESCRIBER TREATMENT INITIATION CHECKLIST

Setting: □ Inpatient □ Outpatient **Patient:** □ new patient □ follow-up visit **Date:**

Introduction

• TOFACI (Tofacitinib citrate) is an inhibitor of Janus kinases (JAKs) approved by Saudi Food and Drug Authority (SFDA)

• TOFACI is an inhibitor of Janus kinases (JAKs), is indicated for the treatment of:

Rheumatoid arthritis

Tofacitinib in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

Psoriatic arthritis

Tofacitinib 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 antirheumatic drug (DMARD) therapy.

Ankylosing spondylitis

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

Ulcerative colitis

Tofacitinib 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)

Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritic), and juvenile psoriatic arthritis (PsA) 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.

- TOFACI should not be used in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine.

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 and an increased incidence of malignancies, particularly NMSC, lung cancer and lymphoma was observed with tofacitinib compared to TNF inhibitors.

Events of serious infections, venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), cardiovascular risk, myocardial infarction, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy (including lymphoma and lung cancer), gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities have been reported in patients treated with tofacitinib in clinical studies.

Serious VTE events including PE, some of which were fatal, and DVT have been observed in patients taking tofacitinib. A dose-dependent increased risk for VTE was observed in clinical study with tofacitinib, compared to TNF inhibitors.

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

-65 years of age and older;

-patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers);

-patients with malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer)

This treatment initiation checklist intends to remind you of the risks associated with use of TOFACI and the recommended tests <u>before</u> TOFACI treatment.

Treatment should be initiated and supervised by specialist physicians in the diagnosis and treatment of rheumatoid arthritis.

PRESCRIBER TREATMENT INITIATION CHECKLIST (for use when first starting patients on tofacitinib treatment)

Prior to administration of TOFACI to patients, please check the following:

Does this patient have any evidence of hepatic impairment (Child-Pugh A, B or C)? • Severe hepatic impairment (Child-Pugh C): TOFACI should not be used • Moderate hepatic impairment (Child-Pugh B): TOFACI 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. • Mild hepatic impairment (Child-Pugh A): No dose adjustment is required	Yes □ No □

Does this patient have any evidence of renal impairment (based on creatinine clearance)? • Severe renal impairment (creatinine clearance <30 mL/min): TOFACI 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. Patients with severe renal impairment should remain on a reduced dose even after hemodialysis • Mild (creatinine clearance 50-80mL/min or moderate renal impairment (creatinine clearance 30-49 ml/min): No dose adjustment is required • Supplemental doses are not necessary in patients after dialysis	Yes □ No □
Is this patient currently pregnant or does this patient intends to become pregnant? • TOFACI should not be used during pregnancy unless clearly necessary • Women of childbearing potential should be advised to use effective contraception during treatment with TOFACI and for at least 4 weeks after the last dose.	Yes □ No □
Is this patient breastfeeding or does this patient intend to breast-feed? • Women should not breast-feed while being treated with TOFACI	Yes □ No □
Is this patient currently taking any biological DMARDs or any potent immunosuppressants? • TOFACI 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-23antagonists, anti-integrins, selective co stimulation modulators and potent immunosuppressants such as azathioprine, 6-mercaptopurine, ciclosporin and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.	Yes □ No □
Is the patient over 65 years of age? If Yes:	Yes □ No □

Have you considered alternative treatment considering the increased risk of serious infections, MI and malignancies and all cause mortality? 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 long-time smoker or have a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors? If Yes: Are there any suitable treatment alternatives available for the patient? Note the following: • Given the increased risk of Major Adverse Cardiovascular Events (including MI), tofacitinib should only be used in these patients if no suitable treatment alternatives are available	Yes □ No □
Have you discussed with the patient how to recognise symptoms of MI and to promptly seek medical attention if they experience these? 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	Yes □ No □
Is the patient over 65 years of age, a current or past long-time smoker or have other malignancy risk factors (e.g. current or history of malignancy other than a successfully treated non-melanoma skin cancer)? If Yes: Are there any suitable treatment alternatives available for the patient? Note the following:	Yes □ No □

• 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? Note the following: • Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage • Refer to the prescriber brochure for the VTE risk factors 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	Yes □ No □
Have you discussed with the patient how to recognise symptoms of VTE and to promptly seek medical attention if they experience these? 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 tofacitinib Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.	Yes □ No □
Does this patient have any active infections including localized infections? • TOFACI should not be initiated in patients with active tuberculosis (TB), serious infections, such as sepsis, or opportunistic infections. • The risks and benefits of treatment should be considered prior to initiating TOFACI 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, ○ who have underlying conditions that may predispose them to infection	Yes □ No □

Has this patient been evaluated and tested for latent or active TB? • Patients should be evaluated and tested for latent or active TB prior to administration of TOFACI • Patients with latent TB should be treated with standard antimycobacterial therapy before administering TOFACI	Yes □ No □
Has anti-TB therapy been considered, particularly if this patient has a past history of latent or active TB? • Antituberculosis therapy should be considered prior to administration of TOFACI in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB, 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	Yes □ No □
Has this patient been evaluated and screened for viral hepatitis in accordance with published guidelines? • The impact of TOFACI on chronic viral hepatitis reactivation is unknown • Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with TOFACI	Yes □ No □
Does this patient have a medical history of diverticulitis? • TOFACI 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 nonsteroidal anti-inflammatory drugs [NSAIDs])	Yes □ No □
Have this patient's lymphocytes, neutrophils, and haemoglobin been measured? • Initiating treatment is not recommended in patients with: ○ Low lymphocyte count (<500 cells/mm^3)	Yes □ No □

○ Low absolute neutrophil count (<1000 cells/mm^3) ○ Low haemoglobin (<9 g/dL)	
Does the patient have abnormal elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST)? • Caution should be exercised when considering initiation of tofacitinib treatment in patients with elevated ALT or AST	Yes □ No □
Have all of this patient's immunizations been brought up to date in agreement with current immunization guidelines? • It is recommended that all patients be brought up to date with all immunisations in agreement with current immunization guidelines prior to initiating TOFACI therapy • The interval between live vaccinations and initiation of TOFACI therapy should be in accordance with current vaccination guidelines regarding immunomodulatory agents. ○ Consistent with these guidelines, 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. Vaccination should occur at least 2 weeks but preferably 4 weeks before initiating immunomodulatory agents such as TOFACI.	Yes □ No □

Discussion with your patients

Have you discussed the overall benefits and risks of TOFACI with your patient?	Yes □ No □
Have you given the patient safety card to your patient?	Yes □ No □
Have you discussed the use of patient safety card with your patient?	Yes □ No □

II TOFACI (TOFACITINIB) PRESCRIBER TREATMENT MAINTENANCE CHECKLIST

Setting: □ Inpatient □ Outpatient **Patient:** □ new patient □ follow-up visit **Date**:

Introduction

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- TOFACI is an inhibitor of Janus kinases (JAKs), is indicated for the treatment of
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- TOFACI should not be used 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-23antagonists, anti-integrins, selective costimulation modulators and potent immunosuppressants such as azathioprine, 6-mercaptopurine, ciclosporin and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

This treatment initiation checklist intends to remind you of the risks associated with use of TOFACI and the recommended tests during TOFACI treatment.

Events of serious infections including tuberculosis (TB) and other opportunistic infections, malignancy, gastrointestinal perforations, and laboratory abnormalities have been reported in RA patients treated with TOFACI in clinical studies. Patients should be closely monitored for any signs and symptoms, and laboratory abnormalities for an early identification of these risks.

During the treatment of TOFACI, please check the following at each office visit:

Is this patient currently pregnant or does this patient intends to become pregnant? • TOFACI should not be used during pregnancy unless clearly necessary • Women of childbearing potential should be advised to use effective contraception during treatment with TOFACI and for at least 4 weeks after the last dose	Yes □ No □
Is this patient breastfeeding or does this patient intend to breast-feed? • Use of tofacitinib during breastfeeding is contraindicated	Yes □ No □
Has the patient developed any risk factors for VTE? **• 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 (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. Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.	Yes □ No □

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For patients over 65 years of age, have you considered whether there are suitable alternative treatments available? • Due to the higher incidence of infection in elderly, for patients over 65 years of age, tofacitinib should only be considered if no suitable alternative treatment is available	Yes □ No □
Does this patient have any new onset signs of symptoms of infections? • Patients should be evaluated and tested for latent or active infection per applicable guidelines during administration of TOFACI • If a new infection develops during treatment, please take the following recommended actions: ○ Interrupt TOFACI treatment ○ Prompt and complete diagnostic testing ○ Appropriate antimicrobial therapy should be initiated ○ Close monitoring of the patient	Yes □ No □
Does this patient have any new onset abdominal signs or symptoms? • Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation	Yes □ No □
Does this patient have any new onset or worsening of signs or symptoms of interstitial lung disease? • Caution is recommended in 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 patients treated with tofacitinib.	Yes □ No □
What is the recent lymphocyte count? • When ALC is greater than 750 cells/mm3, resume tofacitinib as clinically appropriate • If lymphocyte count is between 500 and 750 cells/mm3 (2 sequential values in this range on routine testing) tofacitinib dosing should be reduced or interrupted until ALC is greater than 750cells/mm^3. • If lymphocyte count below 500 cells/mm3 (confirmed by repeated testing), discontinue TOFACI **How Often has lymphocyte count been monitored?**	Yes □ No □

• Lymphocytes should be measured every 3 months during the treatment	
What is the recent neutrophil count? • If the ANC is greater than 1000 cells/mm^3, maintain dose • If the ANC is 500-1000 cells/mm^3, interrupt dosing until ANC is >1000 cells/mm^3 • If the ANC is <500 cells/mm^3 (confirmed by repeat testing), discontinue treatment **How often has neutrophil count been monitored?** • Neutrophils should be measured at baseline, then after 4 to 8 weeks of treatment, and then every 3 months	Yes □ No □
What is the recent haemoglobin level? • If less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL, maintain dose • If greater than 2 g/dL decrease or less than 8.0 g/dL (confirmed by repeat testing) Interrupt the administration of TOFACI until haemoglobin values have normalised **How often has haemoglobin level been monitored?** • Haemoglobin should be measured at baseline, then after 4 to 8 weeks of treatment, and then every 3 months	Yes □ No □
How often has lipid parameters been monitored? Assessment of lipid parameters should be tested after 8 weeks following initiation of TOFACI therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia.	Yes □ No □
Has liver enzyme testing been routinely performed? • 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. • If drug-induced injury is suspected, the administration of tofacitinib should be interrupted until this diagnosis has been excluded.	Yes □ No □

Please report any adverse events through the following:

National Pharmacovigilance & Drug Safety Centre at Saudi Food and Drug Authority (SFDA):
Call Center: 19999
E-mail: npc.drug@sfda.gov.sa
Website: https://ade.sfda.gov.sa/

Marketing Authorization Holder Contact Information:
Saudi Amarox Industrial Company
Razan Almalki
Qualified Person for Pharmacovigilance
Al Jamiyah Street, Al Malaz
Riyadh code 12629, Saudi Arabia
E-mail: r.almalki@Amaroxpharma.com
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