JAKNIB®
(Tofacitinib)

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information.

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS:

Patients treated with tofacitinib are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressant such as methotrexate or corticosteroids. If a serious infection develops, interrupt tofacitinib until the infection is controlled.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extra pulmonary disease. Patients should be tested for latent tuberculosis before tofacitinib use and during therapy. Treatment for latent infection should be initiated prior to tofacitinib use.
- Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.

The risks and benefits of treatment with tofacitinib should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MALIGNANCIES:

Lymphoma and other malignancies have been observed in patients treated with tofacitinib. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with tofacitinib and concomitant immunosuppressive medications.

1. NAME OF THE PRODUCT

JAKNIB® (Tofacitinib) 5mg Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

JAKNIB® 5mg Tablet

Each film coated tablet contains:

Tofacitinib Citrate MS eq. to Tofacitinib……..……..5mg

3. PHARMACEUTICAL FORM

Tablet.

Appearance: Yellow colored, film coated round shaped tablet, plain on both sides.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Rheumatoid arthritis: Tofacitinib in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate.

Psoriatic arthritis: Tofacitinib in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.

Ankylosing spondylitis: Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

Ulcerative colitis: Tofacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

Juvenile idiopathic arthritis (JIA): Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs. Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

Rheumatoid arthritis and psoriatic arthritis: Recommended dose is 5mg twice daily, which should not be exceeded. No dose adjustment is required when used in combination with MTX.

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

Ulcerative colitis:

Induction treatment: Recommended dose is 10mg 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 10mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5mg 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: Recommended dose for maintenance treatment is tofacitinib 5mg given orally twice daily. Tofacitinib 10mg twice daily for maintenance treatment is not recommended in patients with UC who have known venous thromboembolism (VTE), major adverse cardiovascular events (MACE) and malignancy risk factors, unless there is no suitable alternative treatment available. For patients with UC who are not at increased risk for VTE, MACE and malignancy tofacitinib 10mg orally twice daily may be considered if the patient experiences a decrease in response on tofacitinib 5mg twice daily and failed to respond to alternative treatment options for ulcerative colitis such as tumour necrosis factor inhibitor (TNF inhibitor) treatment. Tofacitinib 10mg 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 10mg 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 10mg twice daily therapy.

Polyarticular JIA and juvenile PsA: Tofacitinib may be used as monotherapy or in combination with MTX. The recommended is based upon the weight; ≥ 40kg, 5mg twice daily. Patients ≥ 40kg treated with tofacitinib 5mL oral solution twice daily may be switched to tofacitinib 5mg film-coated tablets twice daily. Patients < 40kg cannot be switched from tofacitinib oral solution.

Dose interruption and discontinuation in adults and paediatric patients: Treatment should be interrupted if a patient develops a serious infection. Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia, and anaemia. 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 750cells/mm^3.

Low absolute lymphocyte count (ALC):

- ***ALC greater than or equal to 750cells/mm^3:*** Dose should be maintained.
- ***ALC 500-750cells/mm^3:*** 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 10mg twice daily, dosing should be reduced to tofacitinib 5mg twice daily/For patients receiving tofacitinib

5mg twice daily, dosing should be interrupted. When ALC is greater than 750cells/mm^3, treatment should be resumed as clinically appropriate.

- ***ALC less than 500cells/mm^3:*** 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 1,000cells/mm^3. It is recommended not to initiate dosing in paediatric patients with an absolute neutrophil count (ANC) less than 1,200cells/mm^3.

Low absolute neutrophil count (ANC):

- ***ANC greater than 1,000cells/mm^3:*** Dose should be maintained.
- ***ANC 500-1,000cells/mm^3:*** 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 5mg twice daily. For patients receiving tofacitinib 5mg twice daily, dosing should be interrupted.
- When ANC is greater than 1,000cells/mm^3, treatment should be resumed as clinically appropriate.
- ***ANC less than 500cells/mm^3:*** 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 9g/dL. It is recommended not to initiate dosing in paediatric patients with haemoglobin less than 10g/dL.

Low haemoglobin value:

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

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.

Paediatric population: 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. 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.

Interactions: 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).

- Tofacitinib dose should be reduced to 5mg once daily in patients receiving 5mg twice daily (adult and paediatric patients).
- Tofacitinib dose should be reduced to 5mg twice daily in patients receiving 10mg 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.

Dose adjustment for hepatic impairment:

Mild Impairment-Child Pugh A: No dose adjustment required.

Moderate Impairment-Child Pugh B: Dose should be reduced to 5mg once daily when the indicated dose in the presence of normal hepatic function is 5mg twice daily. Dose should be reduced to 5mg twice daily when the indicated dose in the presence of normal hepatic function is 10mg twice daily.

Severe Impairment-Child Pugh C: Tofacitinib should not be used in patients with severe hepatic impairment.

Dose adjustment for renal impairment:

Mild Impairment-CrCl 50-80mL/min: No dose adjustment required.

Moderate Impairment-CrCl 30-49mL/min: No dose adjustment required.

Severe renal impairment (including patients undergoing haemodialysis)-CrCl <30mL/min: Dose should be reduced to 5mg once daily when the indicated dose in the presence of normal renal function is 5mg twice daily. Dose should be reduced to 5mg twice daily when the indicated dose in the presence of normal renal function is 10mg twice daily. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis.

Method of administration:

Oral use; 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.
- 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:

Use in patients over 65 years of age: Considering the increased risk of serious infections, myocardial infarction, and malignancies and all cause

mortality with tofacitinib in patients 65 years of age and older, tofacitinib should only be used in these patients if no suitable treatment alternatives are available.

Combination with other therapies: Tofacitinib 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, ciclosporin and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

Venous thromboembolism (VTE): Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), are known to occur with tofacitinib. Tofacitinib 10mg twice daily for maintenance treatment is not recommended in patients with UC who have known VTE MACE and malignancy risk factors, unless there is no suitable alternative treatment available. In patients with cardiovascular or malignancy risk factors tofacitinib should only be used if no suitable treatment alternatives are available. In patients with VTE risk factors other than MACE or malignancy risk factors, tofacitinib should be used with caution. VTE risk factors other than MACE or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk. Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.

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

Serious infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens are known to be reported in patients receiving tofacitinib. Rheumatoid arthritis patients taking corticosteroids may be predisposed to infection. Avoid use during an active serious infection. 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. 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.

Tuberculosis: The risks and benefits of treatment should be considered prior to initiating tofacitinib in patients who have been exposed to TB or who have resided or travelled in areas of endemic TB. Patients with latent TB, who test positive, should be treated with standard anti mycobacterial therapy before administering tofacitinib. 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. 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 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 defenses against malignancies. NMSC lung cancers and lymphoma is known to occur. Other malignancies including breast cancer, melanoma, prostate cancer, and pancreatic cancer are also known to occur. In patients over 65 years of age, tofacitinib should only be used if no suitable treatment alternatives are available. Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer.

Interstitial lung disease: Caution is also recommended in patients with a history of chronic lung disease and infections.

Gastrointestinal perforations: 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 NSAIDs). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Fractures: Fractures have been observed in patients treated with tofacitinib. Tofacitinib should be used with caution in patients with known risk factors for fractures such as elderly patients, female patients and patients with corticosteroid use, regardless of indication and dosage.

Liver enzymes: Known to be 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.

Hypersensitivity: Hypersensitivity associated with tofacitinib administration are known to be reported. Allergic reactions included angioedema and urticaria; serious reactions have occurred. Tofacitinib should be discontinued immediately.

Laboratory parameters:

Lymphocytes and Neutrophils: Laboratory monitoring is recommended due to potential changes in lymphocytes, neutrophils, haemoglobin, liver enzymes and lipids. Lymphocytes should be monitored at baseline and every 3 months thereafter and ANC should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter.

Haemoglobin: Treatment with tofacitinib is known to be associated with decreased haemoglobin levels; not recommended to initiate treatment in adult patients with a Hb less than 9g/dL and in paediatric patients with Hb less than 10g/dL. Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter.

Lipid monitoring: Assessment of lipid parameters should be performed after 8 weeks following initiation of tofacitinib therapy.

Hypoglycaemia in patients treated for diabetes: There have been reports of hypoglycaemia following initiation of tofacitinib in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycaemia occurs.

Vaccinations: It is recommended that live vaccines not be given concurrently with tofacitinib. 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.

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

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib: Tofacitinib exposure is decreased when co-administered with rifampicin. Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to significantly alter the PK of tofacitinib. Co-administration with ketoconazole fluconazole tacrolimus and cyclosporine increased tofacitinib AUC, while rifampicin decreased tofacitinib AUC. Co-administration of tofacitinib with potent CYP inducers (e.g., rifampicin) may result in a loss of or reduced clinical response. Co-administration of potent inducers of CYP3A4 with tofacitinib is not recommended. Co-administration with ketoconazole and fluconazole increased tofacitinib C_{max}, while tacrolimus, ciclosporin and rifampicin decreased tofacitinib C_{max}. Concomitant administration with MTX 15-25mg once weekly had no effect on the PK of tofacitinib in RA patients.

Potential for tofacitinib to influence the PK of other medicinal products: In RA patients, co-administration of tofacitinib with MTX 15-25mg once weekly decreased the AUC and C_{max} 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. FERTILITY, PREGNANCY AND LACTATION:

Fertility: Known to impair female fertility in rats.

Pregnancy: No adequate and well-controlled studies in pregnant women; As a precautionary measure, the use of tofacitinib during pregnancy is contraindicated.

Women of childbearing potential/contraception in females: 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. The use of tofacitinib during breast-feeding is contraindicated.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

No or negligible influence on the ability to drive and use machines.

4.8. UNDESIRABLE EFFECTS:

Common: Pneumonia, influenza, herpes zoster, urinary tract infection, sinusitis, bronchitis, nasopharyngitis, pharyngitis, lymphopenia, anaemia, headache, hypertension, cough, abdominal pain, vomiting, diarrhoea, nausea, gastritis, dyspepsia, rash, acne, arthralgia, oedema peripheral, increased blood creatine phosphokinase.

Uncommon: Tuberculosis, diverticulitis, pyelonephritis, cellulitis, Herpes simplex, viral gastroenteritis, viral infection, lung cancer, non-melanoma skin cancers, leukopenia, neutropenia, dyslipidaemia, hyperlipidaemia, dehydration, insomnia, paraesthesia, venous thromboembolism, myocardial infarction, dyspnoea, sinus congestion, hepatic steatosis, increased hepatic enzyme, transaminases increased, increased gamma glutamyl-transferase, erythema, pruritus, joint swelling, tendonitis, pyrexia, fatigue, increased blood creatinine/blood cholesterol/low density lipoprotein/weight, ligament sprain and muscle strain.

Rare: Sepsis, urosepsis, disseminated TB, bacteraemia, pneumocystis jirovecii pneumonia, pneumococcal pneumonia, bacterial pneumonia, cytomegalovirus infection, arthritis bacterial, lymphoma, abnormal liver function test, musculoskeletal pain.

Very rare: Tuberculosis of central nervous system, cryptococcal meningitis, necrotizing fasciitis, encephalitis, *Staphylococcal bacteraemia, Mycobacterium avium* complex infection, Atypical mycobacterial infection.

Not Known: Hypersensitivity, angioedema, urticaria.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES:

Pharmacotherapeutic groups: Immunosuppressants, Janus-associated kinase (JAK) inhibitors.

ATC code: L04AF01.

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.

5.2. PHARMACOKINETIC PROPERTIES:

The PK profile of tofacitinib is characterized 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%. Co-administration with a high-fat meal resulted in no changes in AUC while C_{max} is known to be reduced by 32%. Tofacitinib binds predominantly to albumin. Tofacitinib distributes equally between red blood cells and plasma. 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; metabolism is primarily mediated by CYP3A4 with minor contribution from CYP2C19. The pharmacologic activity of tofacitinib is attributed to the parent molecule.

5.3. PRECLINICAL SAFETY DATA:

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 5mg or 10mg twice daily), and 0 of 14 juvenile monkeys at 5 or 2.5 times the clinical exposure level of 5mg or 10mg 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 5mg or 10mg twice daily. Other findings at doses exceeding human exposures included effects on the hepatic and gastrointestinal systems. Tofacitinib is not mutagenic or genotoxic based on the results of a series of in vitro and in vivo tests for gene mutations and chromosomal aberrations. The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib was not carcinogenic in mice at exposures up to 38 or 19 times the clinical exposure level at 5mg or 10mg 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 5mg or 10mg twice daily. Benign thymomas were observed in female rats at 187 or 94 times the clinical exposure level at 5mg or 10mg twice daily. Tofacitinib was shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility (decreased pregnancy rate; decreases in the numbers of corpora lutea, implantation sites, and viable foetuses; and an increase in early resorptions), parturition, and peri/postnatal development. Tofacitinib had no effects on male fertility, sperm motility or sperm concentration. Tofacitinib was secreted in milk of lactating rats at concentrations approximately 2-fold those in serum from 1 to 8 hours post dose. In studies conducted in juvenile rats and monkeys, there were no tofacitinib-related effects on bone development in males or females, at exposures similar to those achieved at approved doses in humans. 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.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

Excipients:

- Microcrystalline cellulose
- Lactose monohydrate
- Croscarmellose sodium
- Magnesium stearate

Materials for coating:

- Hydroxypropyl methyl cellulose
- Triacetin
- Lactose monohydrate
- Polyethylene glycol
- Titanium dioxide
- Tartrazine yellow lake color
- Purified water

6.2. INCOMPATIBILITIES:

Not applicable.

6.3. SHELF LIFE:

See expiry on the pack.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C, and protect from heat, light and moisture.
Improper storage may deteriorate the medicine.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Alu/Alu blister, pack size is 10’s.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

Innovator’s Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

110061

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

28th September, 2021

10. DATE OF REVISION OF THE TEXT

جیکنِب® ٹیبلٹ

(ٹوفاسی ٹِینِب)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔

بچوں کی پہنچ سے دور رکھیں۔

دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،

گرمی، روشنی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔