For sale in India only
To be sold by retail on the prescription of a Rheumatologist or Specialist in Internal Medicine only
PRESCRIBING INFORMATION

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

Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with Tofacitinib Oral Solution if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative latent TB test.
- **Higher rate of all-cause mortality, including sudden cardiovascular death with Tofacitinib vs. TNF blockers in rheumatoid arthritis (RA) patients.**
- **Malignancies have occurred in patients treated with Tofacitinib. Higher rate of lymphomas and lung cancers with Tofacitinib vs. TNF blockers in RA patients.**
- **Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with Tofacitinib vs. TNF blockers in RA patients.**
- **Thrombosis has occurred in patients treated with Tofacitinib. Increased incidence of pulmonary embolism, venous and arterial thrombosis with Tofacitinib vs. TNF blockers in RA patients.**

1. GENERIC NAME
Tofacitinib Oral Solution 1 mg/ml
Tofadoz® Oral Solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Tofacitinib Oral solution 1 mg/ml
Each 1 mL oral solution contains 1 mg of Tofacitinib (Equivalent to 1.62 mg of Tofacitinib citrate)

3. DOSAGE FORM AND STRENGTH
DOSAGE FORM: Oral Solution
STRENGTH: 1 mg/ml

4. CLINICAL PARTICULARS
4.1. Indication
It is Indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older.
Limitations of Use: Use of Tofacitinib Oral Solution in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

4.2. Posology and Method of Administration
Tofacitinib may be used as monotherapy or in combination with methotrexate (MTX).
The recommended dose in patients 2 years of age and older is based upon the following weight categories:

Table 1: Tofacitinib dose for patients with polyarticular juvenile idiopathic arthritis in two years of age and older

Body weight (kg)	Dose regimen
10 - < 20	3.2 mg (3.2 mL of oral solution) twice daily
20 - < 40	4 mg (4 mL of oral solution) twice daily
≥ 40	5 mg (5 mL of oral solution or 5 mg film-coated tablet) twice daily

Patients ≥ 40 kg treated with tofacitinib 5 mL oral solution twice daily may be switched to tofacitinib 5 mg film-coated tablets twice daily. Patients < 40 kg cannot be switched from tofacitinib oral solution.

Table 2: Recommended Dosage of Tofacitinib Oral Solution in Patients with pcJIA

Patients receiving: • strong CYP3A4 inhibitors (e.g., ketoconazole), or • a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole)	If taking 3.2 mg twice daily, reduce to 3.2 mg once daily. If taking 4 mg twice daily, reduce to 4 mg once daily. If taking 5 mg twice daily, reduce to 5 mg once daily.
Patients with: • moderate or severe renal impairment • moderate hepatic impairment[a]	If taking 3.2 mg twice daily, reduce to 3.2 mg once daily. If taking 4 mg twice daily, reduce to 4 mg once daily. If taking 5 mg twice daily, reduce to 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 recommended in patients after dialysis.
Patients with lymphocyte count less than 500 cells/mm³, confirmed by repeat testing	Discontinue dosing.
Patients with ANC 500 to 1000 cells/mm³	Interrupt dosing until ANC is greater than 1000 cells/mm³.
Patients with ANC less than 500 cells/mm³	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.

[a] Tofacitinib Oral Solution is not recommended for patients with severe hepatic impairment.

Dose interruption and discontinuation Available data suggest that clinical improvement is observed within 18 weeks of initiation of treatment with tofacitinib.
Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.
Tofacitinib treatment should be interrupted if a patient develops a serious infection until the infection is controlled.
Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia, and anaemia. As described in Tables 3, 4 and 5 below, recommendations for temporary dose interruption or permanent discontinuation of treatment are made according to the severity of laboratory abnormalities.
It is recommended not to initiate dosing in paediatric patients with an absolute lymphocyte count (ALC) less than 750 cells/mm³.

Table 3: Low absolute lymphocyte count

Low absolute lymphocyte count (ALC)	
Laboratory value (cells/mm³)	**Recommendation**
ALC greater than or equal to 750	Dose should be maintained.
ALC 500-750	• For persistent (2 sequential values in this range on routine testing) decrease in this range, dosing should be reduced or interrupted until ALC is greater than 750. • For patients receiving tofacitinib 5 mg twice daily, dosing should be interrupted. • When ALC is greater than 750, treatment should be resumed as clinically appropriate.
ALC less than 500	If laboratory value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in paediatric patients with an absolute neutrophil count (ANC) less than 1,200 cells/mm³.

Table 4: Low absolute neutrophil count

Low absolute neutrophil count (ANC)	
Laboratory Value (cells/mm³)	**Recommendation**
ANC greater than 1,000	Dose should be maintained.
ANC 500-1,000	• For persistent (2 sequential values in this range on routine testing) decreases in this range, dosing should be reduced or interrupted until ANC is greater than 1,000. • For patients receiving tofacitinib 5 mg twice daily, dosing should be interrupted. • When ANC is greater than 1,000, treatment should be resumed as clinically appropriate.
ANC less than 500	If laboratory value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in paediatric patients with haemoglobin less than 10 g/dL.

Table 5: Low haemoglobin value

Low haemoglobin value	
Laboratory value (g/dL)	**Recommendation**
Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Dose should be maintained.
Greater than 2 g/dL decrease or less than 8.0 g/dL (confirmed by repeat testing)	Dosing should be interrupted until haemoglobin values have normalised.

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.

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

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.

Mortality
Rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular risk factor treated with Tofacitinib 5 mg twice a day or Tofacitinib 10 mg twice a day had a higher observed rate of all-cause mortality, including sudden cardiovascular death, compared to those
treated with TNF blockers in a large, randomized, postmarketing safety study. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Tofacitinib Oral Solution.

Tofacitinib Oral Solution 10 mg twice daily dosage is not recommended for the treatment of RA, PsA, or AS.

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 Oral Solution in patients with symptoms of thrombosis.
Avoid Tofacitinib Oral Solution in patients that may be at increased risk of thrombosis. For the treatment of UC, use Tofacitinib Oral Solution 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 Oral Solution 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.

4.5. Drug Interactions
Table 6 includes drugs with clinically important drug interactions when administered concomitantly with Tofacitinib Oral solution and instructions for preventing or managing them.

Table 6: 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 Oral solution is recommended
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to Tofacitinib
Intervention	Dosage adjustment of Tofacitinib Oral solution is recommended
Strong CYP3A4 Inducers (e.g., rifampin)	
Clinical Impact	Decreased exposure to Tofacitinib and may result in loss of or reduced clinical response
Intervention	Coadministration with Tofacitinib Oral solution is not recommended
Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)	
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 Oral solution 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 Oral solution 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 Oral solution 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 7: 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
5.1 Pharmacodynamic 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 Oral solution, peak plasma concentrations are reached within 0.5-1 hour, elimination half-life is about 3 hours and a dose-proportional increase in systemic exposure was observed in the therapeutic dose range. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after twice daily administration.

Absorption and distribution
Tofacitinib is well-absorbed, with an oral bioavailability of 74%. Coadministration of tofacitinib with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. In clinical studies, tofacitinib was administered without regard to meal.
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
Population pharmacokinetic analyses indicated that pharmacokinetic characteristics were similar between patients with rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and UC. The coefficient of variation (%) in AUC of tofacitinib were generally similar across different disease patients, ranging from 22% to 34%.

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.

Pharmacokinetics in paediatric patients with juvenile idiopathic arthritis
Population PK analysis based on results from tofacitinib oral solution weight-based equivalent twice daily indicated that tofacitinib clearance and volume of distribution both decreased with decreasing body weight in JIA patients. The available data indicated that there were no clinically relevant differences in tofacitinib exposure (AUC), based on age, race, gender, patient type or baseline disease severity. The between-subject variability (% coefficient of variation) in (AUC) was estimated to be approximately 24%.

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 the 10mg twice daily dose on 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

1.2 Shelf life
See on the Carton

7.3 Packing Information
Tofacitinib Oral Solution of 100 ml Amber colour pet bottle

7.4 Storage and Handling Instructions
Store at temperature not exceeding 30°C, Protect from light and 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 MARKETED
MSN Laboratories Private Limited,
Plot. No. 7-2-B 47 & B-48, Ground Floor,
Industrial Estate, Sanathnagar,
Fathenagar (V), Balanagar (M),
Medchal - Malkajgiri (D),
Telangana, India.

DETAILS OF MANUFACTURER
M/s MSN Laboratories Private Limited,
C/o M/s Swiss Garnier Life Sciences,
Plot No. 21-23, Industrial Area,
Mehatapur, District Una, (H.P)-174315.

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10. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE
Mfg. Lic. No.: L-MNZ/2020/155 / 04.09.2023

11. DATE OF REVISION
Sep. 2023

MFLL0036-00