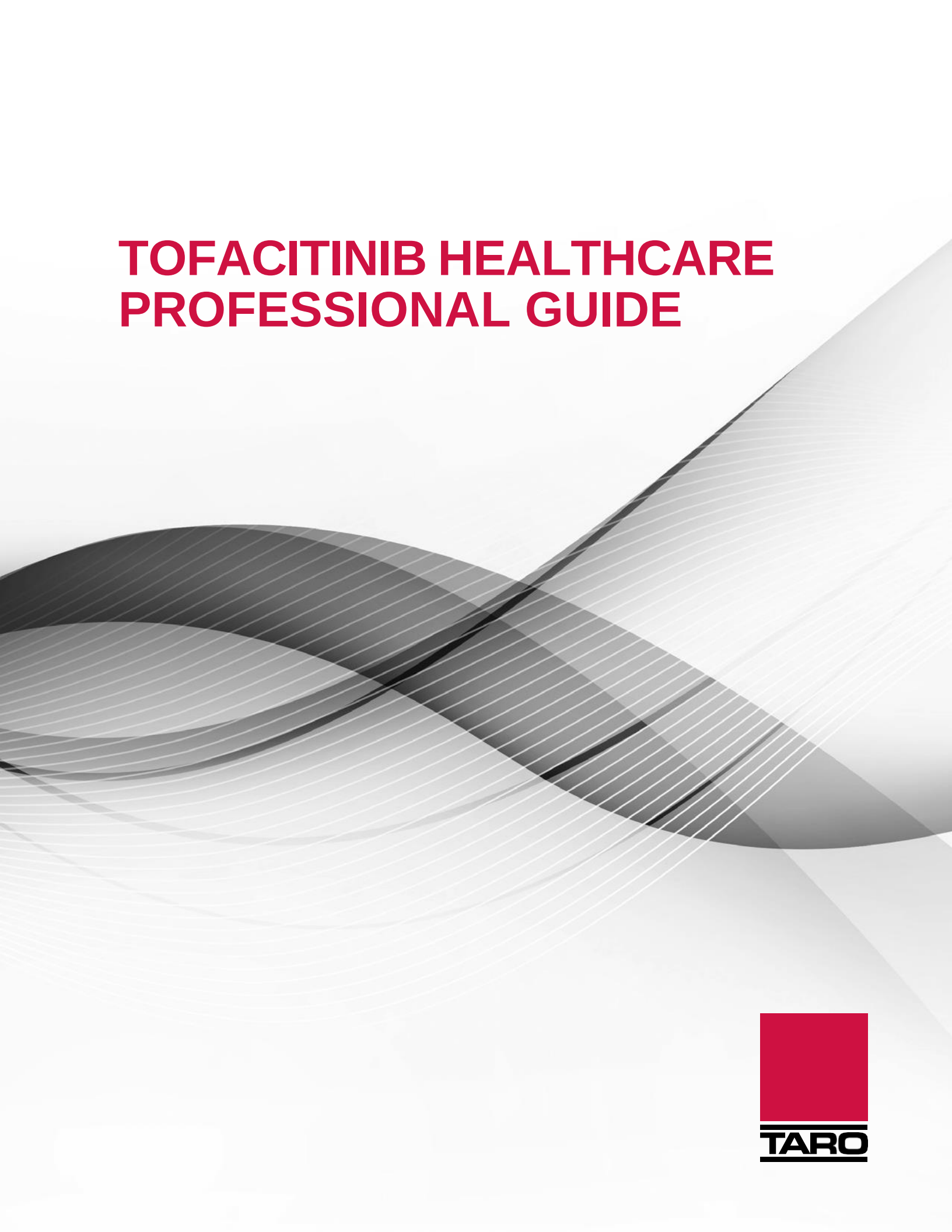
TOFACITINIB HEALTHCARE PROFESSIONAL GUIDE



TARO

Tofacitinib is a selective inhibitor of the enzyme janus kinase. Treatment with tofacitinib leads to modulation of multiple aspects of the immune response, including attenuation of signalling by pro-inflammatory cytokines.

Indications:

Tofacitinib is indicated for:

- reducing the signs and symptoms of rheumatoid arthritis (RA), in combination with methotrexate (MTX), in adult patients with moderately to severely active RA who have had an inadequate response to methotrexate
- reducing the signs and symptoms of psoriatic arthritis (PsA), in combination with MTX or another conventional synthetic disease-modifying antirheumatic drug (DMARD), in adult patients with active PsA when the response to previous DMARD therapy has been inadequate
- 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 TNF-α inhibitor

Dosing

The recommended dose of tofacitinib for adults, based on indication is listed in the table below.

Indication	Recommended Dose	Combination or Monotherapy	Other Considerations
Rheumatoid arthritis	5mg twice daily orally with or without food	In combination with MTX	May be given as monotherapy if the patient cannot tolerate MTX
Psoriatic arthritis	5mg twice daily	In combination with MTX or another conventional synthetic DMARD	N/A
Ulcerative colitis	10mg twice daily orally for induction for at least 8 weeks; 5mg twice daily for maintenance therapy	Monotherapy	• 10mg twice daily may be used for maintenance therapy in some patients • Discontinue induction therapy in patients with no evidence of therapeutic benefit by week 16 • In patients who respond to tofacitinib, corticosteroids may be cautiously reduced and/or discontinued

The dose of tofacitinib may need to be adjusted based on the patient's clinical status, medical conditions and in the case of drug-drug interactions. The chart below outlines dosing adjustments that are recommended in patients with specific clinical situations.

Patient Group	Dose Adjustment	Other Considerations
Neutropenia	If absolute neutrophil count (ANC) is 500 to 1000 cells/mm^3, interrupt or reduce administration of tofacitinib until ANC > 1000 cells/mm^3 • For patients taking 5mg twice daily, interrupt dose. Restart 5mg twice daily when ANC > 1000 cells/mm^3 • For patients taking 10mg twice daily, reduce dose to 5mg twice daily. Increase dose to 10mg twice daily when ANC > 1000 cells/mm^3 based on clinical response. Discontinue tofacitinib if ANC < 500 cells/mm^3	Do not initiate tofacitinib if ANC < 1000 cells/mm^3
Anemia	• Maintain dose if < 2g/dL decrease in hemoglobin (Hgb) and Hgb is ≥ 9g/dL • Pause tofacitinib if ≥ 2g/dL decrease in Hgb and Hgb is < 8g/dL (with repeat testing) until Hgb levels normalize	Do not initiate tofacitinib if Hgb < 9g/dL
Lymphopenia (lymphocytopenia)	• Maintain dose if lymphocyte count is ≥ 500 cells/mm^3 • Discontinue tofacitinib if lymphocyte count is less than 500 cells/mm^3 (with repeat testing)	Do not initiate tofacitinib if lymphocyte count < 500 cells/mm^3
Renal impairment	Reduce dose in patients with moderate (CrCl 30mL/min to < 60mL/min) or severe renal impairment (CrCl 15mL/min to < 30mL/min), including those with end-stage renal disease • 5mg once daily (if dose indicated for normal renal function is 5mg twice daily) • 5mg twice daily (if dose indicated for normal renal function is 10mg twice daily)	For patients on hemodialysis, the dose should be given after a dialysis session on dialysis days. No supplemental dose is required on those days if the dose was given before dialysis. Patients with severe renal impairment should continue to receive a reduced dose even after hemodialysis.
Hepatic impairment	In patients with moderate hepatic impairment: • 5mg once daily (if dose indicated for normal hepatic function is 5mg twice daily) • 5mg twice daily (if dose indicated for normal hepatic function is 10mg twice daily)	Use with caution in patients with hepatic impairment. Tofacitinib is contraindicated in patients with severe hepatic impairment.
Drug interactions	In people taking potent inhibitors of cytochrome P450 3A4 (e.g., ketoconazole) or one or more medications that cause both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole) • Reduce to 5mg twice daily in those taking 10mg twice daily • Reduce to 5mg once daily in those taking 5mg twice daily	Co-administration with potent inducers of CYP3A4 (e.g., rifampin) can reduce response to tofacitinib, and is not recommended.

Safety Considerations

Several precautions and warnings for the use of tofacitinib have been identified. The following sections of this guide summarize safety considerations, patient screening and monitoring, and counselling instructions.

Contraindications

Tofacitinib is contraindicated in the following circumstances:

- In patients with severe hepatic impairment
- During pregnancy and breastfeeding
- In patients with known hypersensitivity to tofacitinib or any of its components

Warnings

Tofacitinib may increase the risk of **serious infections** (including active tuberculosis; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens) that can lead to hospitalization and death. This happens most often in patients who are taking prescribed concomitant immunosuppressants such as methotrexate and corticosteroids. The most common serious infections associated with tofacitinib are pneumonia, cellulitis, herpes zoster, and urinary tract infections.

Tofacitinib should be used with caution in people with a higher risk of infection including people of Asian descent, older adults, people with diabetes, people with COPD, and in those with increasing degrees of lymphopenia.

Tofacitinib should not be started in patients with active infections, including localized infections. The risks and benefits of treatment with tofacitinib should be considered for patients with chronic or recurrent infections, who have been exposed to tuberculosis, who have a history of serious or opportunistic infections, who have lived or travelled in areas with endemic tuberculosis or mycoses, or in people with underlying conditions that may increase their risk of infection.

Tofacitinib can increase the risk of **lymphoma and other malignancies**, including lung cancer, breast cancer, colorectal cancer, gastric cancer, melanoma, prostate cancer, pancreatic cancer, and renal cell carcinoma. There is an increased rate of post-transplant lymphoproliferative disorder associated with Epstein-Barr virus in people who have had a renal transplant and are being treated with tofacitinib with other immunosuppressant medications. Patients with highly active rheumatoid arthritis taking tofacitinib may be at a several-fold higher risk of lymphoma than the general population.

Malignancy has also occurred in people with psoriatic arthritis and ulcerative colitis who received tofacitinib. Nonmelanoma skin cancer occurs more frequently at higher doses of tofacitinib (10mg bid) compared to lower doses (5mg bid). The risks and benefits of starting or continuing tofacitinib in people with current or history of malignancy other than a successfully treated nonmelanoma skin cancer should be evaluated before treatment.

Tofacitinib 10mg bid can increase the risk of **all-cause mortality (including sudden cardiovascular death) and venous thromboembolism** (pulmonary embolism, deep vein thrombosis, and arterial thrombosis) in people 50 years of age and older with rheumatoid arthritis and at least one other cardiovascular risk factor compared to tofacitinib 5mg bid, or tumour necrosis factor blockers. Tofacitinib should not be started in patients at risk of thrombosis and should be stopped in patients who develop symptoms of thrombosis.

Drug Interactions

Taking tofacitinib with potential immunosuppressive medications such as azathioprine, tacrolimus, and cyclosporine can result in additive immunosuppression and increased risk of infection. Combining tofacitinib with these potent immunosuppressive medications or biologic DMARDs (TNF inhibitors, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, and selective costimulation modulators) for the treatment of rheumatoid arthritis, psoriatic arthritis, or ulcerative colitis should be avoided.

Tofacitinib can decrease heart rate and increase the PR interval, so it should be used with caution with medications that can decrease heart rate and/or prolong the PR interval such as antiarrhythmics, beta-blockers, alpha-2 adrenoceptor agonists, nondihydropyridine calcium channel blockers, digoxin, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, and some protease inhibitors.

Potent inducers of CYP3A4 (e.g., rifampin) are not recommended with tofacitinib because there may be a reduced clinical response to tofacitinib.

Potent inhibitors of CYP3A4 (e.g., ketoconazole), or medications that cause both moderate CYP3A4 inhibition and potent CYP2C19 inhibition (e.g., fluconazole), taken with tofacitinib can result in an increased effect of tofacitinib. When tofacitinib is taken with these medications, the dose of tofacitinib should be reduced by 50% (i.e., 5mg daily when 5mg bid is indicated or 5mg bid when 10mg bid is indicated). See “Dosing” section for more details.

Patient Screening and Monitoring

Higher Risk Populations

Tofacitinib should be used with caution in people 65 years of age and older, as people in this age group are more likely to have a serious infection when taking this medication compared to younger people. Tofacitinib should also be used with caution in people of Asian descent, as they may be at higher risk of reduced white blood cell counts, herpes zoster, opportunistic infections, elevated liver enzymes, and interstitial lung disease.

Geriatric patients

Tofacitinib should be used with caution in patients who are current or past smokers, patients with cardiovascular risk factors, and patients with other malignancy risk factors) with potentially higher risk and include the following safety concerns:

a. Lung cancer

b. Myocardial infarction

c. Fractures

Signs of Infection

Patients taking tofacitinib are at increased risk of serious infections that can lead to hospitalization and death, and this occurred when patients were taking concomitant immunosuppressants, including corticosteroids or methotrexate. Tofacitinib should be interrupted in patients who develop a serious infection until the infection is controlled. The types of infections that have been reported with tofacitinib include: tuberculosis, invasive fungal infections (e.g., cryptococcosis and pneumocystosis), as well as bacterial, viral and other infections due to opportunistic pathogens.

Tofacitinib should not be administered to patients with an active infection, including localized infections. Consider the risks and benefits of administering tofacitinib in patients with: chronic or recurrent infections, who have been exposed to tuberculosis, who have a history of serious opportunistic infection, who have lived or travelled in areas with endemic tuberculosis or mycoses or who have conditions that predispose them to infections.

Tofacitinib should be used with caution in people who are at greater risk of infection when taking this medication, including people of Asian descent, older adults, those with diabetes and patients with chronic lung disease.

Risk of infection increases with increasing degrees of lymphopenia.

Monitor for signs and symptoms of infection during and after treatment with tofacitinib, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis prior to starting therapy. Tofacitinib should be stopped if the patient develops a serious infection, an opportunistic infection, or sepsis. The patient should be assessed (with testing appropriate for an immunocompromised patient), treated with anti-microbial therapy, and closely monitored if a new infection develops.

Hematologic monitoring, including lymphocytes, neutrophils, and hemoglobin, is required prior to starting tofacitinib and during treatment, as it has been associated with lymphopenia, neutropenia, and anemia. People of Asian descent are at a greater risk of decreased white blood cell counts when taking tofacitinib. This should be done at baseline, about four to eight weeks after starting tofacitinib, and every three months thereafter. See “Dosing” section for information about dose adjustment based on hematologic parameters.

Malignancies

Lymphoma and other malignancies such as lung cancer, breast cancer, colorectal cancer, gastric cancer, melanoma, prostate cancer, pancreatic cancer and renal cell carcinoma have been reported in patients taking tofacitinib. Epstein Barr virus-associated post-transplant lymphoproliferative disorder is more likely in patients who have received a renal transplant and are treated with tofacitinib and concomitant immunosuppressive medications. Consider the risks and benefits of tofacitinib treatment before starting therapy in those with current or a history of malignancy other than a successfully treated nonmelanoma skin cancer, or when considering continuing therapy in those who develop a malignancy.

Skin

Periodic skin examination is recommended for patients using tofacitinib, as it has been associated with a dose-related risk (higher risk at 10mg bid compared to 5mg bid) of nonmelanoma skin cancer.

Thrombosis

Tofacitinib should be avoided in patients who are at risk of thrombosis. Tofacitinib should be stopped in patients who have symptoms of thrombosis and the patient should be promptly evaluated. In patients with rheumatoid arthritis with at least one cardiovascular risk factor, there was a higher rate of all-cause mortality and thrombosis with tofacitinib 10mg twice daily compared to 5mg twice daily or when used with TNF blockers. A dose of 10mg twice daily is not recommended for treatment of RA or PsA. For patients with ulcerative colitis, tofacitinib should be used at the lowest effective dose for the shortest duration needed to achieve and maintain a therapeutic response.

Lipid Levels

Tofacitinib treatment has been associated with increases in total cholesterol, LDL cholesterol, and HDL cholesterol levels, usually within about six weeks of starting treatment. Lipid levels should be measured at baseline, about four to eight weeks after starting tofacitinib, then every six months thereafter.

Gastrointestinal

Tofacitinib should be used with caution in patients who may be at risk of gastrointestinal perforation. This could include patients with a history of diverticulitis, or who use NSAIDs and/or corticosteroids. Gastrointestinal perforation has been reported in patients with rheumatoid arthritis. Patients with new abdominal symptoms while taking tofacitinib should be evaluated for gastrointestinal perforation.

Cardiovascular

Tofacitinib can decrease heart rate and prolong the PR interval. It should be used with caution in patients with a low baseline heart rate (less than 60 BPM), history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular block, ischemic heart disease, or congestive heart failure. Drugs that decrease heart rate and/or prolong PR interval should be avoided with tofacitinib.

Liver function

Liver function should be assessed before treatment with tofacitinib. Tofacitinib has been associated with elevations in liver enzymes when taken with another DMARD (primarily methotrexate in patients with rheumatoid arthritis and psoriatic arthritis), and in higher doses of tofacitinib when used in patients with ulcerative colitis. People of Asian descent have a higher risk of elevated liver enzymes. See “Dosing” section for information about dose adjustment in hepatic impairment. Liver enzymes should be monitored routinely during treatment with tofacitinib, and treatment should be interrupted if drug-induced liver injury is suspected.

Musculoskeletal

Tofacitinib treatment has been associated with dose-related (higher risk with 10mg bid compared to 5mg bid) increases in creatine kinase within six months after starting therapy. Rhabdomyolysis has been reported with tofacitinib. Creatine kinase should be measured in patients with symptoms of muscle weakness and/or muscle pain to evaluate for rhabdomyolysis.

Tuberculosis

Patients should be tested for latent or active tuberculosis infection before starting tofacitinib and annually while taking this medication. They should be monitored for signs and symptoms of tuberculosis during treatment, even if they tested negative for latent tuberculosis. Antituberculosis therapy should be considered for patients with latent tuberculosis, a past history of latent or active tuberculosis for which treatment cannot be confirmed, and for those who test negative for latent tuberculosis but have risk factors for tuberculosis.

Herpes zoster

When considering therapy with tofacitinib, the patient should be encouraged to receive a nonlive vaccination against herpes zoster prior to taking this medication as viral reactivation may occur. Live herpes zoster vaccine should be considered only for those with a known history of chickenpox or those who are seropositive for varicella-zoster virus. People of Asian descent have a higher risk of herpes zoster. Patients taking tofacitinib should be monitored for signs and symptoms of herpes zoster infection.

Hepatitis B and C

Screening for viral hepatitis should be completed prior to starting tofacitinib, as hepatitis B reactivation has been reported in people taking tofacitinib.

Renal function

Renal function should be assessed prior to starting tofacitinib. See “Dosing” section for information about dose adjustment in renal impairment.

Respiratory

Interstitial lung disease has been associated with tofacitinib use in patients with rheumatoid arthritis who were also taking methotrexate, corticosteroids, and/or sulfasalazine. There is an increased risk of interstitial lung disease in people of Asian descent. Tofacitinib should be used with caution in patients with a history of, or at risk of, interstitial lung disease.

Pregnancy and Breastfeeding

Tofacitinib is contraindicated in pregnancy and in women who are breastfeeding. Women of reproductive age should be counselled to use effective contraception during treatment with tofacitinib and for four to six weeks after stopping the medication.

Vaccination

Live vaccines should not be given concurrently with tofacitinib. In patients with a history of chickenpox or who are seropositive for varicella-zoster virus, live herpes zoster vaccine may be given at least two weeks but preferably four weeks prior to starting tofacitinib.

Patient Counselling

Patients who will be prescribed tofacitinib should be advised to complete all routine and recommended vaccines prior to starting the medication. If women of reproductive age are not already using contraception, they should be advised to start an effective contraception method prior to prescribing tofacitinib.

When starting treatment with tofacitinib, patients should be advised to watch for signs and symptoms of infections, lymphoma, and thrombosis. The Tofacitinib Patient Safety Card outlines other adverse effects to watch for and when to stop treatment and seek medical attention promptly.

Patients should be advised of the importance of laboratory tests that are required before starting treatment and those that will be required on an ongoing basis. The importance of keeping all medical appointments and receiving treatments on time should be discussed with all patients.

Adverse Event Reporting

Healthcare professionals are advised to report any adverse reactions (noxious or unintended responses) to tofacitinib that are observed in patients. This may include those that are serious as well as those that are not serious but are temporally associated with tofacitinib administration. Adverse reactions should be reported to Health Canada (see https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting/drug/health-care-providers.htm)

Reference: Taro Pharmaceuticals Inc. Taro-Tofacitinib Product Monograph. Revised July 2022. https://pdf.hres.ca/dpd_pm/00068405.PDF. Accessed November 29, 2023.