Auro-Tofacitinib
Health Care Professionals (HCP) Guide

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

This Health Care Professionals (HCP) Guide intends to provide guidance on Auro-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 counseling, reporting of adverse events, and a summary of the risk management plan. The Guide should be used in conjunction with the Auro-Tofacitinib Product monograph.

Patients treated with Auro-Tofacitinib should be given a **patient safety card**. To order more copies of the patient safety card, please contact Auro Pharma Inc on www.auropharma.ca or by calling at 1-855-648-6681.

Patients should be advised to keep this card with them for at least 2 months after taking the last dose of Auro-Tofacitinib.

Therapeutic indications:

Rheumatoid Arthritis

Auro-Tofacitinib, in combination with methotrexate (MTX), is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA) in adult patients with moderately to severely active RA who have had an inadequate response to MTX and to one or more disease-modifying anti-rheumatic drugs (DMARDs).

In cases of intolerance to MTX, physicians may consider the use of Auro-Tofacitinib as monotherapy.

Psoriatic Arthritis

Auro-Tofacitinib, in combination with methotrexate (MTX) or another conventional synthetic disease-modifying antirheumatic drug (DMARD), is indicated for reducing the signs and symptoms of psoriatic arthritis (PsA) in adult patients with active PsA when the response to previous DMARD therapy has been inadequate.

Ankylosing Spondylitis

Auro-Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to a biologic DMARD or when use of those therapies is inadvisable.

Ulcerative Colitis

Auro-Tofacitinib is indicated for the 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 inhibitor.

Limitations of Use: Auro-Tofacitinib should not be used in combination other Janus kinase (JAK) inhibitors, immunomodulating biologics (e.g., biologic DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

Geriatrics (>65 years of age)

Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness. The frequency of adverse events including serious infections, all-cause mortality, cardiovascular events, malignancies, non- melanoma skin cancer, gastrointestinal perforations, interstitial lung disease, venous thromboembolism, and arterial thromboembolism in tofacitinib-treated subjects 65 years of age and older was higher than among those under the age of 65. Therefore, caution should be used when treating geriatric patients with Auro-Tofacitinib

Posology:

- Use of Auro-Tofacitinib with other potent systemic immunosuppressants should be avoided. Combined use of Auro-Tofacitinib with potent immunosuppressants or biologic DMARDS (tumor necrosis factor (TNF) antagonists, interleukin 1 receptor (IL-1R) antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists and selective co-stimulation modulators) has not been studied in RA, PsA and UC patients. There is a risk of added immunosuppression when Auro-Tofacitinib is coadministered with potent immunosuppressive drugs (e.g. azathioprine, tacrolimus, cyclosporine).
- Auro-Tofacitinib should not be initiated in patients with an absolute neutrophil count (ANC) less than 1×10^9 cells/L, hemoglobin (Hgb) levels <90 g/L, or with a lymphocyte count less than 0.5×10^9 cells/L
- Auro-Tofacitinib is contraindicated in patients with severe hepatic impairment;

Recommended Dose and Dosage Adjustment

Rheumatoid Arthritis:

- Auro-Tofacitinib is to be used in combination with methotrexate.
- Auro-Tofacitinib, monotherapy may be considered in cases of intolerance to methotrexate and to one or more DMARDs.
- The recommended dose of Auro-Tofacitinib is 5 mg administered twice daily (BID).
- A dosage of Auro-Tofacitinib 10 mg BID is not recommended for the treatment of rheumatoid arthritis.

Psoriatic Arthritis

The recommended dose of Auro-Tofacitinib is 5 mg administered twice daily in combination with MTX or another csDMARD. A dosage of Auro-Tofacitinib 10 mg BID is not recommended for the treatment of psoriatic arthritis.

Ankylosing Spondylitis:

The recommended dose of Auro-Tofacitinib is 5 mg administered BID. A dosage of Auro-Tofacitinib 10 mg BID is not recommended for the treatment of ankylosing spondylitis.

Ulcerative Colitis: The recommended dose is 10 mg given orally twice daily for induction for at least 8 weeks and 5 mg given twice daily for maintenance. Depending on therapeutic response; 10 mg twice daily may also be used for maintenance in some patients. However, the lowest effective dose possible should be used for maintenance therapy to minimize adverse effects. Auro-Tofacitinib induction therapy should be discontinued in patients who show no evidence of adequate therapeutic benefit by Week 16.

In patients who have responded to treatment with Auro-Tofacitinib, corticosteroids may be cautiously reduced and/or discontinued in accordance with standard of care.

Dose Interruption or Discontinuation due to Serious Infections and Cytopenias

- Avoid use of Auro-Tofacitinib if a patient develops a serious infection until the infection is controlled.

Dose interruption is recommended for management of anemia, lymphopenia, and neutropenia as described in Table1.

Table 1: Laboratory measures and dose adjustment recommendations

Laboratory Measure	**Lab Value**	**Recommendation**
Hemoglobin	<20 g/L decrease and ≥90 g/L	Maintain dose
	≥20 g/L decrease or <80 g/L (Confirmed by repeat testing)	Interrupt the administration of Auro-Tofacitinib until hemoglobin values have normalized (above 80
Absolute Neutrophil Count (ANC)	>1 x 10^9 cells/L	Maintain dose
	0.5-1 x 10^9 cells/L	For persistent decreases in this range, interrupt or reduce administration with Auro-Tofacitinib until ANC is >1x 10^9 cells/L • For patients receiving tofacitinib 5 mg BID, interrupt tofacitinib dosing. When ANC is >1 x 10^9 cells/L, resume tofacitinib 5 mg BID. UC patients: • For patients receiving tofacitinib 10 mg BID, reduce dose to tofacitinib 5 mg BID. When ANC is >1 x 10^9 cells/L, increase to tofacitinib 10 mg BID • based on clinical response.
	<0.5 x 10^9 cells/L (Confirmed by repeat testing)	Discontinue treatment with Auro-Tofacitinib
Absolute Lymphocyte Count	≥ 0.5 x 10^9cells/L	Maintain dose
	< 0. 5 x 10^9cells/L (Confirmed by repeat testing)	Discontinue Auro-Tofacitinib

Dose Modification in Patients with Renal or Hepatic Impairment, or Due to Drug Interactions

- Use Auro-Tofacitinib with caution in patients with moderate (CLcr ≥30 and <60 mL/min) or severe (CLcr ≥15 and <30 mL/min) renal insufficiency (including patients with ESRD but not limited to those undergoing hemodialysis). Modified dosing is indicated in Table 2.
- For patients undergoing hemodialysis, dose should be administered after the dialysis session on dialysis days. If a dose was taken before the dialysis procedure, supplemental doses are not recommended in patients after dialysis.
- Patients with severe renal insufficiency should remain on a reduced dose even after hemodialysis.
- Use Auro-Tofacitinib with caution in patients with moderate hepatic impairment. Modified dosing is indicated in Table 2.

- Modified dosing of Auro-Tofacitinib is recommended with concomitant CYP inhibitors as indicated in Table 3.
- Coadministration of potent inducers of CYP3A4 with Auro-Tofacitinib is not recommended.
- Coadministration of potent inducers of CYP3A4 (e.g. rifampin) with Auro-Tofacitinib may result in loss of efficacy or reduced clinical response to tofacitinib

Table 2: Recommended dose adjustment of Auro-Tofacitinib in patients with renal insufficiency or hepatic impairment

		Auro-Tofacitinib	
Indicated dose (in normal renal/hepatic function)		5 mg BID	10 mg BID
Modified dosing	Moderate Renal insufficiency (CrCl ≥30 and <60 mL/min)	5 mg once daily	5 mg BID
	Severe Renal insufficiency (CrCl≥15 and <30 mL/min)		
	Moderate hepatic impairment		
	Severe hepatic impairment	Contraindicated	Contraindicated

Table 3: Recommended dose adjustment of Auro-Tofacitinib in patients with CYP modifiers

		Auro-Tofacitinib	
Indicated dose		5 mg BID	10 mg BID
Modified dosing	Patients receiving: • Potent CYP3A4 inhibitors (e.g. ketoconazole), or • a moderate CYP3A4 inhibitor and a potent CYP2C19 inhibitor (e.g. fluconazole)	5 mg once daily	5 mg BID
	Patients receiving: • Potent CYP3A4 inducers (e.g. rifampin)	Not recommended	Not recommended

Special Populations

Geriatrics (>65 years): No dosage adjustment is required in patients aged 65 years and older.

Pediatrics (<18 years of age): Health Canada has not authorized an indication for pediatric use. No data are available regarding the safety and efficacy of tofacitinib in children aged from neonates to less than 18 years of age. Therefore Auro-Tofacitinib should not be used in this patient population.

Administration

Auro-Tofacitinib is to be taken orally with or without food.

Pregnant Women: Auro-Tofacitinib is contraindicated during pregnancy. There are no adequate and well-controlled studies on the use of tofacitinib in pregnant women. Tofacitinib has been shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility, parturition, and peri/postnatal development.

Women of reproductive potential should be advised to use effective contraception during Auro-Tofacitinib treatment and for 4 to 6 weeks after the last dose.

Nursing Women: Auro-Tofacitinib is contraindicated in women who breastfeed. Auro-Tofacitinib was secreted in milk of lactating rats. It is not known whether Auro-Tofacitinib is excreted in human milk

Geriatrics (>65 years of age): The frequency of adverse events including serious infections, all-cause mortality, cardiovascular events, malignancies, non-melanoma skin cancer, gastrointestinal perforations, interstitial lung disease, venous thromboembolism, and arterial thromboembolism among tofacitinib treated subjects 65 years of age and older was higher than among those under the age of 65. Caution should be used when treating geriatric patients with Auro-Tofacitinib

Asian Patients: Asian patients have an increased risk of herpes zoster and opportunistic infections. Asian patients with RA also have an increased risk of interstitial lung disease. An increased incidence of some adverse events such as elevated transaminases (ALT, AST) and decreased white blood cells (WBCs) were also observed. Therefore, Auro-Tofacitinib should be used with caution in Asian patients.

MISSED DOSE:

For a missed dose, resume at the next scheduled dose.

OVERDOSAGE:

There is no experience with overdose of tofacitinib. There is no specific antidote for overdose with Auro-Tofacitinib. Treatment should be symptomatic and supportive. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

Pharmacokinetic data up to and including a single dose of 100 mg in healthy volunteers indicates that more than 95% of the administered dose is expected to be eliminated within 24 hours.

For management of a suspected drug overdose, contact your regional Poison Control Centre

Contraindications

1. In patients with known hypersensitivity to tofacitinib or ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
2. In patients with severe hepatic impairment.
3. During pregnancy and breastfeeding

For more details on prescribing Auro-Tofacitinib, please refer to the product monograph.

Prior to administering Auro-Tofacitinib

- Discuss the risks with patients using the patient safety card and Auro-Tofacitinib

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)

- 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 atherosclerotic 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.
- Consider the risk and benefits of Auro-Tofacitinib treatment carefully in patients who are at higher risk of developing serious infections, including 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, 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 Auro-Tofacitinib
- Screening for viral hepatitis should be performed in accordance with clinical guidelines.
- Check patients' laboratory parameters including lymphocytes, neutrophils, haemoglobin, lipids, and hepatic enzymes. Initiating treatment is not recommended in patients with:
  - Low absolute lymphocyte count (ALC) (<0.75 cells x109/L in adult and paediatric patients)

- Low absolute neutrophil count (ANC) (<1.00 cells x109/L in adult patients and <1.20 cells x109/L in paediatric patients)
- Low haemoglobin (<9 g/dL in adult patients and <10 g/dL in paediatric patients)

- Patients should be monitored for pulse rate and blood pressure at baseline and periodically during treatment with Auro-Tofacitinib.

Special warnings and precautions for use

Carcinogenesis and Mutagenesis

In patients treated with tofacitinib, malignancies were observed in clinical studies and the post-marketing setting including but not limited to: lymphomas, lung cancer, breast cancer, colorectal cancer, gastric cancer, melanoma, prostate cancer, pancreatic cancer, thyroid cancer and renal cell carcinoma

An increase in malignancies (excluding NMSC) was observed in patients treated with tofacitinib compared with TNF inhibitors in a post-authorization safety study .Malignancies (excluding NMSC) were more common in geriatric patients and in patients who were current or past smokers.

Lung cancers were observed in patients treated with tofacitinib and an increased rate was observed in patients treated with tofacitinib 10 mg BID compared with TNF inhibitors in a post-authorization safety study. Patients with rheumatoid arthritis and taking tofacitinib may be at higher risk than the general population for the development of lung cancer.

Lymphomas were also observed in patients treated with tofacitinib in a post-authorization safety study.

Caution should be used in treating geriatric patients, patients who are current or past smokers, and patients with other malignancy risk factors.

Consider the risks and benefits of Auro-Tofacitinib 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 Auro-Tofacitinib in patients who develop a malignancy. Recommendations for NMSC are presented below.

Rheumatoid Arthritis

In the 5 controlled clinical studies, 5 malignancies (excluding NMSC) were diagnosed in patients receiving tofacitinib 5 mg BID, and 8 malignancies (excluding NMSC) were diagnosed in patients receiving tofacitinib 10 mg BID, compared to 0 malignancies (excluding NMSC) in patients in the placebo/placebo plus DMARD group during the first 12 months. Lymphomas and solid cancers have also been observed in the long-term extension study in patients treated with tofacitinib. Patients with RA particularly those with highly active disease, may be at a higher risk (several fold) than the general population for the development of lymphoma.

In Phase 2B, controlled dose-ranging trials in de-novo renal transplant patients, all of whom received induction therapy with basiliximab, high dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with tofacitinib (2.3%) compared to 0 out of 111 patients treated with cyclosporine.

Psoriatic Arthritis

In the 2 controlled PsA clinical trials, there were 3 malignancies (excluding NMSC) in 474 patients receiving tofacitinib plus csDMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus csDMARD group (3 months exposure) and 0 malignancies in 106 patients in the adalimumab plus DMARD group (12 months exposure). Malignancies have also been observed in the long-term extension study in PsA patients treated with tofacitinib.

Ulcerative Colitis

In the 4 controlled clinical studies for ulcerative colitis (up to 52-week treatment), no malignancies (excluding NMSC) were reported with tofacitinib. In the long-term extension open-label study, malignancies (excluding NMSC) have been observed in patients treated with tofacitinib 10 mg BID, including solid cancers and lymphoma.

Non-Melanoma Skin Cancer: Non-melanoma skin cancers (NMSCs) have been reported in patients treated with tofacitinib. NMSC is a dose related adverse reaction, with a greater risk in patients treated with 10 mg BID of tofacitinib than in patients treated with 5 mg BID. An increase in overall NMSCs, including cutaneous squamous cell carcinomas was observed in patients treated with tofacitinib compared to TNF inhibitors in a post-authorization safety study. Caution should be used when treating geriatric patients and patients with a prior history of NMSC, where a higher incident of NMSC was observed. Periodic skin examination is recommended.

In the UC 52-week maintenance study, NMSC was reported in 3 patients (1.5%) treated with 10 mg BID, as compared with no reported events in patients treated with 5 mg BID and 1 patient (0.5%) treated with placebo. In the long-term open label extension study, NMSC was reported in 6 patients in the 10 mg BID group and 2 patients in the 5 mg BID group.

Cardiovascular

Heart Rate Decrease and PR Interval Prolongation: Tofacitinib caused a decrease in heart rate and a prolongation of the PR interval. Caution should be observed in patients with a low heart rate at baseline (<60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Concomitant medications that result in a decrease in heart rate and/or PR interval prolongation should be avoided to the extent possible during treatment with Tofacitinib.

Thrombosis

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, was observed at an increased incidence in patients treated with tofacitinib in a post-authorization safety study. In this post-authorization safety study, patients treated with tofacitinib 10 mg BID had a higher rate of all- cause mortality, including sudden CV death, and thrombosis compared to those treated with tofacitinib 5 mg given BID or TNF inhibitors. Many of these events were serious and some resulted in death.

In a long-term extension study in patients with ulcerative colitis (UC), four cases of pulmonary embolism were reported in patients taking tofacitinib 10 mg BID, including one death in a patient with advanced cancer.

A dosage of Auro-Tofacitinib 10 mg BID is not recommended for the treatment of RA or PsA

For the treatment of UC, use Auro-Tofacitinib at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

Avoid Auro-Tofacitinib in patients that may be at increased risk of thrombosis. Discontinue Auro-Tofacitinib and promptly evaluate patients with symptoms of thrombosis.

Major Adverse Cardiovascular Events (including Myocardial Infarction)

Major adverse cardiovascular events (MACE), including events of myocardial infarction, were observed in patients were treated with tofacitinib 5 mg BID, tofacitinib 10 mg BID or TNF inhibitors in a post-authorization safety study. An increase in non-fatal myocardial infarctions was observed in patients

treated with tofacitinib compared to TNF inhibitor .MACE, including events of myocardial infarction, were more common in geriatric patients and in patients who were current or past smokers. Caution should be used in treating geriatric patients, patients who are current or past smokers, and patients with other CV risk factors.

Retinal venous thrombosis

Retinal venous thrombosis (RVT) has been reported in patients treated with tofacitinib. Patients should be advised to promptly seek medical care if they experience symptoms suggestive of RVT.

Driving and Operating Machinery

No formal studies have been conducted on the effects on the ability to drive and use machines.

Fractures

Fractures of multiple types, including osteoporotic fractures, have been observed in patients treated with tofacitinib in clinical studies and the postmarketing setting.

Caution should be applied when using Auro-Tofacitinib in patients with known risk factors for fractures such as geriatric patients, female patients, and patients using corticosteroids.

Gastrointestinal

Events of gastrointestinal perforation have been reported with tofacitinib in RA patients, in clinical trials and in the post-market setting. The role of JAK inhibition in these events is not known. Many patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. The relative contribution of these concomitant medications versus Auro-Tofacitinib to the development of gastrointestinal perforations is not known.

There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the tofacitinib arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids.

Auro-Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., use of concomitant NSAIDs and/or corticosteroids, patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Hematologic

Anemia: Treatment with tofacitinib has been associated with decreases in hemoglobin levels. Evaluate hemoglobin prior to initiation of Auro-Tofacitinib . Avoid initiation of Auro-Tofacitinib treatment in patients with low hemoglobin values (i.e., <90 g/L). Treatment with Auro-Tofacitinib should be interrupted in patients who develop hemoglobin levels <80 g/L or whose hemoglobin level drops >20 g/L on treatment.

Lymphopenia:

Treatment with tofacitinib was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts less than 0.5 x 109 cells/L were associated with an increased incidence of treated and serious infections. Evaluate lymphocyte count prior to initiation of Auro-

Tofacitinib approximately 4-8 weeks after initiation with Auro-Tofacitinib treatment, and every 3 months thereafter.

Avoid initiation of Auro-Tofacitinib treatment in patients with a low lymphocyte count (i.e., less than 0.5 x 109cells/L). In patients who develop a confirmed absolute lymphocyte count less than 0.5 x 109cells/L, Auro-Tofacitinib should be discontinued.

Neutropenia: Treatment with tofacitinib was associated with an increased incidence of neutropenia (<2 x 10^9 cells/L) compared to placebo. Evaluate neutrophil count prior to initiation of Auro-Tofacitinib approximately 4-8 weeks after initiation with Auro-Tofacitinib treatment, and every 3 months thereafter.

Avoid initiation of Auro-Tofacitinib treatment in patients with a low neutrophil count (i.e., ANC (absolute neutrophil count) <1 x 10^9 cells/L). For patients who develop a persistent ANC of 0.5 to 1 x 10^9 cells/L, interrupt dosing until ANC is >1 x 10^9cells/L. In patients who develop an absolute neutrophil count <0.5 x 10^9 cells/L, discontinue treatment.

Lipid Elevations: Treatment with tofacitinib was associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol.

Maximum effects were generally observed within 6 weeks. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed at baseline and approximately 4-8 weeks following initiation of tofacitinib therapy, and every 6 months thereafter. Patients should be managed according to local clinical guidelines for the management of hyperlipidemia.

Hepatic/Biliary/Pancreatic

Auro-Tofacitinib is contraindicated in patients with severe hepatic impairment.

Treatment with tofacitinib was associated with an increased incidence of liver enzyme elevation compared to placebo .

Evaluate liver enzymes before initiating Auro-Tofacitinib and thereafter according to routine patient management. Prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury (DILI). If increases in ALT (alanine transaminase) or AST (aspartate transaminase) are observed and DILI is suspected, the administration of Auro-Tofacitinib should be interrupted until the diagnosis is excluded.

Most of the liver enzyme abnormalities in RA and PsA patients occurred in studies with background DMARD (primarily methotrexate) therapy.

One case of DILI was reported in a RA patient treated with tofacitinib 10 mg BID for approximately.

2.5 months. The patient developed symptomatic elevations of AST and ALT with values greater than 3x ULN associated concurrently with total bilirubin value greater than 2x ULN, which required hospitalization and a liver biopsy.

In UC patients, tofacitinib treatment with 5 and 10 mg BID was also associated with an increased incidence of liver enzyme elevation compared to placebo, with a trend for higher incidence with the 10 mg BID as compared to the 5 mg BID.

One patient treated with tofacitinib 10 mg BID in the maintenance UC study experienced an increase in liver enzymes which decreased upon discontinuation of treatment. The case was adjudicated as possible DILI, while noting ultrasound findings of fatty liver.

The impact of Auro-Tofacitinib on chronic viral hepatitis reactivation is unknown. Tofacitinib has not been studied in patients with positive hepatitis B virus or hepatitis C virus serology and should therefore not be used in these populations.

Tofacitinib has not been studied in patients with severe hepatic impairment and should not be used in these patients Dose adjustment of Auro-Tofacitinib is recommended for patients with moderate hepatic impairment.

Immune

Hypersensitivity Reactions: Reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients treated with tofacitinib. Some events were serious. If a hypersensitivity reaction is suspected, promptly discontinue tofacitinib while evaluating the potential cause or causes of the reaction.

Immunocompromised Patients: Auro-Tofacitinib can increase the risk of infections and immunosuppression when co-administered with potent immunosuppressants such as cyclosporine, azathioprine and tacrolimus. Combined use of tofacitinib with potent immunosuppressive drugs has not been studied and is not recommended.

Immunizations: No data are available on the secondary transmission of infection by live vaccines to patients receiving tofacitinib. It is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Auro-Tofacitinib therapy and that live vaccines not be given concurrently with Auro-Tofacitinib. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunomodulatory agents.

In patients being considered for Auro-Tofacitinib therapy, live zoster vaccine 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 Auro-Tofacitinib.

In a clinical trial, a varicella naïve patient treated with tofacitinib and methotrexate developed disseminated infection with the vaccine strain of the varicella zoster virus 16 days after vaccination. A satisfactory immune response to the vaccine was developed 6 weeks post-vaccination.

Antibody levels after vaccination may be lower in patients treated with tofacitinib

Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in RA patients receiving immunomodulatory agents, including tofacitinib. The most common serious infections reported with tofacitinib included pneumonia, urinary tract infection, cellulitis, herpes zoster, bronchitis, septic shock, diverticulitis, gastroenteritis, appendicitis and sepsis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcus, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infections, listeriosis and aspergillosis were reported with tofacitinib .Some patients have presented with disseminated rather than localized disease and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

A dose dependent increase in serious infections was observed in patients treated with tofacitinib compared to TNF inhibitors in a post-authorization safety study. Some of these serious infections resulted in death. Opportunistic infections were also reported in the study.

Patients treated with tofacitinib 10 mg BID are at higher risk of serious infections, and herpes zoster infections compared to those treated with 5 mg BID. The incidence rate per 100 person-years (PYs) for herpes zoster opportunistic infections in the UC 52-week maintenance study was higher in patients treated with tofacitinib 10 mg BID (6.64) as compared to tofacitinib 5 mg BID (2.05) or placebo (0.97).

Auro-Tofacitinib should not be administered in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating Auro-Tofacitinib 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; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Auro-Tofacitinib. Auro-Tofacitinib should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with Auro-Tofacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

As there is a higher incidence of infections in the geriatric and in the diabetic populations in general, caution should be used when treating geriatric patients and patients with diabetes. 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 RA patients treated with tofacitinib in clinical trials and in the post-marketing setting.

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection.

Treatment with tofacitinib was associated with increased rates of infections in Asian patients compared to other races. Auro-Tofacitinib should be used with caution in this population.

Tuberculosis

Patients should be evaluated and tested for latent or active tuberculosis (TB) infection prior to administration of Auro-Tofacitinib and periodically (e.g., annually) while taking Auro-Tofacitinib.

Auro-Tofacitinib should not be given to patients with active TB.

Antituberculosis therapy should also be considered prior to administration of Auro-Tofacitinib in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but have risk factors for tuberculosis infection.

Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering Auro-Tofacitinib.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with tofacitinib. An increase in herpes zoster events was observed in patients treated with tofacitinib compared to TNF inhibitors in a post-authorization safety study. Post-marketing cases of hepatitis B reactivation have been reported in patients treated with tofacitinib. The impact of Auro-Tofacitinib on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with Auro-Tofacitinib.

Monitoring and Laboratory Tests

Lipid tests should be performed at baseline, approximately 4-8 weeks after initiation with Auro-Tofacitinib and every 6 months thereafter. Patients should be managed according to clinical guidelines for the management of hyperlipidemia**.**

Liver enzyme tests are recommended before initiating Auro-Tofacitinib treatment and thereafter according to routine patient management. If increases in ALT or AST are observed during routine patient management and DILI is suspected, the administration of Auro-Tofacitinib should be interrupted until this diagnosis has been excluded.

Assessment of renal function is recommended prior to initiation of Auro-Tofacitinib**.**

Lymphocyte, neutrophil and hemoglobin tests should be performed at baseline, approximately 4-8 weeks after initiation with Auro-Tofacitinib treatment, and every 3 months thereafter.

Vital signs: Patients should be monitored for pulse rate and blood pressure at baseline and periodically during treatment with Auro-Tofacitinib

Musculoskeletal

Treatment with tofacitinib was associated with increases in creatine kinase (CK). Maximum effects were generally observed within 6 months. Rhabdomyolysis was reported in one patient treated with tofacitinib. Creatine kinase levels should be checked in patients with symptoms of muscle weakness and/or muscle pain to evaluate for evidence of rhabdomyolysis. Increases in CK were reported more frequently in patients treated with tofacitinib 10 mg as compared to those treated with 5 mg BID.

Renal

Dosage adjustment of Auro-Tofacitinib is recommended in patients with moderate and severe renal impairment. In clinical trials, tofacitinib was not evaluated in patients with baseline creatinine clearance values (estimated by the Cockcroft-Gault equation) less than 40 mL/min.

Reproductive Health: Female and Male Potential

- **Fertility**: Based on findings in animal studies, tofacitinib may cause decreased fertility when administered to females.
- **Teratogenic Risk**: Based on findings in animal studies, tofacitinib may cause fetal harm when administered to a pregnant woman. Administration of tofacitinib to rats and rabbits during organogenesis caused increases in fetal malformations. Pregnant women should be advised of the potential risk to a fetus. Females of reproductive potential should be advised to use effective contraception during treatment with Auro-Tofacitinib and for 4 to 6 weeks following completion of therapy.

Respiratory

Interstitial Lung Disease: Events of interstitial lung disease (ILD) have been reported in RA clinical trials with tofacitinib, although the role of JAK inhibition in these events is not known. All patients who developed ILD were taking concomitant methotrexate, corticosteroids and/or sulfasalazine, which have been associated with ILD. Asian patients had an increased risk of ILD.

Auro-Tofacitinib should be used with caution in patients with a risk or history of ILD.

Special Populations

Pregnant Women

Auro-Tofacitinib is contraindicated during pregnancy. There are no adequate and well-controlled studies on the use of tofacitinib in pregnant women. Tofacitinib has been shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility, parturition, and peri/postnatal development.

Women of reproductive potential should be advised to use effective contraception during Auro-Tofacitinib treatment and for 4 to 6 weeks after the last dose.

Breast-feeding

Auro-Tofacitinib is contraindicated in women who breastfeed. Auro-Tofacitinib was secreted in milk of lactating rats. It is not known whether Auro-Tofacitinib is excreted in human milk.

Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics

Geriatrics (>65 years of age): The frequency of adverse events including serious infections, all-cause mortality, cardiovascular events, malignancies, non-melanoma skin cancer, gastrointestinal perforations, interstitial lung disease, venous thromboembolism, and arterial thromboembolism among tofacitinib treated subjects 65 years of age and older was higher than among those under the age of 65. Caution should be used when treating geriatric patients with Auro-Tofacitinib.

Asian Patients

Asian patients have an increased risk of herpes zoster and opportunistic infections. Asian patients with RA also have an increased risk of ILD. An increased incidence of some adverse events such as elevated transaminases (ALT, AST) and decreased white blood cells (WBCs) were also observed. Therefore, Auro-Tofacitinib should be used with caution in Asian patients.

Patient Counselling

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

It is important for physicians to:

- Provide the patient safety card to each patient who is prescribed with Auro-Tofacitinib
- 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 carry the patient safety card with them, particularly when they visit any doctors' office and/or the emergency department

You should remind patients to seek immediate medical attention if they experience any of the following signs or 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 Auro-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 Auro-Tofacitinib, or soon after taking Auro-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 Auro-Tofacitinib
- Become pregnant or plan on becoming pregnant

Reporting of Adverse Events

If you become aware of any suspected adverse reactions in association with use of Auro-Tofacitinib, please report the event promptly to Health Canada by https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html or by mail or by fax; or Calling toll-free at 1-866-234-2345.

Any suspected adverse reactions may also be reported to Auro Pharma Inc on www.auropharma.ca or by calling at 1-855-648-6681.