For sale in India only
For the use of a Hospital or a Registered medical practitioner or a Institution
PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE) AND THROMBOSIS

SERIOUS INFECTIONS
Patients treated with Tofacitinib/Tofacitinib Extended-Release are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt Tofacitinib / Tofacitinib Extended-Release until the infection is controlled. Techukundam ankunna
Reported infections include:
• Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before Tofacitinib / Tofacitinib Extended-Release use and during therapy. Treatment for latent infection should be initiated prior to Tofacitinib/Tofacitinib Extended-Release.
• Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
• Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.

The risks and benefits of treatment with Tofacitinib / Tofacitinib Extended-Release should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.
Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Tofacitinib/Tofacitinib Extended-Release, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MORTALITY
In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing Tofacitinib 5 mg twice a day or Tofacitinib 10 mg twice a day to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with Tofacitinib 5 mg twice a day or Tofacitinib 10 mg twice a day. A Tofacitinib / Tofacitinib Oral Solution 10 mg twice daily (or a Tofacitinib Extended-Release 22 mg once daily) dosage is not recommended for the treatment of RA or PsA.

MALIGNANCIES
Malignancies, including lymphomas and solid tumors, have occurred in patients treated with Tofacitinib and other Janus kinase inhibitors used to treat inflammatory conditions. In RA patients, a higher rate of malignancies (excluding NMSC) was observed in patients treated with Tofacitinib 5 mg twice a day or Tofacitinib 10 mg twice a day compared with TNF blockers.

Lymphomas and lung cancers were observed at a higher rate in patients treated with Tofacitinib 5 mg twice a day or Tofacitinib 10 mg twice a day in RA patients compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with Tofacitinib and concomitant immunosuppressive medications.

MAJOR ADVERSE CARDIOVASCULAR EVENTS
RA patients 50 years of age and older with at least one cardiovascular risk factor, treated with Tofacitinib 5 mg twice daily or Tofacitinib 10 mg twice daily, had a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue Tofacitinib/Tofacitinib Extended-Release in patients that have experienced a myocardial infarction or stroke.

THROMBOSIS
Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with Tofacitinib and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death. RA patients 50 years of age and older with at least one cardiovascular risk factor treated with Tofacitinib 5 mg twice daily or Tofacitinib 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid Tofacitinib/Tofacitinib Extended-Release in patients at risk. Discontinue Tofacitinib/ Tofacitinib Extended-Release and promptly evaluate patients with symptoms of thrombosis.

1. GENERIC NAME
Tofacitinib Extended release Tablets 11 mg & 22 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Tofacitinib Extended release Tablets 11 mg
Each film coated Extended release tablet contains
Tofacitinib citrate IP equivalent to Tofacitinib 11 mg
Excipients q.s. Colour: Titanium Dioxide IP

Tofacitinib Extended release Tablets 22 mg
Each film coated Extended release tablet contains
Tofacitinib citrate IP equivalent to Tofacitinib 22 mg
Excipients q.s. Colour: Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH
DOSAGE FORM: Extended release Tablets
STRENGTH: 11 mg & 22 mg

4.CLINICAL PARTICULARS
4.1.Indications
Rheumatoid Arthritis: It is indicated for the treatment of adult patients with moderate to severe active rheumatoid arthritis (RA) who have an inadequate response or intolerance to one or more TNF blockers.
Psoriatic Arthritis: It is indicated for the treatment of adult patients with active psoriatic arthritis (PsA) who have an inadequate response or intolerance to one or more TNF blockers.
Ulcerative Colitis: It is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have an inadequate response or intolerance to one or more TNF blockers.

4.2. Posology and Method of Administration
Important Administration Instructions
• Tofacitinib extended-release tablets is not interchangeable or substitutable with Tofacitinib Oral Solution.
• Changes between Tofacitinib and Tofacitinib extended-release should be made by the healthcare provider.
• Do not initiate Tofacitinib extended-release tablets in patients with an absolute lymphocyte count less than 500 cells/mm3, an absolute neutrophil count (ANC) less than 1000 cells/mm3 or who have hemoglobin levels less than 9 g/dL.
• Dose interruption is recommended for management of lymphopenia, neutropenia, and anemia.
• Interrupt use of Tofacitinib extended-release tablets if a patient develops a serious infection until the infection is controlled.
• Take Tofacitinib extended-release tablets with or without food.
• Swallow Tofacitinib extended-release tablets whole and intact. Do not crush, split, or chew.

Recommended Dosage in Rheumatoid Arthritis
Table 1 displays the recommended adult daily dosage of Tofacitinib extended-release and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, in patients with moderate or severe renal impairment (including but not limited to those with severe insufficiency who are undergoing hemodialysis) or moderate hepatic impairment, with lymphopenia, neutropenia, or anemia.

Table 1: Recommended Dosage of Tofacitinib extended-release in Patients with Rheumatoid Arthritis and Psoriatic Arthritis.

	Tofacitinib extended-release
Adult Patients:	11 mg Once daily
Patients receiving: • Strong CYP3A4 inhibitors (e.g., ketoconazole), or • a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole)	Reduce to Tofacitinib 5 mg Once Daily
Patients with: • moderate or severe renal impairment • moderate hepatic impairment*	Reduce to Tofacitinib 5 mg Once Daily
For patients undergoing hemodialysis**, dose should be administered afterthe dialysis session on dialysis days. If a dose was taken before thedialysis procedure, supplemental doses are not recommended in patientsafter d ialysis.**	
Patients with lymphocyte count less than 500 cells/mm ^{3}, confirmed by repeat testing	Discontinue dosing
Patients with ANC 500 to 1000 cells/mm ^{3}	Interrupt dosing. When ANC is greater than 1000, resume 11 mg once daily
Patients with ANC less than 500 cells/mm ^{3}	Discontinue dosing
Patientswith haemoglobin lessthan8g/dLora decreaseofmorethan2 g/dL	Interrupt dosing until hemoglobin values have normalized.

If Tofacitinib extended-release is used in combination with nonbiologic disease modifying antirheumatic drugs (DMARDs) in psoriatic arthritis. The efficacy of Tofacitinib extended-release as a monotherapy has not been studied in psoriatic arthritis.

* Use of Tofacitinib extended-release in patients with severe hepatic impairment is not recommended.
Switching from Tofacitinib Tablets to Tofacitinib Extended-Release Tablets
Patients treated with Tofacitinib tablets 5 mg twice daily may be switched to Tofacitinib extended-release tablets 11 mg once daily the day following the last dose of Tofacitinib 5 mg.

Recommended Dosage in Ulcerative Colitis
Table 2 displays the recommended adult daily dosage of Tofacitinib extended-release and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, with moderate or severe renal impairment (including but not limited to those with severe insufficiency who are undergoing hemodialysis) or moderate hepatic impairment, with lymphopenia, neutropenia or anemia.

Table 2: Recommended Dosage of Tofacitinib extended-release in Patients with UC

	Tofacitinib extended-release tablet
Adult patients	Induction: 22 mg twice daily for at least 8 weeks; evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed continue 22 mg once daily for a maximum of 16 weeks. Discontinue 22 mg twice daily after 16 weeks if adequate therapeutic response is not achieved. Maintenance: 11 mg twice daily. For patients with loss of response during maintenance treatment, a dosage of 22 mg once daily may be considered and limited to the shortest duration, with careful consideration of the benefits and risks for the individual patient . Use the lowest effective dose needed to maintain response
Patients receiving: • Strong CYP3A4 inhibitors (e.g., Ketoconazole), or • A moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitors (e.g., fluconazole)*	If taking 22 mg once daily, reduce to 11 mg once daily. If taking 11 mg once daily, reduce to Tofacitinib 5 mg once daily.
Patients with: • Moderate or severe renal impairment • Moderate hepatic impairment	If taking 22 mg once daily, reduce to 11 mg once daily. If taking 11 mg twice daily, reduce toTofacitinib 5 mg once daily.
	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 recommende d in patients after dialysis.
Patients with lymphocyte count lessthan 500 cells/mm ^{3}, confirmed byrepeat testing	Discontinue dosing
Patients with ANC 500 to 1000 cells/mm^3	If taking 22 mg once daily, reduce to 11 mg once daily. When ANC is greater than 1000, increase to 22 mg once daily based on clinical response.
	If taking 11 mg once daily, interrupt dosing. When ANC is greater than 1000, resume 11 mg once daily.
Patients with ANC less than 500 cells/mm^3	Discontinue dosing.
Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL	Interrupt dosing until hemoglobin values have normalized.

*Use of Tofacitinib tablets in patients with severe hepatic impairment is not recommended.
Switching from Tofacitinib Tablets to Tofacitinib Extended-Release Tablets
Patients treated with Tofacitinib 5 mg tablets twice daily may be switched to Tofacitinib extended-release tablets 11 mg once daily the day following the last dose of Tofacitinib tablets
5 mg. Patients treated with Tofacitinib 10 mg tablets twice daily may be switched to Tofacitinib extended-release tablets 22 mg once daily the day following the last dose of Tofacitinib 10 mg.

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

4.4.Special Warnings and Precautions for Use
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, ciclosporine 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 Methotrexate (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. A dose dependent increased risk for VTE was observed in a clinical study with Tofacitinib compared to TNF inhibitors.
Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage.
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.
Promptly evaluate patients with signs and symptoms of VTE and discontinue Tofacitinib in patients with suspected VTE, regardless of dose or indication.

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. The risk of opportunistic infections is higher in Asian geographic regions. Rheumatoid arthritis patients taking corticosteroids may be predisposed 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:
•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,
•who are over 65 years of age.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Tofacitinib. Treatment 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 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 elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients over 65 years of age Tofacitinib should only be considered if no suitable alternative treatment is available.

Tuberculosis
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

Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of Tofacitinib.
Patients with latent TB, who test positive, should be treated with standard antimycobacterial therapy before administering Tofacitinib.

Antituberculosis therapy should also be considered prior to administration of Tofacitinib in patients who test negative for TB but who have a past history of latent or active TB and where an adequate course of treatment cannot be confirmed; or those who test negative but who have risk factors for TB infection. Consultation with a healthcare professional with expertise in the treatment of TB is recommended to aid in the decision about whether initiating antituberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral reactivation

Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with 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 trials. 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, 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.

Thrombosis

Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis, have occurred with Tofacitinib and other Janus kinase (JAK) inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death.

Promptly evaluate patients with symptoms of thrombosis and discontinue Tofacitinib/ Tofacitinib extended release in patients with symptoms of thrombosis.

Avoid Tofacitinib/ Tofacitinib extended release in patients that may be at increased risk of thrombosis. For the treatment of UC, use Tofacitinib/Tofacitinib extended release at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response.

Malignancy and lymphoproliferative disorder

Tofacitinib may affect host defences against malignancies.

In patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed with Tofacitinib compared to TNF inhibitors.

Lung cancers and lymphoma in patients treated with Tofacitinib have also been observed in other clinical studies and in the post marketing setting.

The risks and benefits of Tofacitinib treatment should be considered prior to initiating therapy particularly in patients with a known malignancy (other than a successfully treated non-melanoma skin cancer), patients who develop a malignancy while on treatment and patients who are current or past smokers. (USPI)

Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

Non-melanoma skin cancer

NMSCs have been reported in patients treated with Tofacitinib. The risk of NMSC may be higher in patients treated with Tofacitinib 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

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 trials 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 trials 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.

Hypersensitivity

In post-marketing experience, cases of drug hypersensitivity associated with Tofacitinib administration have been reported. Allergic reactions included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, Tofacitinib should be discontinued immediately.

Laboratory parameters

Lymphocytes

Treatment with Tofacitinib was associated with an increased incidence of lymphopenia compared to placebo. Lymphocyte counts less than 750 cells/mm3 were associated with an increased incidence of serious infections. It is not recommended to initiate or continue Tofacitinib treatment in patients with a confirmed lymphocyte count less than 750 cells/mm3. Lymphocytes should be monitored at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts.

Neutrophils

Treatment with Tofacitinib was associated with an increased incidence of neutropenia (less than 2,000 cells/mm3) compared to placebo. It is not recommended to initiate Tofacitinib treatment in patients with an ANC less than 1,000 cells/mm3. ANC should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter.

Haemoglobin

Treatment with Tofacitinib has been associated with decreases in haemoglobin levels. It is not recommended to initiate Tofacitinib treatment in patients with a haemoglobin value less than 9 g/dL. Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter.

Liver Enzyme Elevations

Treatment with Tofacitinib was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy.

Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of Tofacitinib/Tofacitinib extended release should be interrupted until this diagnosis has been excluded.

Lipid monitoring

Treatment with Tofacitinib was associated with increases in lipid parameters such as total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. Assessment of lipid parameters should be performed after 8 weeks following initiation of tofacitinib therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia. Increases in total and LDL cholesterol associated with tofacitinib may be decreased to pretreatment levels with statin therapy.

Vaccinations

Prior to initiating Tofacitinib, it is recommended that all 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 take into account the pre-existing immunosuppression in a given patient.

Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular 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.

Gastrointestinal obstruction with a non-deformable prolonged-release formulation

Caution should be used when administering tofacitinib prolonged-release tablets to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other medicinal products utilising a non-deformable prolongedrelease formulation.

Excipients with known effect

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5.Drug Interactions

Table 3 includes drugs with clinically important drug interactions when administered concomitantly with Tofacitinib/Tofacitinib extended release and instructions for preventing or managing them.

Table 3: Clinical Relevant Interactions Affecting Tofacitinib When Coadministered with Other Drugs

Strong CP3A4 Inhibitors (e.g., ketoconazole)	
Clinical Impact	Increased exposure to Tofacitinib
Intervention	Dosage adjustment of Tofacitinib extended release is recommended
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to Tofacitinib
Intervention	Dosage adjustment of Tofacitinib extended release is recommended
Strong CYP3A4 Inducers (e.g.,rifampin)	
Clinical Impact	Decreased exposure to Tofacitiniband may result in loss of or reduced clinical response
Intervention	Coadministration with Tofacitinib extended release is not recommended
Immunosuppressive Drugs (e.g., azathioprine, tacrolimuscyclosporine)	
Clinical Impact	Risk of added immunosuppression; coadministration with biologic DMARDs or potent immunosuppressants has not been studied in patients with rheumatoid arthritis, psoriatic arthritis and ulcerative colitis
Intervention	Coadministration with Tofacitinib extended release is not recommended

4.6.Use in Special Populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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 to affect parturition and peri/postnatal development.

As a precautionary measure, the use of Tofacitinib during pregnancy is contraindicated.

Women of childbearing potential/contraception in females

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.

Breast-feeding

It is not known whether Tofacitinib is secreted in human milk. A risk to the breast-fed child cannot be excluded. Tofacitinib was secreted in the milk of lactating rats. As a precautionary measure, the use of Tofacitinib during breast-feeding is contraindicated.

Fertility

Formal studies of the potential effect on human fertility have not been conducted. Tofacitinib impaired female fertility but not male fertility in rats.

Pediatric Use

The safety and effectiveness of Tofacitinib extended release in pediatric patients have not been established.

Geriatric Use

As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Use in Diabetics

As there is a higher incidence of infection in diabetic population in general, caution should be used when treating patients with diabetes.

Renal Impairment

Moderate and Severe Impairment

Tofacitinib-treated patients with moderate or severe renal impairment had greater Tofacitinib blood concentrations than Tofacitinib-treated patients with normal renal function. Therefore, dosage adjustment of Tofacitinib/ Tofacitinib extended release is recommended in patients with moderate or severe renal impairment (including but not limited to those with severe insufficiency who are undergoing hemodialysis).

Mild impairment

No dosage adjustment is required in patients with mild renal impairment.

Hepatic Impairment

Severe Impairment

Tofacitinib has not been studied in patients with severe hepatic impairment; therefore, use of Tofacitinib in patients with severe hepatic impairment is not recommended.

Moderate Impairment

Tofacitinib-treated patients with moderate hepatic impairment had greater Tofacitinib blood concentration than Tofacitinib-treated patients with normal hepatic function. Higher blood concentrations may increase the risk of some adverse reactions. Therefore, dosage adjustment of Tofacitinib is recommended in patients with moderate hepatic.

Mild Impairment

No dosage adjustment of Tofacitinib is required in patients with mild hepatic impairment.

Hepatitis B or C Serology

The safety and efficacy of Tofacitinib have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

4.7.Effects on Ability to Drive and Use Machines

Tofacitinib has no or negligible influence on the ability to drive and use machines.

4.8.Undesirable Effects

Tabulated list of adverse reactions

The ADRs listed in the table below are from clinical studies in patients with RA and are presented by System Organ Class (SOC) and frequency categories, defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Adverse Drug Reactions

System organ class	Common =1/100 to <1/10	Uncommon =1/1,000 to <1/100	Rare =1/10,000 to <1/1,000	Very rare <1/10,000	Not known (cannot be estimated from the available data)
Infections and infestations	Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Nasopharyngitis Pharyngitis	Tuberculosis Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection	Sepsis Urosepsis Disseminated TB Necrotizing fasciitis Bacteraemia Staphylococcal bacteraemia *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal Pneumonia bacterial Encephalitis Atypical mycobacterial infection Cytomegalovirus infection Arthritis bacterial	Tuberculosis of central nervous system Meningitis cryptococcal *Mycobacterium avium* complex infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Lung cancer Non-melanoma skin cancers	Lymphoma		
Blood and lymphatic system disorders	Anaemia	Leukopenia Lymphopenia Neutropenia			
Immune system disorders					Drug hypersensitivity Angioedema Urticaria
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia Dehydration			
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache	Paraesthesia			
Vascular disorders	Hypertension	Venous thromboembolism			
Cardiac disorders		Myocardial Infarction			
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea Sinus congestion			
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia				
Hepatobiliary disorders		Hepatic steatosis Hepatic enzyme increased Transaminases increased Liver function test abnormal Gamma glutamyl-transferase increased			
Skin and subcutaneous tissue disorders	Rash	Erythema Pruritus			
Musculoskeletal and connective tissue disorders	Arthralgia	Musculoskeletal pain Joint swelling Tendonitis			
General disorders and administration site conditions	Pyrexia Oedema peripheral Fatigue				
Investigations	Blood creatine phosphokinase increased	Blood creatinine increased Blood cholesterol increased Low density lipoprotein increased Weight increased			
Injury, poisoning and procedural complications		Ligament sprain Muscle strain			

Reporting of suspected adverse reactions
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. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ To report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on 1800 180 3024 or you can report to MSN Labs on +91 40-38265227 Ext- 5295. By reporting side effects, you can help provide more information on the safety of this product.

4.9.Overdose

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. There is no specific antidote for overdose with Tofacitinib. Treatment should be symptomatic and supportive. Pharmacokinetic data up to and including a single dose of 100 mg in healthy volunteers indicate that more than 95% of the administered dose is expected to be eliminated within 24 hours.

5.PHARMACOLOGICAL PROPERTIES

5.1Pharmacodynamic Properties

Mechanism of action
Pharmacotherapeutic groups: Immunosuppressants, Selective Immunosuppressants;

Tofacitinib is a potent, selective inhibitor of the JAK family. In enzymatic assays, Tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In contrast, Tofacitinib has a high degree of selectivity against other kinases in the human genome. In human cells, Tofacitinib preferentially inhibits signalling by heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib attenuates signalling of interleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which will result in modulation of the immune and inflammatory response.

Pharmacodynamic effects
In patients with RA, treatment up to 6 months with Tofacitinib was associated with dose-dependent reductions of circulating CD16/56+ natural killer (NK) cells, with estimated maximum reductions occurring at approximately 8-10 weeks after initiation of therapy. These changes generally resolved within 2-6 weeks after discontinuation of treatment. Treatment with Tofacitinib was associated with dose-dependent increases in B cell counts. Changes in circulating T-lymphocyte counts and T-lymphocyte subsets (CD3+, CD4+ and CD8+) were small and inconsistent.

Following long-term treatment (median duration of Tofacitinib treatment of approximately 5 years), CD4+ and CD8+ counts showed median reductions of 28% and 27%, respectively, from baseline. In contrast to the observed decrease after short-term dosing, CD16/56+ natural killer cell counts showed a median increase of 73% from baseline. CD19+ B cell counts showed no further increases after long-term Tofacitinib treatment. All these lymphocyte subset changes returned toward baseline after temporary discontinuation of treatment. There was no evidence of a relationship between serious or opportunistic infections or herpes zoster and lymphocyte subset counts.

Changes in total serum IgG, IgM, and IgA levels over 6-month Tofacitinib dosing in patients with RA were small, not dose-dependent and similar to those seen on placebo, indicating a lack of systemic humoral suppression. After treatment with Tofacitinib in RA patients, rapid decreases in serum C-reactive protein (CRP) were observed and maintained throughout dosing. Changes in CRP observed with Tofacitinib treatment do not reverse fully within 2 weeks after discontinuation, indicating a longer duration of pharmacodynamic activity compared to the half-life.

5.2 Pharmacokinetic Properties

Following oral administration of Tofacitinib 11 mg prolonged-release tablet, peak plasma concentrations are reached at 4hours and half-life is ~6 hours. Steady state concentrations are achieved within 48 hours with negligible accumulation after once daily administration. Steady-state AUC and Cmax of Tofacitinib for tofacitinib11mgprolonged-releasetablet administered once daily are equivalent to those of Tofacitinib 5 mg film-coated tablets administered twice daily.

Absorption and distribution
Coadministration of Tofacitinib 11 mg prolonged-release tablet with a high-fat meal resulted in no changes in AUC while Cmax was increased by 27%.
After intravenous administration, the volume of distribution is 87 L. Approximately 40% of circulating Tofacitinib is bound to plasma proteins. Tofacitinib binds predominantly to albumin and does not appear to bind to α1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

Biotransformation and elimination

Clearance mechanisms for Tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of Tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabelled study, more than 65% of the total circulating radioactivity was accounted for by unchanged active substance, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. All metabolites have been observed in animal species and are predicted to have less than 10-fold potency than Tofacitinib for JAK1/3 inhibition. No evidence of stereo conversion in human samples was detected. The pharmacologic activity of Tofacitinib is attributed to the parent molecule. In vitro, Tofacitinib is a substrate for MDR1, but not for breast cancer resistance protein (BCRP), OATP1B1/1B3, or OCT1/2.

Pharmacokinetics in patients
The enzymatic activity of CYP enzymes is reduced in RA patients due to chronic inflammation. In RA patients, the oral clearance of Tofacitinib does not vary with time, indicating that treatment with Tofacitinib does not normalise CYP enzyme activity.

Population PK analysis in RA patients indicated that systemic exposure (AUC) of Tofacitinib in the extremes of body weight (40 kg, 140 kg) were similar (within 5%) to that of a 70 kg patient. Elderly patients 80 years of age were estimated to have less than 5% higher AUC relative to the mean age of 55 years. Women were estimated to have 7% lower AUC compared to men. The available data have also shown that there are no major differences in Tofacitinib AUC between White, Black and Asian patients. An approximate linear relationship between body weight and volume of distribution was observed, resulting in higher peak (Cmax) and lower trough (Cmin) concentrations in lighter patients. However, this difference is not considered to be clinically relevant. The between-subject variability (percentage coefficient of variation) in AUC of Tofacitinib is estimated to be approximately 27%.

Renal impairment
Subjects with mild (creatinine clearance 50-80 mL/min), moderate (creatinine clearance 30-49 mL/min), and severe (creatinine clearance < 30 mL/min) renal impairment had 37%, 43% and 123% higher AUC, respectively, compared to subjects with normal renal function. In subjects with end-stage renal disease (ESRD), contribution of dialysis to the total clearance of Tofacitinib was relatively small. Following a single dose of 10 mg, mean AUC in subjects with ESRD based on concentrations measured on a non-dialysis day was approximately 40% (90% confidence intervals: 1.5-95%) higher compared to subjects with normal renal function. In clinical trials, Tofacitinib was not evaluated in patients with baseline creatinine clearance values (estimated by Cockroft-Gault equation) less than 40 mL/min.

Hepatic impairment
Subjects with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had 3%, and 65% higher AUC, respectively, compared to subjects with normal hepatic function. In clinical trials, Tofacitinib was not evaluated in subjects with severe (Child Pugh C) hepatic impairment, or in patients screened positive for hepatitis B or C.

Drug interactions
Tofacitinib is not an inhibitor or inducer of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) and is not an inhibitor of UGTs (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7). Tofacitinib is not an inhibitor of MDR1, OATP1B1/1B3, OCT2, OAT1/3, or MRP at clinically meaningful concentrations.

Comparison of PK of prolonged-release and film-coated tablet formulations
Tofacitinib 11 mg prolonged-release tablets once daily have demonstrated PK equivalence (AUC and Cmax) totofacitinib5 mg film-coated tablets twice daily.

6.NONCLINICAL PROPERTIES
6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of Tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies.
Tofacitinib, at exposure levels approximately 34 times the recommended dose of 5 mg twice daily, and approximately 17 times the 10 mg twice daily dose (on an AUC basis at oral doses of 200 mg/kg/day) was not carcinogenic in mice.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hibernomas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 30 mg/kg/day (approximately 42 times the exposure levels at the recommended dose of 5 mg twice daily, and approximately 21 times the10mgtwicedailydoseon an AUC basis). The relevance of benign Leydig cell tumors to human risk is not known.

Tofacitinib is not mutagenic or genotoxic based on the results of a series of in vitro and in vivo tests for gene mutations and chromosomal aberrations.

In rats, tofacitinib at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the 10 mg twice daily dose (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the recommended dose of 5 mg twice daily, and approximately 0.5 times the 10 mg twice daily dose (on an AUC basis at oral doses of 1 mg/kg/day). Tofacitinib exposure levels at approximately 133 times the recommended dose of 5 mg twice daily, and approximately 67 times the 10 mg twice daily dose (on an AUC basis at oral doses of 100 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration.

7.PHARMACEUTICAL PARTICULARS

7.1 Incompatibilities
None

7.2 Shelf life
Shelf life as refer to carton

7.3 Packing Information
10's Tablets blister pack in carton.

7.4 Storage and Handling Instructions
Storage: Store below 30°C. Protect from light & moisture.

8.PATIENT COUNSELING INFORMATION
Serious Infections
Inform patients that Tofacitinib may lower the ability of their immune system to fight infections. Advise patients not to start taking Tofacitinib if they have an active infection. Instruct patients to contact their healthcare provider immediately during treatment if symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment. Advise patients that the risk of herpes zoster, some cases of which can be serious, is increased in patients treated with Tofacitinib.
Malignancies and Lymphoproliferative Disorders
Inform patients that Tofacitinib may increase their risk of certain cancers, and that lymphoma and other cancers have been observed in patients taking Tofacitinib. Instruct patients to inform their healthcare provider if they have ever had any type of cancer.
Major Adverse Cardiovascular Events
Inform patients that Tofacitinib may increase their risk of major adverse cardiovascular events (MACE) defined as myocardial infarction, stroke, and cardiovascular death. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events.
Thrombosis
Advise patients to stop taking Tofacitinib and to call their healthcare provider right away if they experience any symptoms of thrombosis (sudden shortness of breath, chest pain worsened with breathing, swelling of leg or arm, leg pain or tenderness, red or discolored skin in the affected leg or arm).
Hypersensitivity
Advise patients to stop taking Tofacitinib and to call their healthcare provider right away if they experience any symptoms of allergic reactions while taking Tofacitinib.
Important Information on Laboratory Abnormalities
Inform patients that Tofacitinib may affect certain lab test results, and that blood tests are required before and during Tofacitinib treatment.
Pregnancy
Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy.
Lactation
Advise women not to breastfeed during treatment with Tofacitinib and for at least 18 hours after the last dose of Tofacitinib.
Infertility
Advise females of reproductive potential that Tofacitinib may impair fertility. It is not known if this effect is reversible.

9.DETAILS OF MANUFACTURER
Manufactured by: Mascot Health Series Pvt. Ltd.
Plot No. 79,80, Sec-6A, IIE, Sidcul, Haridwar-249403

10.DETAILS OF PERMISSION OR LICENCE NUMBER
Mfg. Lic. No.: 68/UA/2009
Not Applicable

11.DATE OF REVISION
Nov 2023

MFLL0008-01