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

TRITONIB

1. Generic Name:

Tofacitinib Tablets 5 mg

2. Qualitative and quantitative composition:

Each Film coated tablet contains

Tofacitinib Citrate

Equivalent to Tofacitinib ……. 5 mg

Excipients…….……..q.s.

Colour: Titanium Dioxide I.P.

The excipients are Lactose, Croscarmellose Sodium,Microcrystalline Cellulose, Dioxide, Magnesium stearate, Instacoat Aqua-III (IA- III-40001)

3. Dosage form and strength:

Dosage form: Tablet

Strength: 5 mg

4. Clinical particulars:

4.1 Therapeutic indication:

TRITONIB is a Janus kinase (JAK) inhibitor indicated for:

Rheumatoid Arthritis: TRITONIB is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

Psoriatic Arthritis: TRITONIB is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to one or more TNF blockers.

Ankylosing Spondylitis: TRITONIB is indicated for the treatment of adult patients with active ankylosing spondylitis who have had an inadequate response or intolerance to one or more TNF blockers.

Ulcerative Colitis: TRITONIB is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or intolerance to one or more TNF blockers.

Polyarticular Course Juvenile Idiopathic Arthritis: TRITONIB is indicated for the treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blockers.

Limitations of Use: Use of TRITONIB in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

4.2 Posology and method of administration:

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which tofacitinib is indicated.

Posology

Rheumatoid arthritis and psoriatic arthritis

The recommended dose is 5 mg film-coated tablets administered twice daily, which should not be exceeded.

No dose adjustment is required when used in combination with MTX.

For information on switching between tofacitinib film-coated tablets and tofacitinib prolonged-release tablets.

Table 1: Switching between tofacitinib film-coated tablets and tofacitinib prolonged-release tablets

Switching between tofacitinib 5 mg film-coated tablets and tofacitinib 11 mg prolonged-release tablet[a]	Treatment with tofacitinib 5 mg film-coated tablets twice daily and tofacitinib 11 mg prolonged-release tablet once daily may be switched between each other on the day following the last dose of either tablet.
[a] See section for comparison of pharmacokinetics of prolonged-release and film-coated formulations.	

Ankylosing spondylitis

The recommended dose of tofacitinib is 5 mg administered twice daily.

Ulcerative colitis

Induction treatment

The recommended dose is 10 mg given orally twice daily for induction for 8 weeks.

For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. Tofacitinib induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

Maintenance treatment

The recommended dose for maintenance treatment is tofacitinib 5 mg given orally twice daily.

Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known venous thromboembolism (VTE) risk factors, unless there is no suitable alternative treatment available.

For patients with UC who are not at increased risk for VTE, tofacitinib 10 mg orally twice daily may be considered if the patient experiences a decrease in response on tofacitinib 5 mg twice daily and failed to respond to alternative treatment options for ulcerative colitis such as tumour necrosis factor inhibitor (TNF inhibitor) treatment. Tofacitinib 10 mg twice daily for maintenance treatment should be used for the shortest duration possible. The lowest effective dose needed to maintain response should be used.

In patients who have responded to treatment with tofacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Retreatment in UC

If therapy is interrupted, restarting treatment with tofacitinib can be considered. If there has been a loss of response, reinduction with tofacitinib 10 mg twice daily may be considered. The treatment interruption period in clinical studies extended up to 1 year. Efficacy may be regained by 8 weeks of 10 mg twice daily therapy.

Polyarticular JIA and juvenile PsA (children between 2 and 18 years of age)

Tofacitinib may be used as monotherapy or in combination with MTX.

The recommended dose in patients 2 years of age and older is based upon the following weight categories:

Table 2: Tofacitinib dose for patients with polyarticular juvenile idiopathic arthritis and juvenile PsA two years of age and older

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

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

Dose interruption and discontinuation in adults and paediatric patients

Tofacitinib treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia, and anaemia. As described in Tables 3, 4 and 5 below, recommendations for temporary dose interruption or permanent discontinuation of treatment are made according to the severity of laboratory abnormalities.

It is recommended not to initiate dosing in patients with an absolute lymphocyte count (ALC) less than 750 cells/mm^3.

Table 3: Low absolute lymphocyte count

Low absolute lymphocyte count (ALC)	
Lab value (cells/mm^3)	**Recommendation**
ALC greater than or equal to 750	Dose should be maintained.
ALC 500-750	For persistent (2 sequential values in this range on routine testing) decrease in this range, dosing should be reduced or interrupted. For patients receiving tofacitinib 10 mg twice daily, dosing should be reduced to tofacitinib 5 mg twice daily. For patients receiving tofacitinib 5 mg twice daily, dosing should be interrupted. When ALC is greater than 750, treatment should be resumed as clinically appropriate.
ALC less than 500	If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in adult patients with an absolute neutrophil count (ANC) less than 1,000 cells/mm3. It is recommended not to initiate dosing in paediatric patients with an absolute neutrophil count (ANC) less than 1,200 cells/mm3.

Table 4: Low absolute neutrophil count

Low absolute neutrophil count (ANC)	
Lab Value (cells/mm^3)	**Recommendation**
ANC greater than 1,000	Dose should be maintained.
ANC 500-1,000	For persistent (2 sequential values in this range on routine testing) decreases in this range, dosing should be reduced or interrupted. For patients receiving tofacitinib 10 mg twice daily, dosing should be reduced to tofacitinib 5 mg twice daily. For patients receiving tofacitinib 5 mg twice daily, dosing should be interrupted. When ANC is greater than 1,000, treatment should be resumed as clinically appropriate.
ANC less than 500	If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in adult patients with haemoglobin less than 9 g/dL. It is recommended not to initiate dosing in paediatric patients with haemoglobin less than 10 g/dL.

Table 5: Low haemoglobin value

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

Interactions

Tofacitinib total daily dose should be reduced by half in patients receiving potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) and in patients receiving 1 or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g., fluconazole) as follows:

• Tofacitinib dose should be reduced to 5 mg once daily in patients receiving 5 mg twice daily (adult and paediatric patients).

• Tofacitinib dose should be reduced to 5 mg twice daily in patients receiving 10 mg twice daily (adult patients).

Only in paediatric patients: available data suggest that clinical improvement is observed within 18 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

Dose discontinuation in AS

Available data suggest that clinical improvement in AS is observed within 16 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

Special populations

Elderly

No dose adjustment is required in patients aged 65 years and older. There are limited data in patients aged 75 years and older.

Hepatic impairment

Table 6: Dose adjustment for hepatic impairment

Hepatic impairment category	**Classification**	**Dose adjustment in hepatic impairment for different strength tablets**
Mild	Child Pugh A	No dose adjustment required.
Moderate	Child Pugh B	Dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily. Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily.
Severe	Child Pugh C	Tofacitinib should not be used in patients with severe hepatic impairment.

Renal impairment

Table 7: Dose adjustment for renal impairment

Renal impairment category	**Creatinine clearance**	**Dose adjustment in renal impairment for different strength tablets**
Mild	50-80 mL/min	No dose adjustment required.
Moderate	30-49 mL/min	No dose adjustment required.
Severe (including patients undergoing haemodialysis)	< 30 mL/min	Dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal renal function is 5 mg twice daily. Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis.

Paediatric population

The safety and efficacy of tofacitinib in children less than 2 years of age with polyarticular JIA and juvenile PsA has not been established. No data are available.

The safety and efficacy of tofacitinib in children less than 18 years of age with other indications (e.g., ulcerative colitis) has not been established. No data are available.

Method of administration

Oral use.

Tofacitinib is given orally with or without food.

For patients who have difficulties swallowing, tofacitinib tablets may be crushed and taken with water.

4.3 Contraindications:

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

4.4 Special warnings and precautions for use:

The signs and symptoms of orthostasis (postural hypotension, dizziness, and vertigo) were detected more frequently in TRITONIB treated patients than in placebo recipients. As with other alpha adrenergic blocking agents there is a potential risk of syncope Patients beginning treatment with TRITONIB Tablet should be cautioned to avoid situations in which injury could result should syncope occur.

Use in patients over 65 years of age

Considering the increased risk of serious infections, myocardial infarction, and malignancies with tofacitinib in patients over 65 years of age, tofacitinib should only be used in these patients if no suitable treatment alternatives are available.

Combination with other therapies

Tofacitinib has not been studied and its use should be avoided in combination with biologics such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, selective co-stimulation modulators and potent immunosuppressants such as azathioprine, 6-mercaptopurine, ciclosporine and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

There was a higher incidence of adverse events for the combination of tofacitinib with MTX versus tofacitinib as monotherapy in RA clinical studies.

The use of tofacitinib in combination with phosphodiesterase 4 inhibitors has not been studied in tofacitinib clinical studies.

Venous thromboembolism (VTE)

Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), have been observed in patients taking tofacitinib. In a randomised post authorisation safety study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, a dose dependent increased risk for VTE was observed with tofacitinib compared to TNF inhibitors.

In a post hoc exploratory analysis within this study, in patients with known VTE risk factors, occurrences of subsequent VTEs were observed more frequently in tofacitinib-treated patients that, at 12 months treatment, had D-dimer level ≥2× ULN versus those with D-dimer level <2×

ULN; this was not evident in TNF inhibitor-treated patients. Interpretation is limited by the low number of VTE events and restricted D-dimer test availability (only assessed at Baseline, Month 12, and at the end of the study). In patients who did not have a VTE during the study, mean D-dimer levels were significantly reduced at Month 12 relative to Baseline across all treatment arms. However, D-dimer levels ≥2× ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D-Dimer testing in this study.

Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage.

Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available.

VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, and use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (BMI ≥30), diabetes, hypertension, and smoking status should also be considered. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.

For patients with RA with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is ≥ 2× ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib.

Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.

Serious infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving tofacitinib. The risk of opportunistic infections is higher in Asian geographic regions Rheumatoid arthritis patients taking corticosteroids may be predisposed to infection.

Tofacitinib should not be initiated in patients with active infections, including localised infections.

The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients:

• With recurrent infections,

• With a history of a serious or an opportunistic infection,

• Who have resided or travelled in areas of endemic mycoses,

• Who have underlying conditions that may predispose them to infection?

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tofacitinib. Treatment should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with tofacitinib should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. In patients over 65 years of age tofacitinib should only be used if no suitable treatment alternatives are available.

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.

Tuberculosis

The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients:

• Who have been exposed to TB

• Who have resided or travelled in areas of endemic TB.

Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of tofacitinib.

Patients with latent TB, who test positive, should be treated with standard antimycobacterial therapy before administering tofacitinib.

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

Viral reactivation

Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with tofacitinib. In patients treated with tofacitinib, the incidence of herpes zoster appears to be increased in:

• Japanese or Korean patients.

• Patients with an ALC less than 1,000 cells/mm^3

• Patients with long standing RA who have previously received two or more biological disease modifying antirheumatic drugs (DMARDs).

• Patients treated with 10 mg twice daily.

The impact of tofacitinib on chronic viral hepatitis reactivation is unknown. Patients screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with tofacitinib.

Major adverse cardiovascular events (including myocardial infarction)

Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib.

In a reported randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared to TNF inhibitors. (In patients over 65 years of age, patients who are current or past smokers, and patients with other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.

Malignancy and lymphoproliferative disorder

Tofacitinib may affect host defences against malignancies.

In a reported randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors .

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

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

In patients over 65 years of age, patients who are current or past smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.

Non-melanoma skin cancer

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

Interstitial lung disease

Caution is also recommended in patients with a history of chronic lung disease as they may be more prone to infections. Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with tofacitinib in RA clinical trials and in the post-marketing setting although the role of Janus kinase (JAK) inhibition in these events is not known. Asian RA patients are known to be at higher risk of interstitial lung disease, thus caution should be exercised in treating these patients.

Gastrointestinal perforations

Events of gastrointestinal perforation have been reported in clinical trials although the role of JAK inhibition in these events is not known. Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis, patients with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory drugs). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Liver enzymes

Treatment with tofacitinib was associated with an increased incidence of liver enzyme elevation in some patients. Caution should be exercised when considering initiation of tofacitinib treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST), particularly when initiated in combination with potentially hepatotoxic medicinal products such as MTX. Following initiation, routine monitoring of liver tests and prompt investigation of the causes of any observed liver enzyme elevations are recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of tofacitinib should be interrupted until this diagnosis has been excluded.

Hypersensitivity

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

Laboratory parameters

Lymphocytes

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

Neutrophils

Treatment with tofacitinib was associated with an increased incidence of neutropenia (less than 2,000 cells/mm^3) compared to placebo. It is not recommended to initiate tofacitinib treatment in adult patients with an ANC less than 1,000 cells/mm^3 and in paediatric patients with an ANC less than 1,200 cells/mm^3. ANC should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on ANC.

Haemoglobin

Treatment with tofacitinib has been associated with decreases in haemoglobin levels. It is not recommended to initiate tofacitinib treatment in adult patients with a haemoglobin value less than 9 g/dL and in paediatric patients with a haemoglobin value less than 10 g/dL. Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on haemoglobin level.

Lipid monitoring

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

Vaccinations

Prior to initiating tofacitinib, it is recommended that all patients, particularly pJIA and jPsA patients, be brought up to date with all immunisations in agreement with current immunisation guidelines. It is recommended that live vaccines not be given concurrently with tofacitinib. The decision to use live vaccines prior to tofacitinib treatment should take into account the pre-existing immunosuppression in a given patient.

Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular consideration should be given to patients with longstanding RA who have previously received two or more biological DMARDs. If live zoster vaccine is administered; it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus (VZV). If the history of chickenpox is considered doubtful or unreliable it is recommended to test for antibodies against VZV.

Vaccination with live vaccines should occur at least 2 weeks but preferably 4 weeks prior to initiation of tofacitinib or in accordance with current vaccination guidelines regarding immunomodulatory medicinal products. No data are available on the secondary transmission of infection by live vaccines to patients receiving tofacitinib.

Excipients contents

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

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Drug-Interaction:

Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib

Since tofacitinib is metabolised by CYP3A4, interaction with medicinal products that inhibit or induce CYP3A4 is likely. Tofacitinib exposure is increased when coadministered with potent inhibitors of CYP3A4 (e.g., ketoconazole) or when administration of one or more concomitant medicinal products results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

Tofacitinib exposure is decreased when coadministered with potent CYP inducers (e.g., rifampicin). Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to significantly alter the PK of tofacitinib.

Coadministration with ketoconazole (strong CYP3A4 inhibitor), fluconazole (moderate CYP3A4 and potent CYP2C19 inhibitor), tacrolimus (mild CYP3A4 inhibitor) and ciclosporine (moderate CYP3A4 inhibitor) increased tofacitinib AUC, while rifampicin (potent CYP inducer) decreased tofacitinib AUC. Coadministration of tofacitinib with potent CYP inducers (e.g., rifampicin) may result in a loss of or reduced clinical response. Coadministration of potent inducers of CYP3A4 with tofacitinib is not recommended. Coadministration with ketoconazole and fluconazole increased tofacitinib C_{max}, while tacrolimus, ciclosporine and rifampicin decreased tofacitinib C_{max}. Concomitant administration with MTX 15-25 mg once weekly had no effect on the PK of tofacitinib in RA patients.

a Tofacitinib dose should be reduced to 5 mg twice daily in patients receiving 10 mg twice daily. Tofacitinib dose should be reduced to 5 mg once daily in patients receiving 5 mg twice daily.

Potential for tofacitinib to influence the PK of other medicinal products

Coadministration of tofacitinib did not have an effect on the PK of oral contraceptives, levonorgestrel and ethinyl estradiol, in healthy female volunteers.

In RA patients, coadministration of tofacitinib with MTX 15-25 mg once weekly decreased the AUC and Cmax of MTX by 10% and 13%, respectively. The extent of decrease in MTX exposure does not warrant modifications to the individualised dosing of MTX.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Use in special populations:

Pregnancy

There are no adequate and well-controlled studies on the use of tofacitinib in pregnant women. Tofacitinib has been shown to be teratogenic in rats and rabbits, and to affect parturition and peri/postnatal development.

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

Women of childbearing potential/contraception in females

Women of childbearing potential should be advised to use effective contraception during treatment with tofacitinib and for at least 4 weeks after the last dose.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines:

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

4.8 Undesirable effects:

Rheumatoid arthritis

The most common serious adverse reactions were serious infections. In the long-term safety all exposure population, the most common serious infections reported with tofacitinib were pneumonia (1.7%), herpes zoster (0.6%), urinary tract infection (0.4%), cellulitis (0.4%), diverticulitis (0.3%), and appendicitis (0.2%). Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus, BK virus infections and listeriosis were reported with tofacitinib. Some patients have presented with disseminated rather than localised disease. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

The most commonly reported adverse reactions during the first 3 months of the double-blind, placebo or MTX controlled clinical trials were headache (3.9%), upper respiratory tract infections (3.8%), viral upper respiratory tract infection (3.3%), diarrhoea (2.9%), nausea (2.7%), and hypertension (2.2%).

The proportion of patients who discontinued treatment due to adverse reactions during first 3 months of the double-blind, placebo or MTX controlled studies was 3.8% for patients taking tofacitinib. The most common infections resulting in discontinuation of therapy during the first 3 months in controlled clinical trials were herpes zoster (0.19%) and pneumonia (0.15%).

Psoriatic arthritis

Overall, the safety profile observed in patients with active PsA treated with tofacitinib was consistent with the safety profile observed in patients with RA treated with tofacitinib.

Ankylosing spondylitis

Overall, the safety profile observed in patients with active AS treated with tofacitinib was consistent with the safety profile observed in patients with RA treated with tofacitinib.

Ulcerative colitis

The most commonly reported adverse reactions in patients receiving tofacitinib 10 mg twice daily in the induction studies were headache, nasopharyngitis, nausea, and arthralgia.

In the induction and maintenance studies, across tofacitinib and placebo treatment groups, the most common categories of serious adverse reactions were gastrointestinal disorders and infections, and the most common serious adverse reaction was worsening of UC.

Overall, the safety profile observed in patients with UC treated with tofacitinib was consistent with the safety profile of tofacitinib in the RA indication.

Tabulated list of adverse reactions

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

Table 8: Adverse reactions

System organ class	**Common ≥1/100 to <1/10**	**Uncommon ≥1/1,000 to <1/100**	**Rare ≥1/10,000 to <1/1,000**	**Very rare <1/10,000**	**Not known (cannot be estimated from the available data)**
Infections and infestations	Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Nasopharyngitis Pharyngitis	Tuberculosis Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection	Sepsis Urosepsis Disseminated TB Necrotizing fasciitis Bacteraemia Staphylococcal bacteraemia *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal Pneumonia bacterial Encephalitis Atypical mycobacterial infection Cytomegalovirus infection Arthritis bacterial	Tuberculosis of central nervous system Meningitis cryptococcal *Mycobacterium avium* complex infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Lung cancer Non-melanoma skin cancers	Lymphoma		
Blood and lymphatic system disorders	Anaemia	Leukopenia Lymphopenia Neutropenia			
Immune system disorders					Drug hypersensitivity*

					Angioedema* Urticaria*
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia Dehydration			
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache	Paraesthesia			
Vascular disorders	Hypertension	Venous thromboembolism **			
Cardiac disorders		Myocardial infarction			
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea Sinus congestion			
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia				
Hepatobiliary disorders		Hepatic steatosis Hepatic enzyme increased Transaminases increased Liver function test abnormal Gamma glutamyl-transferase increased			
Skin and subcutaneous tissue disorders	Rash	Erythema Pruritus			
Musculoskeletal and connective tissue disorders	Arthralgia	Musculoskeletal pain Joint swelling Tendonitis			
General disorders and administration site conditions	Pyrexia Oedema peripheral Fatigue				

Investigations	Blood creatine phosphokinase increased	Blood creatinine increased Blood cholesterol increased Low density lipoprotein increased Weight increased			
Injury, poisoning and procedural complications		Ligament sprain Muscle strain			

*Spontaneous reporting data

**Venous thromboembolism includes PE and DVT

Description of selected adverse reactions

Venous thromboembolism

Rheumatoid arthritis

In a Reported large, randomised post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors. The majority of these events were serious and some resulted in death. In an interim safety analysis, the incidence rates (95% CI) for PE for tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, and TNF inhibitors were 0.54 (0.32-0.87), 0.27 (0.12-0.52), and 0.09 (0.02-0.26) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for PE was 5.96 (1.75-20.33) and 2.99 (0.81-11.06) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily, respectively.

In a subgroup analysis in patients with VTE risk factors in the above-mentioned interim analysis of the study, the risk for PE was further increased. Compared with TNF inhibitors, the HR for PE was 9.14 (2.11-39.56) for tofacitinib 10 mg twice daily and 3.92 (0.83-18.48) for tofacitinib 5 mg twice daily.

Ankylosing spondylitis

In the combined Phase 2 and Phase 3 randomised controlled clinical trials, there were no VTE events in 420 patients (233 patient-years of observation) receiving tofacitinib up to 48 weeks.

Ulcerative colitis (UC)

In the UC ongoing extension trial, cases of PE and DVT have been observed in patients using tofacitinib 10 mg twice daily and with underlying VTE risk factor(s).

Overall infections

Rheumatoid arthritis

In a reported controlled phase 3 clinical studies, the rates of infections over 0-3 months in the 5 mg twice daily (total 616 patients) and 10 mg twice daily (total 642 patients) tofacitinib monotherapy groups were 16.2% (100 patients) and 17.9% (115 patients), respectively, compared to 18.9% (23 patients) in the placebo group (total 122 patients). In controlled phase 3 clinical studies with background DMARDs, the rates of infections over 0-3 months in the 5 mg twice daily (total 973 patients) and 10 mg twice daily (total 969 patients) tofacitinib plus DMARD group were

21.3% (207 patients) and 21.8% (211 patients), respectively, compared to 18.4% (103 patients) in the placebo plus DMARD group (total 559 patients).

The most commonly reported infections were upper respiratory tract infections and nasopharyngitis (3.7% and 3.2%, respectively).

The overall incidence rate of infections with tofacitinib in the long-term safety all exposure population (total 4,867 patients) was 46.1 patients with events per 100 patient-years (43.8 and 47.2 patients with events for 5 mg and 10 mg twice daily, respectively). For patients (total 1,750) on monotherapy, the rates were 48.9 and 41.9 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively. For patients (total 3,117) on background DMARDs, the rates were 41.0 and 50.3 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively.

Ankylosing spondylitis

In the reported combined Phase 2 and Phase 3 clinical trials, during the placebo-controlled period of up to 16 weeks, the frequency of infections in the tofacitinib 5 mg twice daily group (185 patients) was 27.6% and the frequency in the placebo group (187 patients) was 23.0%. In the combined Phase 2 and Phase 3 clinical trials, among the 316 patients treated with tofacitinib 5 mg twice daily for up to 48 weeks, the frequency of infections was 35.1%.

Ulcerative colitis

In the reported randomised 8-week Phase 2/3 induction studies, the proportions of patients with infections were 21.1% (198 patients) in the tofacitinib 10 mg twice daily group compared to 15.2% (43 patients) in the placebo group. In the randomised 52-week phase 3 maintenance study, the proportion of patients with infections were 35.9% (71 patients) in the 5 mg twice daily and 39.8% (78 patients) in the 10 mg twice daily tofacitinib groups, compared to 24.2% (48 patients) in the placebo group.

In the entire treatment experience with tofacitinib, the most commonly reported infection was nasopharyngitis, occurring in 18.2% of patients (211 patients).

In the entire treatment experience with tofacitinib, the overall incidence rate of infections was 60.3 events per 100 patient-years (involving 49.4% of patients; total 572 patients).

Serious infections

Rheumatoid arthritis

In the 6-month and 24-month, controlled reported clinical studies, the rate of serious infections in the 5 mg twice daily tofacitinib monotherapy group was 1.7 patients with events per 100 patient-years. In the 10 mg twice daily tofacitinib monotherapy group the rate was 1.6 patients with events per 100 patient-years, the rate was 0 events per 100 patient-years for the placebo group, and the rate was 1.9 patients with events per 100 patient-years for the MTX group.

In studies of 6-, 12-, or 24-month duration, the rates of serious infections in the 5 mg twice daily and 10 mg twice daily tofacitinib plus DMARD groups were 3.6 and 3.4 patients with events per 100 patient-years, respectively, compared to 1.7 patients with events per 100 patient-years in the placebo plus DMARD group.

In the long-term safety all exposure population, the overall rates of serious infections were 2.4 and 3.0 patients with events per 100 patient-years for 5 mg and 10 mg twice daily tofacitinib groups, respectively. The most common serious infections included pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis and diverticulitis. Cases of opportunistic infections have been reported.

Ankylosing spondylitis

In the reported combined Phase 2 and Phase 3 clinical trials, among the 316 patients treated with tofacitinib 5 mg twice daily for up to 48 weeks, there was one serious infection (aseptic meningitis) yielding a rate of 0.43 patients with events per 100 patient-years.

Ulcerative colitis

The incidence rates and types of serious infections in the UC clinical studies were generally similar to those reported in RA clinical studies with tofacitinib monotherapy treatment groups.

Serious infections in the elderly

Of the 4,271 patients who enrolled in RA studies I-VI, a total of 608 RA patients were 65 years of age and older, including 85 patients 75 years and older. The frequency of serious infection among tofacitinib-treated patients 65 years of age and older was higher than those under the age of 65 (4.8 per 100 patient-years versus 2.4 per 100 patient-years, respectively). As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Serious infections from non-interventional post approval safety study

Data from a non-interventional post approval safety study that evaluated tofacitinib in RA patients from a registry (US Corrona) showed that a numerically higher incidence rate of serious infection was observed for the 11 mg prolonged-release tablet administered once daily than the 5 mg film-coated tablet administered twice daily. Crude incidence rates (95% CI) (i.e., not adjusted for age or sex) from availability of each formulation at 12 months following initiation of treatment were 3.45 (1.93, 5.69) and 2.78 (1.74, 4.21) and at 36 months were 4.71 (3.08, 6.91) and 2.79 (2.01, 3.77) patients with events per 100 patient-years in the 11 mg prolonged-release tablet once daily and 5 mg film-coated tablet twice daily groups, respectively. The unadjusted hazard ratio was 1.30 (95% CI: 0.67, 2.50) at 12 months and 1.93 (95% CI: 1.15, 3.24) at 36 months for the 11 mg prolonged-release once daily dose compared to the 5 mg film-coated twice daily dose. Data is based on a small number of patients with events observed with relatively large confidence intervals and limited follow up time.

Viral reactivation

Patients treated with tofacitinib who are Japanese or Korean, or patients with long standing RA who have previously received two or more biological DMARDs, or patients with an ALC less than 1,000 cells/mm^3, or patients treated with 10 mg twice daily may have an increased risk of herpes zoster.

Laboratory tests

Lymphocytes

In the controlled RA clinical studies, confirmed decreases in ALC below 500 cells/mm^3 occurred in 0.3% of patients and for ALC between 500 and 750 cells/mm^3 in 1.9% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

In the RA long-term safety population, confirmed decreases in ALC below 500 cells/mm^3 occurred in 1.3% of patients and for ALC between 500 and 750 cells/mm^3 in 8.4% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

Confirmed ALC less than 750 cells/mm^3 were associated with an increased incidence of serious infections.

In the reported clinical studies in UC, changes in ALC observed with tofacitinib treatment were similar to the changes observed in clinical studies in RA.

Neutrophils

In the controlled RA clinical studies, confirmed decreases in ANC below 1,000 cells/mm^3 occurred in 0.08% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. There were no confirmed decreases in ANC below 500 cells/mm^3 observed in any treatment group. There was no clear relationship between neutropenia and the occurrence of serious infections.

In the RA long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical studies.

In the clinical studies in UC, changes in ANC observed with tofacitinib treatment were similar to the changes observed in clinical studies in RA.

Platelets

Patients in the Phase 3 controlled clinical studies (RA, PsA, AS, UC) were required to have a platelet count ≥ 100,000 cells/mm^3 to be eligible for enrolment, therefore, there is no information available for patients with a platelet count < 100,000 cells/mm^3 before starting treatment with tofacitinib.

Liver enzyme tests

Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were uncommonly observed in RA patients. In those 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 normalisation of liver enzymes.

In the controlled portion of the RA phase 3 monotherapy study (0-3 months) (study I), ALT elevations greater than 3x ULN were observed in 1.65%, 0.41%, and 0% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 1.65%, 0.41% and 0% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the RA phase 3 monotherapy study (0-24 months) (study VI, ALT elevations greater than 3x ULN were observed in 7.1%, 3.0%, and 3.0% of patients receiving MTX, tofacitinib 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 3.3%, 1.6% and 1.5% of patients receiving MTX, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the controlled portion of the RA phase 3 studies on background DMARDs (0-3 months) (studies II-V, ALT elevations greater than 3x ULN were observed in 0.9%, 1.24% and 1.14% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively. In these studies, AST elevations greater than 3x ULN were observed in 0.72%, 0.5% and 0.31% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the RA long-term extension studies, on monotherapy, ALT elevations greater than 3x ULN were observed in 1.1% and 1.4% of patients receiving tofacitinib 5 mg and 10 mg twice daily, respectively. AST elevations greater than 3x ULN were observed in < 1.0% in both the tofacitinib 5 mg and 10 mg twice daily groups.

In the RA long-term extension studies, on background DMARDs, ALT elevations greater than 3x ULN were observed in 1.8% and 1.6% of patients receiving tofacitinib 5 mg and 10 mg twice daily, respectively. AST elevations greater than 3x ULN were observed in < 1.0% in both the tofacitinib 5 mg and 10 mg twice daily groups.

In the clinical studies in UC, changes in liver enzyme tests observed with tofacitinib treatment were similar to the changes observed in clinical studies in RA.

Lipids

Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were first assessed at 1 month following initiation of tofacitinib in the controlled double-blind clinical trials of RA. Increases were observed at this time point and remained stable thereafter.

Changes in lipid parameters from baseline through the end of the study (6-24 months) in the controlled clinical studies in RA are summarised below:

• Mean LDL cholesterol increased by 15% in the tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at month 12, and increased by 16% in the tofacitinib 5 mg twice daily arm and 19% in the tofacitinib 10 mg twice daily arm at month 24.

• Mean HDL cholesterol increased by 17% in the tofacitinib 5 mg twice daily arm and 18% in the tofacitinib 10 mg twice daily arm at month 12, and increased by 19% in the tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at month 24.

Upon withdrawal of tofacitinib treatment, lipid levels returned to baseline.

Mean LDL cholesterol/HDL cholesterol ratios and Apolipoprotein B (ApoB)/ApoA1 ratios were essentially unchanged in tofacitinib-treated patients.

In an RA controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy.

In the RA long-term safety populations, elevations in the lipid parameters remained consistent with what was seen in the controlled clinical studies.

In the clinical studies in UC, changes in lipids observed with tofacitinib treatment were similar to the changes observed in clinical studies in RA.

Myocardial infarction

Rheumatoid arthritis

In a reported large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for non-fatal myocardial infarction for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), and 0.16 (0.07, 0.31) patients with events per 100 patient-years, respectively. Few fatal myocardial infarctions were reported with rates similar in patients treated with tofacitinib compared to TNF inhibitors. The study required at least 1500 patients to be followed for 3 years.

Malignancies excluding NMSC

Rheumatoid arthritis

In a reported large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for lung cancer for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.23 (0.12, 0.40), 0.32 (0.18, 0.51), and 0.13 (0.05, 0.26) patients with events per 100 patient-years, respectively. The study required at least 1500 patients to be followed for 3 years.

The incidence rates (95% CI) for lymphoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), and 0.02 (0.00, 0.10) patients with events per 100 patient-years, respectively.

Paediatric population

Polyarticular juvenile idiopathic arthritis and juvenile PsA

The adverse reactions in JIA patients in the clinical development program were consistent in type and frequency with those seen in adult RA patients, with the exception of some infections (influenza, pharyngitis, sinusitis, viral infection) and gastrointestinal or general disorders (abdominal pain, nausea, vomiting, pyrexia, headache, cough), which were more common in JIA paediatric population. MTX was the most frequent concomitant csDMARD used (on Day 1, 156 of 157 patients on csDMARDs took MTX). There are insufficient data regarding the safety profile of tofacitinib used concomitantly with any other csDMARDs.

Infections

In the reported double-blind portion of the pivotal Phase 3 trial (Study JIA-I), infection was the most commonly reported adverse reaction (44.3%). The infections were generally mild to moderate in severity.

In the integrated safety population, 7 patients had serious infections during treatment with tofacitinib within the reporting period (up to 28 days after the last dose of study medication), representing an incidence rate of 1.92 patients with events per 100 patient-years: pneumonia, epidural empyema (with sinusitis and subperiosteal abscess), pilonidal cyst, appendicitis, escherichia pyelonephritis, abscess limb, and UTI.

In the integrated safety population, 3 patients had non-serious events of herpes zoster within the reporting window representing an incidence rate of 0.82 patients with events per 100 patient-years. One (1) additional patient had an event of serious HZ outside the reporting window.

Hepatic events

Patients in the reported JIA pivotal study were required to have AST and ALT levels less than 1.5 times the upper limit of normal to be eligible for enrolment. In the integrated safety population, there were 2 patients with ALT elevations ≥ 3 times the ULN at 2 consecutive visits. Neither event met Hy's Law criteria. Both patients were on background MTX therapy and each event resolved after discontinuation of MTX and permanent discontinuation of tofacitinib.

Laboratory tests

Changes in laboratory tests in JIA patients in the clinical development program were consistent with those seen in adult RA patients. Patients in the JIA pivotal study were required to have a platelet count ≥ 100,000 cells/mm^3 to be eligible for enrolment, therefore, there is no information available for JIA patients with a platelet count <100,000 cells/mm^3 before starting treatment with tofacitinib.

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:

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. There is no specific antidote for overdose with tofacitinib. Treatment should be symptomatic and supportive.

Pharmacokinetic data up to and including a single dose of 100 mg in healthy volunteers indicate that more than 95% of the administered dose is expected to be eliminated within 24 hours.

5. Pharmacological properties:

Mechanism of Action:

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

5.1 Pharmacodynamic properties:

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

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

Changes in total serum IgG, IgM, and IgA levels over 6-month tofacitinib dosing in patients with RA were small, not dose-dependent and similar to those seen on placebo, indicating a lack of systemic humoral suppression.

After treatment with tofacitinib in RA patients, rapid decreases in serum C-reactive protein (CRP) were observed and maintained throughout dosing. Changes in CRP observed with tofacitinib treatment do not reverse fully within 2 weeks after discontinuation, indicating a longer duration of pharmacodynamic activity compared to the half-life.

5.2 Pharmacokinetic properties:

The PK profile of tofacitinib is characterised by rapid absorption (peak plasma concentrations are reached within 0.5-1 hour), rapid elimination (half-life of ~3 hours) and dose-proportional increases in systemic exposure. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after twice daily administration.

Absorption and distribution

Tofacitinib is well-absorbed, with an oral bioavailability of 74%. Coadministration of tofacitinib with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. In clinical trials, tofacitinib was administered without regard to meal.

After intravenous administration, the volume of distribution is 87 L. Approximately 40% of circulating tofacitinib is bound to plasma proteins. Tofacitinib binds predominantly to albumin and does not appear to bind to α1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

Biotransformation and elimination

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

Pharmacokinetics in patients

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

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

Results from population PK analysis in patients with active PsA or moderate to severe UC were consistent with those in patients with RA.

Renal impairment

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

Hepatic impairment

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

Interactions

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

Comparison of PK of prolonged-release and film-coated tablet formulations

Tofacitinib 11 mg prolonged-release tablets once daily have demonstrated PK equivalence (AUC and C_{max}) to tofacitinib 5 mg film-coated tablets twice daily.

Paediatric population

Pharmacokinetics in paediatric patients with juvenile idiopathic arthritis

Population PK analysis based on results from both tofacitinib 5 mg film-coated tablets twice daily and tofacitinib oral solution weight-based equivalent twice daily indicated that tofacitinib clearance and volume of distribution both decreased with decreasing body weight in JIA patients. The available data indicated that there were no clinically relevant differences in tofacitinib exposure (AUC), based on age, race, gender, patient type or baseline disease severity. The between-subject variability (% coefficient of variation) in (AUC) was estimated to be approximately 24%.

6. Nonclinical properties:

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

6.1 Animal Toxicology or Pharmacology

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

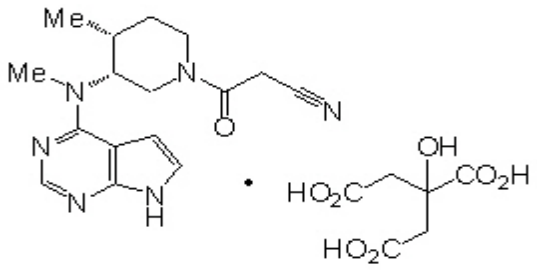
The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib was not carcinogenic in mice at exposures up to 38 or 19 times the clinical exposure level at 5 mg or 10 mg twice daily. Benign testicular interstitial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

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

No tofacitinib-related findings were observed in juvenile animal studies that indicate a higher sensitivity of paediatric populations compared with adults. In the juvenile rat fertility study, there was no evidence of developmental toxicity, no effects on sexual maturation, and no evidence of reproductive toxicity (mating and fertility) was noted after sexual maturity. In 1-month juvenile rat and 39-week juvenile monkey studies tofacitinib-related effects on immune and haematology parameters consistent with JAK1/3 and JAK2 inhibition were observed. These effects were reversible and consistent with those also observed in adult animals at similar exposures.

7. Description:

Tofacitinib Citrate is (3R, 4R)-4-methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-ß-oxo1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1). Its empirical formula is $C_{16}H_{20}N_6O \bullet C_6H_8O_7$ and its structural formula is:



Tofacitinib Citrate An off white to white powder with a molecular weight of 504.5. It is slightly soluble in 0.1 N HCL solution.

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 5 mg is Available in 4 Blister strip pack of 15 tablets.

8.4 Storage and handing instructions:

STORE PROTECTED FROM MOISTURE, AT A TEMPERATURE NOT EXCEEDING 30°C.

9. Patient Counselling Information

Package leaflet: Information for the user

TRITONIB

Tofacitinib

Film coated tablet 5 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?

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

TRITONIB Tablet contains Tofacitinib 5 mg film coated tablet.

It is used for the treatment of rheumatoid arthritis, Psoriatic Arthritis, Ankylosing Spondylitis, Ulcerative Colitis, Polyarticular Course Juvenile Idiopathic Arthritis.

What you need to know before you take TRITONIB

Do not take TRITONIB

- If you are allergic to tofacitinib or any of the other ingredients of this medicine
- If you have a severe infection such as bloodstream infection or active tuberculosis
- If you have been informed that you have severe liver problems, including cirrhosis (scarring of the liver)
- If you are pregnant or breast-feeding

If you are not sure regarding any of the information provided above, please contact your doctor.

Warnings and precautions

Talk to your doctor or pharmacist before taking TRITONIB:

- if you think you have an infection or have symptoms of an infection such as fever, sweating, chills, muscle aches, cough, shortness of breath, new phlegm or change in phlegm, weight loss, warm or red or painful skin or sores on your body, difficulty or pain when swallowing, diarrhoea or stomach pain, burning when you urinate or urinating more often than normal, feeling very tired

- If you have any condition that increases your chance of infection (e.g., diabetes, HIV/AIDS, or a weak immune system)

- If you have any kind of infection, are being treated for any infection, or if you have infections that keep coming back. Tell your doctor immediately if you feel unwell. TRITONIB can reduce your body's ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection

- If you have or have a history of tuberculosis or have been in close contact with someone with tuberculosis. Your doctor will test you for tuberculosis before starting TRITONIB and may retest during treatment

- If you have any chronic lung disease

- If you have liver problems

- If you have or had hepatitis B or hepatitis C (viruses that affect the liver). The virus may become active while you are taking TRITONIB. Your doctor may do blood tests for hepatitis before you start treatment with TRITONIB and while you are taking TRITONIB

- If you are older than 65 years, if you have ever had any type of cancer, and also if you are a current or past smoker. TRITONIB may increase your risk of certain cancers. White blood cell

cancer, lung cancer and other cancers (such as breast, melanoma, prostate and pancreatic) have been reported in patients treated with TRITONIB. If you develop cancer while taking TRITONIB your doctor will review whether to stop TRITONIB treatment.

- If you are at high risk of developing skin cancer, your doctor may recommend that you have regular skin examinations while taking TRITONIB.

- If you have had diverticulitis (a type of inflammation of the large intestine) or ulcers in stomach or intestines

- If you have kidney problems

- If you are planning to get vaccinated, tell your doctor. Certain types of vaccines should not be given when taking TRITONIB. Before you start TRITONIB, you should be up to date with all recommended vaccinations. Your doctor will decide whether you need to have herpes zoster vaccination.

- If you have heart problems, high blood pressure, high cholesterol, and also if you are a current or past smoker

There have been reports of patients treated with TRITONIB who have developed blood clots in the lungs or veins. Your doctor will evaluate your risk to develop blood clots in the lungs or veins and determine if TRITONIB is appropriate for you. If you have already had problems on developing blood clots in lungs and veins or have an increased risk for developing this (for example: if you are seriously overweight, if you have cancer, heart problems, diabetes, experienced a heart attack (within previous 3 months), recent major surgery, if you use hormonal contraceptives\hormonal replacement therapy, if a coagulation defect is identified in you or your close relatives), if you are of older age, or if you smoke currently or in the past, your doctor may decide that TRITONIB is not suitable for you.

Talk to your doctor straight away if you develop sudden shortness of breath or difficulty breathing, chest pain or pain in upper back, swelling of the leg or arm, leg pain or tenderness, or redness or discoloration in the leg or arm while taking TRITONIB, as these may be signs of a clot in the lungs or veins.

There have been reports of patients treated with TRITONIB who have had a heart problem, including heart attack. Your doctor will evaluate your risk to develop a heart problem and determine if TRITONIB is appropriate for you. Talk to your doctor straight away if you develop signs and symptoms of a heart attack including severe chest pain or tightness (that may spread to arms, jaw, neck, back), shortness of breath, cold sweat, light headedness or sudden dizziness.

Additional monitoring tests

Your doctor should perform blood tests before you start taking TRITONIB, and after 4 to 8 weeks of treatment and then every 3 months, to determine if you have a low white blood cell (neutrophil or lymphocyte) count, or a low red blood cell count (anaemia).
You should not receive TRITONIB if your white blood cell (neutrophil or lymphocyte) count or red blood cell count is too low. If needed, your doctor may interrupt your TRITONIB treatment to reduce the risk of infection (white blood cell counts) or anaemia (red blood cell counts).
Your doctor may also perform other tests, for example to check your blood cholesterol levels or monitor the health of your liver. Your doctor should test your cholesterol levels 8 weeks after you start receiving TRITONIB. Your doctor should perform liver tests periodically.

Elderly

There is a higher rate of infections in patients aged 65 years and older. Tell your doctor as soon as you notice any signs or symptoms of infections.

Patients aged 65 years and older may be at increased risk of infections, heart attack and some types of cancer. Your doctor may decide that TRITONIB is not suitable for you.

Asian patients

There is a higher rate of shingles in Japanese and Korean patients. Tell your doctor if you notice any painful blisters on your skin.
You may also be at higher risk of certain lung problems. Tell your doctor if you notice any breathing difficulties.

Children and adolescents

The safety and benefits of TRITONIB in children have not yet been established in patients less than 2 years of age.

Other medicines and TRITONIB

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. If taken with TRITONIB, they could alter the level of TRITONIB in your body, and the dose of TRITONIB 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

TRITONIB is not recommended for use with medicines that depress the immune system, including so-called targeted biologic (antibody) therapies, such as those that inhibit tumour necrosis factor, interleukin-17, interleukin-12/interleukin-23, anti-integrins, and strong chemical immunosuppressants including azathioprine, mercaptopurine, ciclosporine, and tacrolimus. Taking TRITONIB with these medicines may increase your risk of side effects including infection.
Serious infections may happen more often in people who also take corticosteroids (e.g., prednisone).

Pregnancy and breast-feeding

If you are a woman of childbearing age, you should use effective birth control during treatment with TRITONIB and for at least 4 weeks after the last dose.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. TRITONIB must not be used during pregnancy. Tell your doctor right away if you become pregnant while taking TRITONIB.
If you are taking TRITONIB and breast-feeding, you must stop breast-feeding until you talk to your doctor about stopping treatment with TRITONIB.

Driving and using machines

TRITONIB has no or limited effect on your ability to drive or use machines.

TRITONIB contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

TRITONIB contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet that is to say essentially 'sodium free'.

9.2. How to take TRITONIB 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.

Rheumatoid arthritis

• The recommended dose is 5 mg twice a day.

Psoriatic arthritis

• The recommended dose is 5 mg twice a day.

If you suffer from rheumatoid arthritis or psoriatic arthritis, your doctor may switch your tablets between TRITONIB 5 mg film-coated tablets twice daily and TRITONIB 11 mg prolonged-release tablet once daily. You can start the TRITONIB prolonged-release tablet once daily or TRITONIB film-coated tablets twice daily on the day following the last dose of either tablet. You should not switch between TRITONIB film-coated tablets and TRITONIB prolonged-release tablet unless instructed by your doctor.

Ankylosing spondylitis

• The recommended dose is 5 mg twice a day.

• Your doctor may decide to stop TRITONIB if TRITONIB does not work for you within 16 weeks.

Ulcerative colitis

• The recommended dose is 10 mg twice a day for 8 weeks, followed by 5 mg twice a day.

• Your doctor may decide to extend the initial 10 mg twice a day treatment by an additional 8 weeks (16 weeks in total), followed by 5 mg twice a day.

• Your doctor may decide to stop TRITONIB if TRITONIB does not work for you within 16 weeks.

• For patients, who have previously taken biologic medicines to treat ulcerative colitis (such as those that block the activity of tumour necrosis factor in the body) and these medicines did not work, the doctor may decide to increase your dose of TRITONIB to 10 mg twice a day if you do not respond sufficiently to 5 mg twice a day. Your doctor will consider the potential risks, including that of developing blood clots in the lungs or veins, and potential benefits to you. Your doctor will tell you if this applies to you.

• If your treatment is interrupted, your doctor may decide to restart your treatment.

Use in children and adolescents

Polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis

• The recommended dose is 5 mg twice a day for patient's ≥40 kg.

Try to take your tablet at the same time every day (one tablet in the morning and one tablet in the evening).

Tofacitinib tablets may be crushed and taken with water.

Your doctor may reduce the dose if you have liver or kidney problems or if you are prescribed

certain other medicines. Your doctor may also stop treatment temporarily or permanently if blood tests show low white blood cell or red blood cell counts.

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

If you take more TRITONIB than you should

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

If you forget to take TRITONIB

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

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

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

9.3. 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.

Side effects in patients with polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis were consistent with those seen in adult rheumatoid arthritis patients with the exception of some infections (influenza, pharyngitis, sinusitis, viral infection) and gastrointestinal or general disorders (abdominal pain, nausea, vomiting, fever, headache, cough), which were more common in juvenile idiopathic arthritis paediatric population.

Possible serious side effects

In rare cases, infection may be life-threatening

Lung cancer, white blood cell cancer and heart attack have also been reported.

If you notice any of the following serious side affects you need to tell a doctor straight away.

Signs of serious infections (common) include

• Fever and chills

• Cough

• Skin blisters

• Stomach ache

• Persistent headaches

Signs of ulcers or holes in your stomach (uncommon) include

• Fever

• Stomach or abdominal pain

• Blood in the stool

• Unexplained changes in bowel habits

Holes in stomach or intestines happen most often in people who also take nonsteroidal anti-inflammatory drugs or corticosteroids (e.g., prednisone).

Signs of allergic reactions (unknown) include

• Chest tightness

• wheezing

• Severe dizziness or light-headedness

• Swelling of the lips, tongue or throat

• Hives (itching or skin rash)

Signs of blood clots in lungs or veins (uncommon: venous thromboembolism) include

• Sudden shortness of breath or difficulty breathing

• Chest pain or pain in upper back

• Swelling of the leg or arm

• Leg pain or tenderness

• Redness or discoloration in the leg or arm

Signs of a heart attack (uncommon) include

• Severe chest pain or tightness (that may spread to arms, jaw, neck, back)

• Shortness of breath

• Cold sweat

• Light headedness or sudden dizziness

Other side effects which have been observed with TRITONIB are listed below.

Common (may affect up to 1 in 10 people): lung infection (pneumonia and bronchitis), shingles (herpes zoster), infections of nose, throat or the windpipe (nasopharyngitis), influenza, sinusitis, urinary bladder infection (cystitis), sore throat (pharyngitis), increased muscle enzymes in the blood (sign of muscle problems), stomach (belly) pain (which may be from inflammation of the stomach lining), vomiting, diarrhoea, feeling sick (nausea), indigestion, low red blood cell count (anaemia), fever, fatigue (tiredness), swelling of the feet and hands, headache, high blood pressure (hypertension), cough, rash.

Uncommon (may affect up to 1 in 100 people): lung cancer, tuberculosis, kidney infection, skin infection, herpes simplex or cold sores (oral herpes), low white blood cell counts, increased liver enzymes in the blood (sign of liver problems), blood creatinine increased (a possible sign of kidney problems), increased cholesterol (including increased LDL), weight gain, dehydration, muscle strain, pain in the muscles and joints, tendonitis, joint swelling, joint sprain, abnormal sensations, poor sleep, sinus congestion, shortness of breath or difficulty breathing, skin redness, itching, fatty liver, painful inflammation of small pockets in the lining of your intestine (diverticulitis), viral infections, viral infections affecting the gut, some types of skin cancers (non-melanoma-types).

Rare (may affect up to 1 in 1,000 people): blood infection (sepsis), lymphoma (white blood cell cancer), disseminated tuberculosis involving bones and other organs, other unusual infections, joint infections.

Very rare (may affect up to 1 in 10,000 people): tuberculosis involving the brain and spinal cord, meningitis.

In general, fewer side effects were seen when TRITONIB was used alone than in combination with methotrexate in rheumatoid arthritis.

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.

9.4. How to store TRITONIB TABLET

STORE PROTECTED FROM MOISTURE, AT A TEMPERATURE NOT EXCEEDING 30°C.

9.5. Contents of the pack and other information.

Tofacitinib tablets

White to off white colored, round, biconvex film coated tablets plain on both sides.

The excipients are Lactose, Croscarmellose Sodium,Microcrystalline Cellulose, Dioxide, Magnesium stearate, Instacoat Aqua-III (IA- III-40001)

Available in 4 Blister strip pack of 15 tablets.

10. Details of manufacturer

Indrad-382721, Dist.Mehsana,India.

At: Plot No.65, 66, 67, Phase II,

Atgaon Industrial complex,

Atgaon, Shahpur,Thane -421601

11. Details of permission or licence number with date

Mfg Lic No.: MH/104151A issued on 22/09/2021

12. Date of revision

Not applicable

MARKETED BY

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IN/TRITONIB 5 mg/AUG-22/01/PI