

#### Cardiovascular risk

RA and PsA patients have an increased risk for cardiovascular disorders. Patients treated with tofacitinib should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care.

#### Liver enzymes

Treatment with tofacitinib was associated with an increased incidence of liver enzyme elevation

#### HYPERSENSITIVITY

##### Fertility, pregnancy and lactation

##### 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.

#### PRESENTATION

Tofacit 5mg tablet is available in blister packs of 10's.

#### STORAGE CONDITIONS AND INSTRUCTIONS

- Store below 30°C in a dry place, protect from light.
- To be dispensed on the prescription of a registered medical practitioner only.
- Keep out of the reach of children.

#### ہدایات:

- خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
- دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
- صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کریں۔
- بچوں کی پہنچ سے دور رکھیں۔

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Art No: 698/1

# Tofacit 5<sub>mg</sub>

(Tofacitinib) Tablets

ٹوفا سیٹ (ٹوفا سینیب) ۵ مگ ٹیبلٹ

#### COMPOSITION

Each film coated tablet contains:  
Tofacitinib (as Citrate) ..... 5mg  
(Product complies Innovator's Specs).

#### WARNING: SERIOUS INFECTIONS AND MALIGNANCY

- Prior to starting TOFACIT, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting TOFACIT.
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative.
- Lymphoma and other malignancies have been observed in patients treated with TOFACIT. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with TOFACIT and concomitant immunosuppressive medications.

#### Effects of this medicine

Tofacit is used for the treatment of the following inflammatory diseases:

- rheumatoid arthritis
- psoriatic arthritis
- ulcerative colitis.

#### CLINICAL PHARMACOLOGY

##### Pharmacodynamics:

*Pharmacotherapeutic groups:* Immunosuppressants, Selective Immunosuppressants

##### 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.

##### Pharmacokinetics

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<sub>max</sub> 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 α<sub>1</sub>-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.

#### POSLOGY

*Rheumatoid arthritis and psoriatic arthritis*

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

#### ***Rheumatoid arthritis***

Switching between tofacitinib 5 mg film-coated tablets and tofacitinib 11 mg prolonged-release tablets. Patients treated with tofacitinib 5 mg film-coated tablets twice daily may be switched to tofacitinib 11 mg prolonged-release tablets once daily on the day following the last dose of tofacitinib 5 mg film-coated tablets. Patients treated with tofacitinib 11 mg prolonged-release tablets once daily may be switched to tofacitinib 5 mg film-coated tablets twice daily on the day following the last dose of tofacitinib 11 mg prolonged-release tablets.

#### ***Dose adjustment:***

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

#### ***Psoriatic arthritis***

The recommended dose is 5 mg twice a day.

#### ***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 Tofacit, if Tofacit 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 Tofacit 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.

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.

#### **METHOD OF ADMINISTRATION**

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

#### **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.

#### **WARNINGS AND PRECAUTIONS**

##### ***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. 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.

#### ***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,
- who are over 65 years of age.

#### ***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.

#### ***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<sup>3</sup>.
- 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.

#### ***Malignancy and lymphoproliferative disorder***

The risks and benefits of tofacitinib treatment should be considered prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing tofacitinib in patients who develop a malignancy. The possibility exists for tofacitinib to affect host defences against malignancies.

#### ***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.

#### ***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.