Jakenz

Tofacitinib **5mg, 10mg**

PRESCRIBER BROCHURE

This Prescriber Brochure is an important risk minimisation measure and contains important safety information for prescribers. It aims to provide guidance on tofacitinib to the prescribing physicians with respect to therapeutic indications, dosing and administration including considerations for administration, instruction on monitoring laboratory parameters, precautions and warnings, patient counselling, reporting of adverse events, and a summary of the risk management plan.

The purpose of the Prescriber Brochure is to inform healthcare professionals as to how they can minimise the important risks associated with tofacitinib. It is a mandatory condition of the marketing authorisation.

This document is approved by The Executive Directorate of Pharmacovigilance, at SFDA

Version: 1.0
Date: October 2023

Contents

Therapeutic indications

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. 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 anti-rheumatic drug (DMARD) therapy.

Ankylosing spondylitis (AS)

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

Ulcerative colitis

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 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.

Prior to administering tofacitinib and special warnings and precautions for use

Discuss the risks with patients using the patient alert card and tofacitinib 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 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)

Use in patients aged 65 years and older

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.

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 23 antagonists, 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.

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 patients with VTE risk factors other than MACE or malignancy risk factors, tofacitinib should be used with caution.

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.

The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients:

- who have been exposed to TB
- who have resided or travelled in areas of endemic TB.

Viral reactivation

Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) have been observed in patients receiving tofacitinib.

In patients treated with tofacitinib, the incidence of herpes zoster appears to be increased in:

- Japanese or Korean patients.
- Patients with an ALC less than 1,000 cells/mm3
- Patients with long standing RA who have previously received two or more biological disease modifying antirheumatic drugs (DMARDs).
- Patients treated with 10 mg twice daily.

The impact of tofacitinib on chronic viral hepatitis reactivation is unknown. Patients screened positive for hepatitis B or C were excluded from clinical studies. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with tofacitinib.

Major adverse cardiovascular events (including myocardial infarction)

Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib. In patients over 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.

Malignancies and lymphoproliferative disorders

Tofacitinib may affect host defences against malignancies. In patients over 65 years of age, patients who are current or past long-term smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available. Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer.

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.

Interstitial lung disease

Caution is also 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 in RA clinical studies and in the post-marketing setting although the role of Janus kinase (JAK) inhibition in these events is not known. Asian RA patients are known to be at higher risk of interstitial lung disease, thus caution should be exercised in treating these patients.

Gastrointestinal perforations

Events of gastrointestinal perforation have been reported in clinical studies although the role of JAK inhibition in these events is not known. 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 nonsteroidal anti-inflammatory drugs). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Liver enzymes

Treatment with tofacitinib was associated with an increased incidence of liver enzyme elevation in some patients. Caution should be exercised when considering initiation of tofacitinib treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST), particularly when initiated in combination with potentially hepatotoxic medicinal products such as MTX. Following initiation, routine monitoring of liver tests and prompt investigation of the causes of any observed liver enzyme elevations are recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of tofacitinib should be interrupted until this diagnosis has been excluded.

Vaccinations

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 tofacitinib treatment should consider the pre-existing immunosuppression in each patient.

Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Consideration should be given to patients with longstanding RA who have previously received two or more biological DMARDs. If live zoster vaccine is administered; it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus (VZV). If the history of chickenpox is considered doubtful or unreliable it is recommended to test for antibodies against VZV.

Vaccination with live vaccines should occur at least 2 weeks but preferably 4 weeks prior to initiation of tofacitinib or in accordance with current vaccination guidelines regarding immunomodulatory medicinal products. No data are available on the secondary transmission of infection by live vaccines to patients receiving tofacitinib.

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). Severe renal impairment (creatinine clearance <30 mL/min): Dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal renal function is 5 mg twice daily or 11 mg prolonged release once daily (indicated in RA). Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily in patients with UC. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis.

Patients with hepatic impairment

No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A). Moderate hepatic impairment (Child Pugh B): Dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily or 11 mg prolonged release once daily (indicated in RA). Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily in patients with UC. Tofacitinib should not be used in patients with severe hepatic impairment (Child Pugh C).

Pediatric patients

The safety and efficacy of tofacitinib in children less than 2 years of age with pJIA and jPsA has not been established. No data are available. The safety and efficacy of tofacitinib in children less than 18 years of age with other indications (e.g. ulcerative colitis) has not been established. No data are available.

Only in paediatric patients: Available data suggest that clinical improvement is observed within 18 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception during treatment with tofacitinib and for at least 4 weeks after the last dose.

Tofacitinib use is contraindicated in the following special populations

- Patients with hypersensitivity to the active substance or to any of the excipients
- Patients with active tuberculosis (TB), serious infections such as sepsis, or opportunistic infections
- Patients with severe hepatic impairment
- Patients who are pregnant or lactating

Monitoring of laboratory parameters:

Laboratory parameters	*Routine monitoring*	*Laboratory value*	*Recommended actions*
Lymphocytes (ALC)	**At baseline, then every 3 months**	Greater than or equal to 0.75 x 10^9 cells/L	Dose should be maintained
		Between 0.50 and 0.75 x 10^9 cells/L (2 sequential values in this range on routine testing)	Dosing should be reduced or interrupted For patients receiving tofacitinib 5 mg twice daily or 11 mg prolonged release once daily, dosing should be interrupted. For patients with UC receiving tofacitinib 10 mg twice daily, dosing should be reduced to tofacitinib 5 mg twice daily When ALC is greater than 0.75, resume treatment as clinically appropriate
		Less than 0.50 x 10^9 cells/L (confirmed by repeat testing within 7 days)	Dosing should be discontinued
Neutrophils (ANC)	**At baseline, after 4 to 8 weeks of treatment, and then every 3 months**	ANC greater than 1.0 x 10^9 cells/L	Dose should be maintained
		ANC 0.50–1.0 x 10^9 cells/L (2 sequential values in this range on routine testing)	For persistent decreases in this range, reduce or interrupt dosing For patients receiving tofacitinib 5 mg twice daily or 11 mg prolonged release once daily, dosing should be interrupted. For patients with UC receiving tofacitinib 10 mg twice daily, dosing should be reduced to tofacitinib 5 mg twice daily. When ANC is greater than 1.0 x 10^9 cells/L resume treatment as clinically appropriate
		ANC less than 0.50 x 10^9 cells/L (confirmed by repeat testing within 7 days)	Dosing should be discontinued
Haemoglobin	**At baseline, after 4 to 8 weeks of treatment, and then every 3 months**	Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Dose should be maintained
		Greater than 2 g/dL decrease or less than 8.0 g/dL (confirmed by repeat testing)	Interrupt dosing until haemoglobin values have normalised
Lipids	**After 8 weeks following initiation of therapy**	NA	Managed according to clinical guidelines for the management of hyperlipidaemia
Liver enzymes	**Routine monitoring**	NA	Following initiation, routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; NA, not applicable

Patient Counselling

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

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

It is important for physicians to:

- provide the patient alert card to each patient who is prescribed with tofacitinib
- remind patients to use the patient alert card
- discuss the risks with each patient and ensure patient understanding of the treatment potential risks
- ensure patients carry the patient alert card with them, particularly when they visit doctors' office and/or the emergency room

You should remind patients to seek immediate medical attention if they experience any of the following signs and symptoms:

- Sudden shortness of breath or difficulty breathing, chest pain or pain in upper back, swelling of the leg or arm, leg pain or tenderness, or redness or discoloration in the leg or arm while taking tofacitinib, as these may be signs of a clot in the lungs or veins
- Experience possible symptoms of allergic reactions such as chest tightness, wheezing, severe dizziness or light-headedness, swelling of the lips, tongue or throat, itching or skin rash when taking tofacitinib, or soon after taking tofacitinib
- Develop symptoms of an infection, such as fever, persistent cough, weight loss or excessive tiredness
- Develop symptoms of herpes zoster, such as painful rash or blisters
- Have been in close contact with a person with TB
- Develop severe chest pain or tightness (that may spread to arms, jaw, neck and back), shortness of breath, cold sweat, light headedness or sudden dizziness as these may be signs of a heart attack
- Notice any new growth on the skin or any changes in existing moles or spots
- Develop symptoms of interstitial lung diseases, such as shortness of breath
- Develop abdominal signs and symptoms such as stomach pain, abdominal pain, blood in stool, or any change in bowel habits with fever
- Develop yellow skin, nausea or vomiting
- Are due to receive any vaccine. Patients should not receive certain types of vaccines while taking tofacitinib
- Become pregnant or plan on becoming pregnant

Risk communication

In order to communicate certain risks about tofacitinib, Sudair has worked with the SFDA to develop a detailed communication plan to communicate the risks described in the summary of product characteristics, these include the following items:

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

Two (2) treatment checklists: initiation checklist and maintenance checklists, are developed for you to use prior to and during tofacitinib treatment. They intend to remind you of the risks associated with the use of tofacitinib and the recommended tests before and during tofacitinib treatment.

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

Reporting of adverse events

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 the Saudi Food and Drug Authority (SFDA) via:

Website: https://ade.sfda.gov.sa
Email: npc.drug@sfda.gov.sa
Call center: 19999

Also, you can report to Sudair Pharma Company via:

Phone: +966-920001432 Ext. 107
Email: Pharmacovigilance@SudairPharma.com

Prescriber website for tofacitinib

All the educational materials including the patient alert card and the treatment initiation and maintenance checklists are available at: https://www.sfda.gov.sa/en/RMM

Adverse events should be reported. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Jakenz

Tofacitinib **5mg, 10mg**

PRESCRIBER BROCHURE

SPC
سدير للأدوية

Version: 1.0
Date: October 2023