Summary of Product Characteristics
(Product Data Sheet)

1.	**Name of the Medical Product**
	1.1 Product Name: XELTIN (Tofacitinib Tablets 5 mg)
	1.2 Strength : Each film coated tablet contains: Tofacitinib citrate equivalent to Tofacitinib: 5 mg
	1.3 Pharmaceutical Dosage Form : Film Coated Tablets
2.	**Qualitative & Quantitative Composition:** Each film coated tablet contains: Tofacitinib citrate equivalent to Tofacitinib 5 mg Colour: Titanium Dioxide Excipients q.s. For a full list of excipients, see section 6.1 of SmPC
3.	**Pharmaceutical Form:** White to off-white colored, round, biconvex film-coated tablets debossed with "T V" on one side and plain on other side.
4.	**Clinical Particulars**
	4.1 Therapeutic Indications: 1. Rheumatoid Arthritis: Tofacitinib Tablets 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). 2. Psoriatic Arthritis: Tofacitinib Tablets is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs). 3. Ulcerative Colitis: Tofacitinib Tablets is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC).

4.2 Posology and Method of administration:

- Do not initiate Tofacitinib Tablets if absolute lymphocyte count <500 cells/mm.^{3} an absolute neutrophil count (ANC)<1000cells/mm^3 or haemoglobin <9g/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.

Rheumatoid Arthritis: Tofacitinib Tablets 5 mg twice daily.

- Tofacitinib may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis.
- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is Tofacitinib Tablets 5 mg once daily.

Psoriatic Arthritis (in combination with nonbiologic DMARDs): Tofacitinib Tablets 5 mg twice daily.

- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment is Tofacitinib Tablets 5 mg once daily.

Ulcerative Colitis Tofacitinib 10 mg twice daily for at least 8 weeks; then 5 or 10 mg twice daily. Discontinue after 16 weeks of 10 mg twice daily, if adequate therapeutic benefit is not achieved. Use the lowest effective dose to maintain response.

- Recommended dosage in patients with moderate and severe renal impairment or moderate hepatic impairment: half the total daily dosage recommended for patients with normal renal and hepatic function.

  Use of Tofacitinib Tablets in patients with severe hepatic impairment is not recommended in any patient population.

Table 1 displays the recommended adult daily dosage of Tofacitinib Tablets and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, in patients with moderate or severe renal impairment or moderate hepatic impairment, with lymphopenia, neutropenia, or anemia.

Table.1.Recommended Dosage of Tofacitinib Tablets in Patients with Rheumatoid Arthritis and Psoriatic Arthritis.

	Tofacitinib Tablets
Adult patients	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
Patients with lymphocyte count less than 500 cells/mm3 , 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.

Recommended Dosage in Ulcerative Colitis Table 2 displays the recommended adult daily dosage of Tofacitinib Tablets and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, with moderate or severe renal impairment or moderate hepatic impairment, with lymphopenia, neutropenia or anemia.

Table.2 Recommended Dosage of Tofacitinib Tablets in Patients with UC

	Tofacitinib Tablets
Adult patients	10 mg twice daily for at least 8 weeks; followed by 5 or 10 mg twice daily, depending on therapeutic response Use the lowest effective dose to maintain response Discontinue Tofacitinib after 16 weeks of treatment with 10 mg twice daily, if adequate therapeutic benefit is not achieved.
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 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, reduce to 5 mg once daily.
Patients with: • moderate or severe renal impairment • moderate hepatic impairment	If taking 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, reduce to 5 mg once daily.
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	If taking 10 mg twice daily, reduce to 5 mg twice daily. When ANC is greater than 1000, increase to 10 mg twice daily based on clinical response. If taking 5 mg twice daily, 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.

4.3 Contraindications:

None

4.4 Special warning and precautions for use:

1. <u>Serious Infections</u>

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 included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infection, and listeriosis were reported with TOFACITINIB. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids. In the UC population, TOFACITINIB treatment with 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Additionally, opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with TOFACITINIB 10 mg twice daily. 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 immune compromised 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. (Dosage and administration).

2. <u>Tuberculosis</u>

Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of TOFACITINIB. Anti-tuberculosis therapy should also be considered prior to administration of TOFACITINIB in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating anti-tuberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering TOFACITINIB.

3. **<u>Viral Reactivation</u>**

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with TOFACITINIB. The impact of TOFACITINIB on chronic viral hepatitis reactivation is unknown. Patients who screened positive for

hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with TOFACITINIB. The risk of herpes zoster is increased in patients treated with TOFACITINIB and appears to be higher in patients treated with TOFACITINIB in Japan and Korea.

4. <u>Malignancy and Lymphoproliferative Disorders</u>

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.

In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving TOFACITINIB with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with TOFACITINIB. During the 2 PsA controlled clinical studies there were 3 malignancies (excluding NMSC) in 474 patients receiving TOFACITINIB plus nonbiologic DMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus nonbiologic DMARD group (3 months exposure) and 0 malignancies in 106 patients in the adalimumab plus nonbiologic DMARD group (12 months exposure). No lymphomas were reported. Malignancies have also been observed in the long-term extension study in psoriatic arthritis patients treated with TOFACITINIB.

During the UC controlled clinical studies (8-week induction and 52-week maintenance studies), which included 1220 patients, 0 cases of solid cancer or lymphoma were observed in TOFACITINIB-treated patients. In the long-term extension study, malignancies (including solid cancers and lymphomas) were observed more often in patients treated with TOFACITINIB 10 mg twice daily. In Phase 2B, controlled dose-

ranging trials in de-novo renal transplant patients, all of whom received induction therapy with basiliximab, high-dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with TOFACITINIB (2.3%) compared to 0 out of 111 patients treated with cyclosporine. 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: 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. In the UC population, treatment with TOFACITINIB 10 mg twice daily was associated with greater risk of NMSC.

5. Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical studies with TOFACITINIB, although the role of JAK inhibition in these events is not known. In these studies, many patients with rheumatoid arthritis were receiving background therapy with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs). There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the TOFACITINIB arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids. 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.

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/mm^3 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. For recommended modifications based on lymphocyte counts.(see dosage and administration) *Neutropenia* Treatment with TOFACITINIB was associated with an increased incidence of neutropenia (less than 2000 cells/mm^3) compared to placebo. 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/mm^3. 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. For recommended modifications based on ANC results . (see dosage and administration) *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. For recommended modifications based on hemoglobin results. .(see dosage and administration). *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. 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.
	4.5 Interactions with other medicinal products and other forms of Interactions : **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: Co administration 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, psoriatic arthritis, or UC. Intervention: Co administration with TOFACITINIB is not recommended
	4.6 Pregnancy and Lactation: **Pregnancy** Risk Summary: Available data with TOFACITINIB use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy. In animal reproduction studies, fetocidal and teratogenic effects were noted when pregnant rats and rabbits received TOFACITINIB during the period of organogenesis at exposures multiples of 73-times and 6.3-times the maximum recommended dose of 10 mg twice daily, respectively. Further, in a peri and post-natal study in rats, TOFACITINIB resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73-times the recommended dose of 5 mg twice daily and approximately 36 times the maximum recommended dose of 10 mg twice daily, respectively. The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks o of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Animal Data: In a rat embryofetal developmental study, in which pregnant rats received TOFACITINIB during organogenesis, TOFACITINIB was teratogenic at exposure levels approximately 146 times the recommended dose of 5 mg twice daily, and approximately 73 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 100 mg/kg/day in rats). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively; and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). In addition, there was an increase in post-implantation loss, consisting of early and late resorptions, resulting in a reduced number of viable fetuses. Mean fetal body weight was reduced. No developmental toxicity was observed in rats at exposure levels approximately 58 times the recommended dose of 5 mg twice daily, and approximately 29 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in pregnant rats). In a rabbit embryofetal developmental study in which pregnant rabbits received TOFACITINIB during the period of organogenesis, TOFACITINIB was teratogenic at exposure levels approximately 13 times the recommended dose of 5 mg twice daily, and approximately 6.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail

	defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3 times the recommended dose of 5 mg, and approximately 1.5 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in pregnant rabbits). In a peri- and postnatal development study in pregnant rats that received TOFACITINIB from gestation day 6 through day 20 of lactation, there were reductions in live litter size, postnatal survival, and pup body weights at exposure levels approximately 73 times the recommended dose of 5 mg twice daily, and approximately 36 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 50 mg/kg/day in rats). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the maximum recommended dose of 10 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in rats). **Lactation** Risk Summary There are no data on the presence of TOFACITINIB in human milk, the effects on a breastfed infant, or the effects on milk production. TOFACITINIB is present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in adults treated with TOFACITINIB, such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 18 hours after the last dose of TOFACITINIB or 36 hours after the last dose of TOFACITINIB (approximately 6 elimination half-lives). Data Following administration of TOFACITINIB to lactating rats, concentrations of TOFACITINIB in milk over time paralleled those in serum, and were approximately 2 times higher in milk relative to maternal serum at all time points measured.

Pediatric Use

The safety and effectiveness of TOFACITINIB in pediatric patients have not been established.

Geriatric Use

Of the 3315 patients who enrolled in rheumatoid arthritis Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among TOFACITINIB-treated subjects 65 years of age and older was higher than among those under the age of 65. Of the 1156 TOFACITINIB-treated patients in the UC program, a total of 77 patients (7%) were 65 years of age or older. The number of patients aged 65 years and older was not sufficient to determine whether they responded differently from younger patients. 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.

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 impairment. 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 machine: TOFACITINIB has no or negligible influence on the ability to drive and use machines.
	4.8 Undesirable Effects: **Clinical Trials Experience** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice. *Rheumatoid Arthritis* The clinical studies described in the following sections were conducted using TOFACITINIB. Although other doses of TOFACITINIB have been studied, the recommended dose of TOFACITINIB is 5 mg twice daily. The following data includes two Phase 2 and five Phase 3 double-blind, controlled, multicenter trials. In these trials, patients were randomized to doses of TOFACITINIB

	5 mg twice daily (292 patients) and 10 mg twice daily (306 patients) monotherapy, TOFACITINIB 5 mg twice daily (1044 patients) and 10 mg twice daily (1043 patients) in combination with DMARDs (including methotrexate) and placebo (809 patients). All seven protocols included provisions for patients taking placebo to receive treatment with TOFACITINIB at Month 3 or Month 6 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Therefore, some analyses that follow include patients who changed treatment by design or by patient response from placebo to TOFACITINIB in both the placebo and TOFACITINIB group of a given interval. Comparisons between placebo and TOFACITINIB were based on the first 3 months of exposure, and comparisons between TOFACITINIB 5 mg twice daily and TOFACITINIB 10 mg twice daily were based on the first 12 months of exposure. The long-term safety population includes all patients who participated in a double-blind, controlled trial (including earlier development phase studies) and then participated in one of two long-term safety studies. The design of the long-term safety studies allowed for modification of TOFACITINIB doses according to clinical judgment. This limits the interpretation of the long-term safety data with respect to dose. The most common serious adverse reactions were serious infections The proportion of patients who discontinued treatment due to any adverse reaction during the 0 to 3 months exposure in the double-blind, placebo-controlled trials was 4% for patients taking TOFACITINIB and 3% for placebo-treated patients. *Overall Infections*: In the seven controlled trials, during the 0 to 3 months exposure, the overall frequency of infections was 20% and 22% in the 5 mg twice daily and 10 mg twice daily groups, respectively, and 18% in the placebo group. The most commonly reported infections with TOFACITINIB were upper respiratory tract infections, nasopharyngitis, and urinary tract infections (4%, 3%, and 2% of patients, respectively). *Serious Infections*: In the seven controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.5 events per 100 patient-years) who

	received placebo and 11 patients (1.7 events per 100 patient-years) who received TOFACITINIB 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 1.1 (-0.4, 2.5) events per 100 patient-years for the combined 5 mg twice daily and 10 mg twice daily TOFACITINIB group minus placebo. In the seven controlled trials, during the 0 to 12 months exposure, serious infections were reported in 34 patients (2.7 events per 100 patient-years) who received 5 mg twice daily of TOFACITINIB and 33 patients (2.7 events per 100 patient-years) who received 10 mg twice daily of TOFACITINIB. The rate difference between TOFACITINIB doses (and the corresponding 95% confidence interval) was -0.1 (-1.3, 1.2) events per 100 patient-years for 10 mg twice daily TOFACITINIB minus 5 mg twice daily TOFACITINIB. The most common serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infection. *Tuberculosis*: the seven controlled trials, during the 0 to 3 months exposure, tuberculosis was not reported in patients who received placebo, 5 mg twice daily of TOFACITINIB, or 10 mg twice daily of TOFACITINIB. In the seven controlled trials, during the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg twice daily of TOFACITINIB and 6 patients (0.5 events per 100 patient-years) who received 10 mg twice daily of TOFACITINIB. The rate difference between TOFACITINIB doses (and the corresponding 95% confidence interval) was 0.5 (0.1, 0.9) events per 100 patient-years for 10 mg twice daily TOFACITINIB minus 5 mg twice daily TOFACITINIB. Cases of disseminated tuberculosis were also reported. The median TOFACITINIB exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days). *Opportunistic Infections (excluding tuberculosis)* :In the seven controlled trials, during the 0 to 3 months exposure, opportunistic infections were not reported in patients who received placebo, 5 mg twice daily of TOFACITINIB, or 10 mg twice daily of TOFACITINIB. In the seven controlled trials, during the 0 to 12 months exposure, opportunistic infections were reported in 4 patients (0.3 events per 100 patient-years) who received 5 mg twice daily of TOFACITINIB and 4 patients (0.3 events per 100 patient-years) who received 10 mg twice daily of TOFACITINIB. The rate difference

between TOFACITINIB doses (and the corresponding 95% confidence interval) was 0 (-0.5, 0.5) events per 100 patient-years for 10 mg twice daily TOFACITINIB minus 5 mg twice daily TOFACITINIB. The median TOFACITINIB exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days).

Malignancy: In the seven controlled trials, during the 0 to 3 months exposure, malignancies excluding NMSC were reported in 0 patients who received placebo and 2 patients (0.3 events per 100 patient-years) who received either TOFACITINIB 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 0.3 (-0.1, 0.7) events per 100 patient-years for the combined 5 mg and 10 mg twice daily TOFACITINIB group minus placebo. In the seven controlled trials, during the 0 to 12 months exposure, malignancies excluding NMSC were reported in 5 patients (0.4 events per 100 patient-years) who received 5 mg twice daily of TOFACITINIB and 7 patients (0.6 events per 100 patient-years) who received 10 mg twice daily of TOFACITINIB. The rate difference between TOFACITINIB doses (and the corresponding 95% confidence interval) was 0.2 (-0.4, 0.7) events per 100 patient-years for 10 mg twice daily TOFACITINIB minus 5 mg twice daily TOFACITINIB. One of these malignancies was a case of lymphoma that occurred during the 0 to 12 month period in a patient treated with TOFACITINIB 10 mg twice daily. The most common types of malignancy, including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma, and malignant melanoma.

Laboratory Abnormalities

- Lymphopenia: In the controlled clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm^3 occurred in 0.04% of patients for the 5 mg twice daily and 10 mg twice daily TOFACITINIB groups combined during the first 3 months of exposure. Confirmed lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections.
- Neutropenia: In the controlled clinical trials, confirmed decreases in ANC below 1000 cells/mm^3 occurred in 0.07% of patients for the 5 mg twice daily and 10 mg

twice daily TOFACITINIB groups combined during the first 3 months of exposure. There were no confirmed decreases in ANC below 500 cells/mm3 observed in any treatment group. There was no clear relationship between neutropenia and the occurrence of serious infections. In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical trials.

- Liver Enzyme Elevations: Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were observed in patients treated with TOFACITINIB. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of TOFACITINIB, or reduction in TOFACITINIB dose, resulted in decrease or normalization of liver enzymes. In the controlled monotherapy trials (0-3 months), no differences in the incidence of ALT or AST elevations were observed between the placebo, and TOFACITINIB 5 mg, and 10 mg twice daily groups. In the controlled background DMARD trials (0-3 months), ALT elevations greater than 3x ULN were observed in 1.0%, 1.3% and 1.2% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. In these trials, AST elevations greater than 3x ULN were observed in 0.6%, 0.5% and 0.4% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. One case of drug-induced liver injury was reported in a patient treated with TOFACITINIB 10 mg twice daily for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT greater than 3x ULN and bilirubin elevations greater than 2x ULN, which required hospitalizations and a liver biopsy.
- Lipid Elevations: In the controlled clinical trials, dose-related elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were observed at one month of exposure and remained stable thereafter. Changes in lipid parameters during the first 3 months of exposure in the controlled clinical trials are summarized below:
    - Mean LDL cholesterol increased by 15% in the TOFACITINIB 5 mg twice daily arm and 19% in the TOFACITINIB 10 mg twice daily arm.

- Mean HDL cholesterol increased by 10% in the TOFACITINIB 5 mg twice daily arm and 12% in the TOFACITINIB 10 mg twice daily arm.
- Mean LDL/HDL ratios were essentially unchanged in TOFACITINIB-treated patients.

  In a controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy. In the long-term safety population, elevations in lipid parameters remained consistent with what was seen in the controlled clinical trials.
- Serum Creatinine Elevations: In the controlled clinical trials, dose-related elevations in serum creatinine were observed with TOFACITINIB treatment. The mean increase in serum creatinine was <0.1mg/dl in the 12-month pooled safety analysis; however with increasing duration of exposure in the long-term extensions, up to 2% of patients were discontinued from TOFACITINIB treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

Other adverse reactions occurring in controlled and open-label extension studies included:

- Blood and lymphatic system disorders: Anemia
- Infections and infestations: Diverticulitis
- Metabolism and nutrition disorders: Dehydration
- Psychiatric disorders: Insomnia
- Nervous system disorders: Paresthesia
- Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion, interstitial lung disease (cases were limited to patients with rheumatoid arthritis and some were fatal)
- Gastrointestinal disorders: Abdominal pain, dyspepsia, vomiting, gastritis, nausea
- Hepatobiliary disorders: Hepatic steatosis

	• Skin and subcutaneous tissue disorders: Rash, erythema, pruritus • Musculoskeletal, connective tissue and bone disorders: Musculoskeletal pain, arthralgia, tendonitis, joint swelling • Neoplasms benign, malignant and unspecified (including cysts and polyps): Non-melanoma skin cancers • General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema
	4.9 Overdosage: There is no specific antidote for overdose with Tofacitinib Tablets. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions.
5.	**Pharmacological properties**
	5.1 Pharmacodynamic Properties: **Mechanism of Action** TOFACITINIB is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. TOFACITINIB modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). TOFACITINIB inhibited the in vitro activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC50 of 406, 56, and 1377 nM, respectively. Treatment with TOFACITINIB was associated with dose-dependent reductions of circulating CD16/56+ natural killer 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. The clinical significance of these changes is unknown. Total serum IgG, IgM, and IgA levels after 6-month dosing in patients with rheumatoid arthritis were lower than placebo; however, changes were small and not dose-dependent. After treatment with TOFACITINIB in patients with rheumatoid arthritis, 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 pharmacokinetic half-life. Similar changes in T cells, B cells, and serum CRP have been observed in patients with active psoriatic arthritis although reversibility was not assessed. Total serum immunoglobulins were not assessed in patients with active psoriatic arthritis.
	5.2 Pharmacokinetics Properties: TOFACITINIB Following oral administration of TOFACITINIB, 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: The absolute oral bioavailability of TOFACITINIB is 74%. Coadministration of TOFACITINIB with a high-fat meal resulted in no changes in AUC while Cmax was reduced by 32%. In clinical trials, TOFACITINIB was administered without regard to meals. Distribution: After intravenous administration, the volume of distribution is 87 L. The protein binding of TOFACITINIB is approximately 40%. TOFACITINIB binds predominantly to albumin and does not appear to bind to α1-acid glycoprotein. TOFACITINIB distributes equally between red blood cells and plasma. Metabolism and Excretion: 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 radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged TOFACITINIB, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of TOFACITINIB is attributed to the parent molecule.
	5.3 Preclinical Safety data: NONCLINICAL TOXICOLOGY *Carcinogenesis, Mutagenesis, Impairment of Fertility* In a 39-week toxicology study in monkeys, TOFACITINIB at exposure levels approximately 6 times the recommended dose of 5 mg twice daily, and approximately 3 times the 10 mg twice daily dose (on an AUC basis at oral doses of 5 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1 times 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 twice daily). 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 10 mg twice daily dose on an AUC basis). The relevance of benign Leydig cell tumors to human risk is not known. TOFACITINIB was not mutagenic in the bacterial reverse mutation assay. 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.
6.	**Pharmaceutical particulars**
	6.1 List of Excipients: Microcrystalline Cellulose USPNF, Lactose Monohydrate USPNF, Lactose Monohydrate USPNF, Croscarmellose Sodium USPNF, Magnesium Stearate USPNF, Opadry 03B28796 White IH and Purified Water.
	6.2 Incompatibilities: Not applicable
	6.3 Shelf life: 2 years
	6.4 Special Precautions for storage: Store below 30°C. Protect from Moisture.
	6.5 Nature and contents of container: 10 tablets are packed in Alu-PVC/PVdC blister, 3 such blisters are packed in a carton along with package insert.
7.	**Marketing Authorization Holder:** Ajanta Pharma Ltd. Ajanta House, Charkop Kandivli (West) Mumbai - 400 067 India. Tel : +91-22-6606 1000 Fax : +91-22-6606 1200 Email : info@ajantapharma.com
	Marketing Authorization Numbers: Not Applicable
8.	**Date of first authorization/ renewal of the authorization:** Not Applicable
9.	**Date of revision of text:** Mar 07, 2023