For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory Only

TRITONIB 10

1. **Generic Name:**

   Tofacitinib Tablets I.P. 10 mg

2. **Qualitative and quantitative composition:**

   Each film coated tablet contains:

   Tofacitinib Citrate I.P. …….16.16 mg

   Eqv. to Tofacitinib……10 mg

   Excipients……..q.s.

   Colours: Brilliant Blue Lake & Titanium Dioxide I.P.

   The excipients used are Microcrystalline Cellulose, Lactose, Polyvinylpyrrolidone K 30, Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose, Polyethylene Glycol 6000, Titanium dioxide, Colour Brilliant Blue Lake, Isopropyl Alcohol, Methylene Dichloride.

3. **Dosage form and strength:**

   Dosage form: Film Coated Tablet

   Strength: 10 mg

4. **Clinical particulars:**

4.1 Therapeutic indication:

- It 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).
- For the treatment of adult patients with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to Methotrexate or other non-biologic disease modifying antirheumatic drugs (DMARDs).

4.2 Posology and method of administration:

Once a day or as directed Physician

To be taken orally

4.3 Contraindications:

Hypersensitivity to the active substance.

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 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 immune modulating 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 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.

Tuberculosis

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.

Viral Reactivation

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.

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.

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.

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/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/mm3). In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm3, treatment with Tofacitinib is not recommended.

Monitor lymphocyte counts at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts.

Neutropenia

Treatment with Tofacitinib was associated with an increased incidence of neutropenia (less than 2000 cells/mm3) compared to placebo.

Avoid initiation of Tofacitinib treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm3). For patients who develop a persistent ANC of 500 to 1000 cells/mm3, interrupt Tofacitinib dosing until ANC is greater than or equal to 1000 cells/mm3. In patients who develop an ANC less than 500 cells/mm3, 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.

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.

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.

Risk of Gastrointestinal Obstruction with a Non-Deformable Extended-Release Formulation such as Tofacitinib

As with any other non-deformable material, caution should be used when administering Tofacitinib to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable extended-release formulation.

Other General Warnings

Talk to your doctor if

- You experience any allergic reactions after taking Tofacitinib.
- You are getting suicidal thoughts after taking this medicine, talk to your doctor immediately.
- You are experiencing vision problems or dizziness and sleepiness.

4.5 Drug 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 / Tofacitinib XR is recommended
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of Tofacitinib / Tofacitinib XR 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 / Tofacitinib XR 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	Coadministration with Tofacitinib / Tofacitinib XR is not recommended

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

Pregnancy

Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Tofacitinib during pregnancy. Patients should be encouraged to enroll in the Tofacitinib pregnancy registry if they become pregnant.

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. The background risks in the U.S. general population of major birth defects and miscarriages are 2 to 4% and 15 to 20% of clinically recognized pregnancies, respectively.

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 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 twice daily, 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 (see Data). 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.

Females and Males of Reproductive Potential

Contraception

Females

In an animal reproduction study, tofacitinib at AUC multiples of 13 times the recommended dose of 5 mg twice daily and 6.3 times the maximum recommended dose of 10 mg twice daily demonstrated adverse embryo-fetal findings [see Use in Specific Populations (8.1)]. However, there is uncertainty as to how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential.

Infertility

Females

Based on findings in rats, treatment with Tofacitinib may result in reduced fertility in females of reproductive potential. It is not known if this effect is reversible.

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.

- Rheumatoid arthritis and psoriatic arthritis patients with moderate or severe renal impairment receiving Tofacitinib should switch to Tofacitinib and adjust the dosage.

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.

Rheumatoid arthritis and psoriatic arthritis patients receiving Tofacitinib should switch to Tofacitinib and adjust the dosage.

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:

Driving and use of machines

While taking Tofacitinib do not drive or operate machinery unless you are alert.

4.8 Undesirable effects:

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections
- Malignancy and Lymphoproliferative Disorders
- Gastrointestinal Perforations

- Laboratory Abnormalities

Reporting of side effects:

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

4.9 Overdose:

There is no specific antidote for overdose with Tofacitinib. 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 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. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known.

5.2 Pharmacodynamic properties

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.

5.3 Pharmacokinetic 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.

Title of the Study

An open label, randomized, balanced, two treatment, two sequence, two period, cross-over, single-dose oral bioequivalence study of Tofacitinib Tablets 10mg (T) of Synokem Pharmaceuticals Ltd., India with Tofadoz (Tofacitinib Tablets 5mg) (R) of MSN Laboratories Private Limited, India in healthy, adult male subjects under fasting condition.

Objectives

To compare the rate and extent of absorption of Tofacitinib from Tofacitinib Tablets 10mg of Synokem Pharmaceuticals Ltd., India (test product) and Tofadoz (Tofacitinib Tablets 5mg) of MSN Laboratories Private Limited, India (reference product) in healthy, adult, human male subjects under fasting conditions.

To monitor the safety and tolerability of a single dose of investigational products in healthy, adult, human male subjects under fasting conditions.

The sponsor aims to market the test product as a pharmaceutical equivalent of the reference product, provided the test and reference products are bioequivalent.

Methodology

Clinical personnel explained all study related procedures, duration, dates and timings, information on the study treatments and confidentiality of the subjects data clearly to the subjects during the informed consent procedure. Subjects who signed the consent form and showed their willingness to participate in the study were enrolled. Subjects who were eligible when assessed against the inclusion and exclusion criteria and who were found to be healthy on physical examination with laboratory investigation values within reference limits were considered for admission to the study. Subjects whose pre-study laboratory values were outside the reference range were also considered for participation provided these values were considered clinically non-significant by the investigator. The eligible subjects reported to the study site on 05Mar2022 for period 01 and on 12Mar2022 for period 02. Treatments were allocated to subjects per the randomization schedule generated using statistical techniques with SAS® (SAS Institute Inc., USA) version 9.4. Blood samples were drawn before dosing (0.00 hour) and up to 24.00 hours after dosing in each period.

Plasma concentrations of Tofacitinib were analyzed using a LC-MS/MS method developed at Synergen Bio Pvt. Ltd., Pune, India.

Statistical analysis was performed to assess bioequivalence between the pharmacokinetic parameters of test and reference formulations using SAS® (SAS Institute Inc., USA) version 9.4.

Results:

A) Pharmacokinetic and Statistical Evaluation:

Table A: Descriptive Statistics of Pharmacokinetic Parameters of Test Product (T) and Reference Product (R) for Tofacitinib (N = 23)

Form	Variable	Mean	SD	Minimum	Median	Maximum	CV%
R	C_{max} (ng/mL)	125.6660	34.8406	68.5760	121.3550	198.8740	27.7247
	T_{max} (hr)	0.6226	0.3816	0.3300	0.5000	1.6700	61.2870
	AUC_{0-t} (ng.hr/mL)	421.1201	120.9584	218.9790	420.6450	682.7380	28.7230
	$AUC_{0-\infty}$ (ng.hr/mL)	430.8703	124.1293	224.3590	430.5570	694.9460	28.8090
	K_{el} (hr^{-1})	0.2155	0.0358	0.1360	0.2140	0.2870	16.6112
	$t_{1/2}$ (hr)	3.3130	0.6153	2.4200	3.2300	5.1000	18.5710
	$AUC_{\_\%Extrap\_obs}$	2.2213	1.2959	0.5900	2.0300	5.9100	58.3418
T	C_{max} (ng/mL)	130.4800	30.6360	79.8890	138.3520	186.8680	23.4794
	T_{max} (hr)	0.5943	0.2180	0.3300	0.5000	1.3300	36.6760
	AUC_{0-t} (ng.hr/mL)	405.2306	89.4502	246.9410	420.0070	624.7140	22.0739
	$AUC_{0-\infty}$ (ng.hr/mL)	414.0025	92.0422	250.1550	438.8350	633.9300	22.2323
	K_{el} (hr^{-1})	0.2052	0.0353	0.1490	0.1990	0.2960	17.2191
	$t_{1/2}$ (hr)	3.4674	0.5564	2.3400	3.4900	4.6400	16.0467
	$AUC_{\_\%Extrap\_obs}$	2.0626	1.3149	0.6600	1.4500	5.5700	63.7481

Table B: Geometric Least Squares Means, Ratios, ISCV and 90% Confidence Intervals for Pharmacokinetic Parameters (C_{max}, AUC_{0-t} and $AUC_{0-\infty}$) of Tofacitinib (N = 23)

B) Safety Evaluation:

Pharmacokinetic Parameters (Units)	Geometric Least Squares Mean		T/R ratio (%)	ISCV (%)	90% Confidence Interval
	Test Product (T)	Reference Product (R)			
C_{max} (ng/mL)	126.927	121.024	104.88	16.60	(96.45% - 114.04%)
AUC_{0-t} (ng.hr/mL)	396.177	404.719	97.89	16.40	(90.11% - 106.33%)
$AUC_{0-\infty}$ (ng.hr/mL)	404.503	413.927	97.72	16.44	(89.94% - 106.18%)

No moderate and serious or life-threatening adverse events were reported during the course of the study.

Two (02) adverse events were observed in the study, involving 02 subjects (subject nos. 04 and 07) out of 24; during the conduct of the study. Both adverse events were observed in clinical laboratory safety evaluation (clinically significant changes in laboratory parameters).

Both adverse events were ‘mild’ in intensity and ‘possibly’ related to the investigational products.

Subject nos. 04 and 07 did not report to clinical facility for repeat safety assessment and hence, they were considered as lost to follow-up for their post-study adverse event.

The test (T) and reference (R) products were comparable in their safety and tolerability.

The test product (T) was found to be safe and well tolerated upon administration of single dose of Tofacitinib Tablets 10mg in healthy, adult human male subjects under fasting conditions.

Conclusion:

The 90% confidence intervals of the differences of least squares means for the Ln-transformed pharmacokinetic parameters Cmax, AUC0-t and AUC0-∞ of Tofacitinib is within the bioequivalence acceptance limits of 80.00 - 125.00%.

Hence, it is concluded that the test product (T) Tofacitinib Tablets 10mg of Synokem Pharmaceuticals Ltd., India and reference product (R) Tofadoz (Tofacitinib Tablets 5mg) of MSN Laboratories Private Limited, India are bioequivalent with respect to rate and extent of absorption

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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.

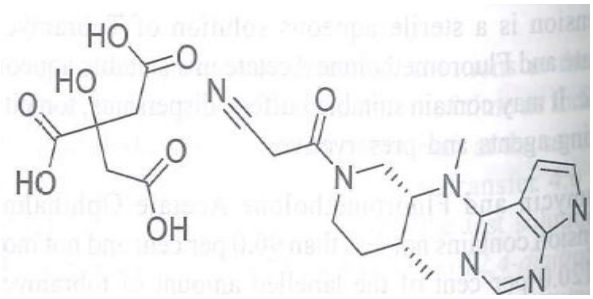
In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hibernomas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 30 mg/kg/day (approximately 42 times the exposure levels at the recommended dose of 5 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. It was positive for clastogenicity in the in vitro chromosome aberration assay with human lymphocytes in the presence of metabolic enzymes, but negative in the absence of metabolic enzymes. Tofacitinib was negative in the in vivo rat micronucleus assay and in the in vitro CHO-HGPRT assay and the in vivo rat hepatocyte unscheduled DNA synthesis assay.

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. Description:

Tofacitinib Citrate is 3-{(3R, 4R)-4-methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl) amino]piperidin-1-yl)-3-oxo Propanenitrile 2-hydroxypropane-1,2,3-tricarboxylic acid., Its empirical formula is $C_{22}H_{28}N_6O_8$ and molecular weight is 504.5 g/mol the Chemical structure of :



TRITONIB 10

Tofacitinib Tablets are light blue to blue coloured, round, biconvex, film coated tablets, plain on both sides. The Excipients used are Microcrystalline Cellulose, Lactose, Polyvinylpyrrolidone K 30, Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose., Polyethylene Glycol 6000, Titanium dioxide, Colour Brilliant Blue Lake, Isopropyl Alcohol, Methylene Dichloride.

8. Pharmaceutical particulars:

8.1 Incompatibilities:

None stated.

8.2 Shelf-life:

Do not use later than date of expiry.

8.3 Packaging information:

TRITONIB 10 is available in pack of 10 Tablets

8.4 Storage and handing instructions:

Store below 30°C & Protect from light and moisture.

9. Patient Counselling Information

Package leaflet: Information for the user

TRITONIB 10

(Tofacitinib Tablets I.P. 10 mg)

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

What is in this leaflet:

9.4 Possible side effects.

9.5 How to store TRITONIB 10 Tablet

9.6 Contents of the pack and other information.

9.1. What TRITONIB 10 Tablet is and what it is used for

TRITONIB 10 Tablet contains Tofacitinib Tablets I.P. 10 mg excipients The Excipients used are Microcrystalline Cellulose, Lactose, Polyvinylpyrrolidone K 30, Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose., Polyethylene Glycol 6000, Titanium dioxide, Colour Brilliant Blue Lake, Isopropyl Alcohol, Methylene Dichloride.

What Torvate is used for

9.2. What you need to know before you take TRITONIB 10

Do not take TRITONIB 10

- If you are allergic to tofacitinib or any of the other ingredients of this medicine.
- If you are getting suicidal thoughts after taking this medicine.
- If you have a severe infection such as bloodstream infection or active tuberculosis.
- If you are experiencing vision problems or dizziness and sleepiness.
- If you are not sure regarding any of the information provided above, please contact your doctor.

Warnings and precautions

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 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 immune modulating 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 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.

Tuberculosis

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.

Viral Reactivation

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.

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.

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.

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/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/mm3). In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm3, treatment with Tofacitinib is not recommended.

Monitor lymphocyte counts at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts.

Neutropenia

Treatment with Tofacitinib was associated with an increased incidence of neutropenia (less than 2000 cells/mm3) compared to placebo.

Avoid initiation of Tofacitinib treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm3). For patients who develop a persistent ANC of 500 to 1000 cells/mm3,

interrupt Tofacitinib dosing until ANC is greater than or equal to 1000 cells/mm3. In patients who develop an ANC less than 500 cells/mm3, 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.

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.

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.

Risk of Gastrointestinal Obstruction with a Non-Deformable Extended-Release Formulation such as Tofacitinib

As with any other non-deformable material, caution should be used when administering Tofacitinib to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable extended-

Other medicines and TRITONIB 10

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Some medicines should not be taken with TRITONIB 10. If taken with TRITONIB 10, they could alter the level of TRITONIB 10 in your body, and the dose of TRITONIB 10 may require adjustment. You should tell your doctor if you are using medicines (taken by mouth) that contain any of the following active substances:

- antibiotics such as rifampicin, used to treat bacterial infections
- fluconazole, ketoconazole, used to treat fungal infections

Strong CP3A4 Inhibitors (e.g., ketoconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of Tofacitinib / Tofacitinib XR is recommended
Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of Tofacitinib / Tofacitinib XR 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 / Tofacitinib XR 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	Coadministration with Tofacitinib / Tofacitinib XR is not recommended

9.3. How to take TRITONIB 10 Tablet

This medicine is provided to you and supervised by a specialised doctor who knows how to treat your condition.

Always take this medicine exactly as your doctor has told you, the recommended dose should not be exceeded. Check with your doctor or pharmacist if you are not sure.

Once a day or as directed by R.M.P

TRITONIB 10 is for oral use. You can take TRITONIB 10 with or without food.

If you take more TRITONIB 10 than you should

If you take more tablets than you should, immediately tell your doctor or pharmacist.

If you forget to take TRITONIB 10

Do not take a double dose to make up for a forgotten tablet. Take your next tablet at the usual time and continue as before.

If you stop taking TRITONIB 10

You should not stop taking TRITONIB 10 without discussing this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4. Possible side effects.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some may be serious and need medical attention.

- Serious Infections.
- Malignancy and Lymphoproliferative Disorders.
- Gastrointestinal Perforations.
- Laboratory Abnormalities.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

9.5. How to store TRITONIB 10 TABLET

Store below 30^{o}C & Protect from light and moisture.

9.6. Contents of the pack and other information.

Tritonib 10 Consists of Tofacitinib Citrate I.P. As active ingredient.

The Excipients used are Microcrystalline Cellulose, Lactose, Polyvinylpyrrolidone K 30, Colloidal Silicon Dioxide, Croscarmellose Sodium, Magnesium Stearate, Hydroxy Propyl Methyl Cellulose., Polyethylene Glycol 6000, Titanium dioxide, Colour Brilliant Blue Lake, Isopropyl Alcohol, Methylene Dichloride.

TRITONIB 10 is available in pack of 10 Tablets

10. Details of manufacturer

Synokem Pharmaceuticals Ltd

Plot No.: 35-36, Sector-6A,

I.I.E (SIDCUL), Ranipur (BHEL),

Haridwar-249403 (Uttarakhand).

11. Details of permission or licence number with date

Mfg. Licence. No: 19/UA/2005 issued on 18.11.2022

12. Date of revision

Not applicable

MARKETED BY

torrent PHARMA

TORRENT PHARMACEUTICALS LTD.

IN/TRITONIB 10 mg/APR-23/01/PI