PRESCRIBER BROCHURE

TOFACI (Tofacitinib Citrate) 5mg& 10 mg Tablets

The contents of the Prescriber Brochure will be based on the final approved Summary of Product Characteristics (SPC).

This Prescriber Brochure intends to provide guidance on TOFACI 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.

TOFACI Prescriber Brochure

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

Therapeutic indications

- TOFACI, 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.

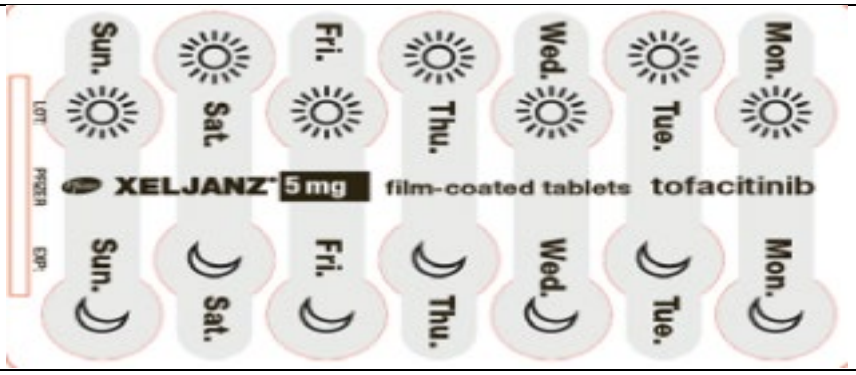
  Juvenile idiopathic arthritis (JIA)
  Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritic), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and 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

Posology and method of administration

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

Oral dosing	TOFACI is available in 5 mg tablets
TOFACI 5 mg BID	
Recommended dose is 5 mg administered twice daily	

TOFACI should be avoided in combination with biological DMARDs and potent immunosuppressants because of the possibility of increased immunosuppression and increased risk of infection.

Considerations for administration

Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed.
- Active tuberculosis (TB), serious infections such as sepsis, or opportunistic infections.
- Severe hepatic impairment.
- Pregnancy and lactation

Prior to administering TOFACI

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

• Assess the patient's cardiovascular risk factors (including age over 65, current or past long-time smoking, history of atheosclerotic cardiovascular disease) – Only use tofacitinib in patients with cardiovascular risk factors if no suitable treatment alternatives are available

• Assess the patient's malignancy risk factors (including age over 65, current or past long-time smoking, and history of malignancy other than a successfully treated non-melanoma skin

cancer) – Only use tofacitinib in patients with malignancy risk factors if no suitable treatment alternatives are available

• Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known VTE, MACE and malignancy risk factors, unless there is no suitable alternative treatment available

• Use with caution in patients with VTE risk factors

- Discuss the risks with patients using **patient safety card** and **TOFACI treatment initiation checklist** (see enclosed checklist for more details).

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

• 65 years of age and old

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

- Consider the risk and benefits of **TOFACI** treatment carefully in patients who are at higher risk of developing serious infections including patients:

o with chronic or recurrent infections,
o who have been exposed to tuberculosis,
o with a history of a serious or an opportunistic infection,
o who have resided or travelled in areas of endemic tuberculosis or endemic mycoses,
o 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 TOFACI.
- All patients should be brought up to date with all immunisations in agreement with current immunisation guidelines.
- Screening for viral hepatitis should be performed in accordance with clinical guidelines.
- Consider the risks and benefits of TOFACI 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 TOFACI in patients who develop a malignancy
- Check patients' laboratory parameters including lymphocytes, neutrophils, and haemoglobin. Initiating treatment is not recommended in patients with:

  o Low lymphocyte count (<500 cells/mm^3)
  o Low absolute neutrophil count (<1000 cells/mm^3)
  o Low haemoglobin (<9 g/dL)

Patients treated with TOFACI should be given a patient safety card. An adequate supply will be provided to prescribers for distribution to patients (through Pfizer local country office

distribution channels). **Patient should be advised to keep this card with them for at least 2 months after taking the last dose of TOFACI.**

Monitoring of laboratory parameters:

Laboratory parameters	Routine Monitoring	Laboratory value	Recommended Actions
Lymphocytes	At baseline, then every 3 months	Greater than or equal to 500 cells/mm^3	Maintain dose
		Less than 500 cells/mm^3 (confirmed by repeat testing)	Discontinue treatment
Neutrophils	At baseline after 4 to 8 weeks of treatment, and then every 3 months	ANC greater than 1000 cells/mm^3	Maintain dose
		ANC 500-1000 cells/mm^3	For persistent decreases in this range, interrupt TOFACI dosing until ANC is greater than 1000 cells/mm^3. When ANC is greater than 1000, cells/mrn^3 resume TOFACI 5 mg twice daily.
		ANC less than 500 cells/mm^3	Discontinue treatment
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	Maintain dose
		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 normalized
Lipids	After 8 weeks following initiation Of TOFACI 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

ANC = absolute neutrophil counts; NA=not applicable

Special warnings and precautions for use

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. Consider the risks and benefits of tofacitinib treatment carefully in patients who are at higher risk of developing serious infections including patients:

- With recurrent infections
- With a history of a serious or an opportunistic infection
- Who have resided or travelled in areas of endemic mycoses
- Who have underlying conditions that may predispose them to infection

Tofacitinib should not be initiated in patients with active infections, including localised infections.

Tuberculosis
The risks and benefits of treatment should be considered prior to initiating TOFACI 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 TOFACI.

Viral reactivation

Viral reactivation has been reported with DMARD treatment and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with TOFACI. The impact of TOFACI on chronic viral hepatitis reactivation is unknown. The risk of herpes zoster appears to be higher in Japanese patients treated with TOFACI.

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

The possibility exists for TOFACI to affect host defenses against malignancies. The impact of treatment with TOFACI on the development and course of malignancies is not known, but malignancies were observed in clinical studies with TOFACI.

Lymphomas have been observed in patients treated with TOFACI. Patients with rheumatoid arthritis, particularly those with highly active disease, may be at a higher risk than the general population (up to several-fold) for the development of lymphoma, the role of TOFACI, a

Janus-kinase inhibitor, in the development of lymphoma is uncertain.

Non-melanoma skin cancer

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with TOFACI. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

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. Events were primarily reported as diverticular perforation, peritonitis, abdominal abscess and appendicitis.
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 presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Vaccination

- No data are available on the secondary transmission of infection by live vaccines to patients receiving TOFACI.

- It is recommended that live vaccines not be given concurrently with TOFACI.

- It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation 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.

- Combination with other therapies
Tofacitinib has not been studied and its use 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.

There was a higher incidence of adverse events for the combination of tofacitinib with MTX versus tofacitinib as monotherapy in RA clinical studies.
The use of tofacitinib in combination with phosphodiesterase 4 inhibitors has not been studied in tofacitinib clinical studies.

- Use in patients over 65 years of age

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.

- 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 tofacitinib. 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 tofacitinib compared to TNF inhibitors.

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×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.

Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dose.
Tofacitinib 10 mg 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.

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 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.
Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE regardless of dose or indication.

- Major adverse cardiovascular events (including myocardial infarction)

Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib. 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 tofacitinib compared to TNF inhibitors. In patients over 65 years of age, patients 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.

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 tofacitinib in patients over 65 years of age, tofacitinib 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).

- TOFACI dose should be reduced to 5 mg once daily in patients with severe renal impairment (creatinine clearance <30mL/min).

Patients with hepatic impairment

- No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A).

- TOFACI dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment (Child Pugh B).

- Treatment with TOFACI should not be used in patients with severe hepatic impairment (Child Pugh C).

Pediatric patients

The safety and efficacy of TOFACI in children and adolescents less than 18 years of age have not yet been established.

Pregnancy and lactation

- TOFACI should not be used during pregnancy unless clearly necessary.

- Women should not breast-feed while being treated with TOFACI.

Women of childbearing potential

- 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.

FOR MORE DETAILS ON PRESCRIBING TOFACI, PLEASE REFER TO THE

SUMMARY OF PRODUCT CHARACTERISTICS.

Patient Counseling

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

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

It is important for physicians to:

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

- 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 TOFACI, or soon after taking TOFACI.
- 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 TOFACI, as these may be signs of a clot in the lungs or veins.
- 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 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 TOFACI.
- Become pregnant or plan on becoming pregnant.

Risk Communication

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

- patient safety card
- prescriber brochure
- 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 TOFACI treatment. They intend to remind you of the risks associated with use of TOFACI and the recommended tests before and during the TOFACI treatment.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to:

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

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