To be sold by retail on the prescription of a Registered Medical Practitioner only.

PRESCRIBING INFORMATION

TOFACITINIB TABLETS 5 mg

Tofadoz

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WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY AND THROMBOSIS

SERIOUS INFECTIONS (See section 4.4)
MORTALITY (See section 4.4)
MALIGNANCIES (See section 4.4)
THROMBOSIS (See section 4.4)

1. GENERIC NAME

Tofacitinib Tablets 5 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tofacitinib Tablets 5 mg
Each Film Coated Tablet Contains
Tofacitinib Citrate 8.08 mg
Equivalent to Tofacitinib 5 mg

3. DOSAGE FORM AND STRENGTH

Tofacitinib is available as 5 mg immediate-release film-coated tablets.

4. CLINICAL PARTICULARS

4.1. Indications

Tofacitinib is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to Methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).

4.2. Posology and Method of Administration

Important Administration Instructions

- Do not initiate Tofacitinib tablets in patients with an absolute lymphocyte count less than 500 cells/mm^3, an absolute neutrophil count (ANC) less than 1000 cells/mm^3 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 tablets if a patient develops a serious infection until the infection is controlled.
- Take Tofacitinib tablets with or without food.
- Swallow Tofacitinib 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 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 in Patients with Rheumatoid Arthritis.

Adult Patients:	Tofacitnib 5 mg twice daily
Patients receiving: • Strong CYP3A4 inhibitors (e.g., ketoconazole), or • a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole)	5 mg Once Daily
Patients with: • moderate or severe renal impairment • moderate hepatic impairment*	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/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 5 mg twice 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 in patients with severe hepatic impairment is not recommended

4.3. Contraindications

Tofacitinib is contraindicated in patients with:

- 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

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 most common serious infections reported with Tofacitinib (See Section 4.8) 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).
Avoid use of Tofacitinib in patients with an active, serious infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating Tofacitinib in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled 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 Tofacitinib. 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 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.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infections.

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. Discontinuation and monitoring criteria for lymphopenia are recommended.

Mortality

Rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular (CV) risk factor treated with Tofacitinib 10 mg twice a day had a higher rate of all-cause mortality, including sudden CV death, compared to those treated with Tofacitinib 5 mg given twice daily or TNF blockers in a large, ongoing, post-marketing safety study.

Malignancy and Lymphoproliferative Disorders

Consider the risks and benefits of Tofacitinib treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing Tofacitinib in patients who develop a malignancy. Malignancies were observed in clinical studies of Tofacitinib.

Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with Tofacitinib.

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

Non-Melanoma Skin Cancer

Non-melanoma skin cancers (NMSCs) have been reported in patients treated with Tofacitinib. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

Thrombosis

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with Tofacitinib and other Janus kinase (JAK) inhibitors used to treat inflammatory conditions. Patients with rheumatoid arthritis 50 years of age and older with at least one CV risk factor treated with Tofacitinib 10 mg twice daily compared to Tofacitinib 5 mg twice daily or TNF blockers in a large, ongoing post-marketing study had an observed increase in incidence of these events. Many of these events were serious and some resulted in death.

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

Avoid Tofacitinib in patients that may be at increased risk of thrombosis.

Gastrointestinal Perforations

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 or taking NSAIDs). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Hypersensitivity

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

Laboratory Abnormalities

Lymphocyte Abnormalities

Treatment with Tofacitinib was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean absolute lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts less than 500 cells/mm3 were associated with an increased incidence of treated and serious infections.

Avoid initiation of Tofacitinib treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm^3). In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3, treatment with Tofacitinib is not recommended.

Monitor lymphocyte counts at baseline and every 3 months thereafter.

Neutropenia Treatment with Tofacitinib was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3).

Avoid initiation of Tofacitinib treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm^3). For patients who develop a persistent ANC of 500 to 1000 cells/mm^3, interrupt Tofacitinib dosing until ANC is greater than or equal to 1000 cells/mm3. In patients who develop an ANC less than 500 cells/mm^3, treatment with Tofacitinib is not recommended.

Monitor neutrophil counts at baseline and after 4-8 weeks of treatment and every 3 months thereafter.

Anemia

Avoid initiation of Tofacitinib treatment in patients with a low hemoglobin level (i.e., less than 9 g/dL). Treatment with Tofacitinib should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment.
Monitor hemoglobin at baseline and after 4-8 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 should be interrupted until this diagnosis has been excluded.

Lipid Elevations Treatment with Tofacitinib was associated with dose-dependent 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. There were no clinically relevant changes in LDL/HDL cholesterol ratios. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed approximately 4-8 weeks following initiation of Tofacitinib therapy.

Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

Vaccinations

Avoid use of live vaccines concurrently with Tofacitinib. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

A patient experienced dissemination of the vaccine strain of varicella zoster virus, 16 days after vaccination with live attenuated (Zostavax) virus vaccine and 2 days after treatment start with tofacitinib 5 mg twice daily. The patient was varicella virus naïve, as evidenced by no previous history of varicella infection and no anti-varicella antibodies at baseline. Tofacitinib was discontinued and the patient recovered after treatment with standard doses of antiviral medication.

Update immunizations in agreement with current immunization guidelines prior to initiating Tofacitinib therapy.

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 2 includes drugs with clinically important drug interactions when administered concomitantly with Tofacitinib and instructions for preventing or managing them.

Table 2: 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 is recommended
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of Tofacitinib 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 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.
Intervention	Coadministration with Tofacitinib 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

Adverse reactions observed in pediatric patients receiving Tofacitinib were consistent with those reported in RA patients.

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 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

Table 3: 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 bacteria.	Tuberculosis of central nervous system, Meningitis Cryptococcal, *Mycobacterium avium* complex infection.	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Non-melanoma skin, cancers			
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**			
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 proceduralcomplications		Ligament sprain Muscle strain			

*Spontaneous reporting data

**Venous thromboembolism includes PE and DVT

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 *(Ref: Summary of Product Characteristics Pfizer Limited, XELJANZ 5 mg film-coated tablets, dated 06-Feb-2020)*

5.1 Pharmacodynamic Properties

Mechanism of action

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

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 (see section 4.2). 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.

6. NONCLINICAL PROPERTIES

In non-clinical studies, effects were observed on the immune and haematopoietic systems that were attributed to the pharmacological properties (JAK inhibition) of tofacitinib. Secondary effects from immunosuppression, such as bacterial and viral infections and lymphoma were observed at clinically relevant doses. Lymphoma was observed in 3 of 8 adult monkeys at 6 or 3 times the clinical tofacitinib exposure level (unbound AUC in humans at a dose of 5 mg or 10 mg twice daily), and 0 of 14 juvenile monkeys at 5 or 2.5 times the clinical exposure level of 5 mg or 10 mg twice daily. Exposure in monkeys at the no observed adverse effect level (NOAEL) for the lymphomas was approximately 1 or 0.5 times the clinical exposure level of 5 mg or 10 mg twice daily. Other findings at doses exceeding human exposures included effects on the hepatic and gastrointestinal systems.

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.

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib was not carcinogenic in mice at exposures up to 38 or 19 times the clinical exposure level at 5 mg or 10 mg twice daily. Benign testicular interstitial (Leydig) cell tumours were observed in rats: benign Leydig cell tumours in rats are not associated with a risk of Leydig cell tumours in humans. Hibernomas (malignancy of brown adipose tissue) were observed in female rats at exposures greater than or equal to 83 or 41 times the clinical exposure level at 5 mg or 10 mg twice daily. Benign thymomas were observed in female rats at 187 or 94 times the clinical exposure level at 5 mg or 10 mg twice daily.

Tofacitinib was shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility (decreased pregnancy rate; decreases in the numbers of corpora lutea, implantation sites, and viable foetuses; and an increase in early resorptions), parturition, and peri/postnatal development. Tofacitinib had no effects on male fertility, sperm motility or sperm concentration. Tofacitinib was secreted in milk of lactating rats at concentrations approximately 2-fold those in serum from 1 to 8 hours post dose.

7. DESCRIPTION

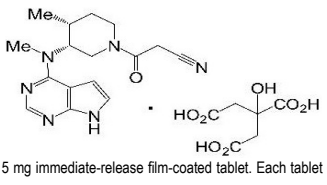
Tofacitinib tablets are formulated with the citrate salt of tofacitinib, a JAK inhibitor.

Tofacitinib citrate is an off-white powder with the following chemical name: (3R, 4R)-4-methyl-3-(methyl-7H-pyrrolo [2, 3-d] pyrimidin-4-ylamino)-ß-oxo-1-piperidine propanenitrile, 2-hydroxy-1, 2, 3-propanetricarboxylate (1:1).

Tofacitinib citrate is sparingly soluble in 20% aqueous acetic acid, slightly soluble in methanol and water, insoluble in dichloromethane.

Tofacitinib citrate has a molecular weight of 504.5 Daltons (or 312.4 Daltons as the tofacitinib free base) and a molecular formula of $C_{16}H_{20}N_6O \cdot C_6H_8O_7$.

The chemical structure of tofacitinib citrate is:



Tofacitinib is supplied for oral administration as a 5 mg immediate-release film-coated tablet. Each tablet of Tofacitinib contains 5 mg tofacitinib (equivalent to 8.08 mg tofacitinib citrate).

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

None

8.2 Packing Information

10's Blister.

8.3 Storage and Handling Instructions

Do not store above 30^0C.

9. PATIENT COUNSELING INFORMATION

See section 4.4 and 4.6.

10. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited,

Formulation Division, Unit-II, Sy.no. 1277, 1319 to 1324, Nandigama (Village & Mandal),
Rangareddy (District), Telangana - 509 228, India.

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Not Applicable

12. DATE OF REVISION

October - 2020

D03975-00