

Tofacinix

Tofacitinib Citrate INN

COMPOSITION

Tofacinix Tablet: Each film coated tablet contains Tofacitinib Citrate INN equivalent to Tofacitinib 5 mg.

Therapeutic Class: Antirheumatic drug.

CLINICAL PHARMACOLOGY

Mechanism of Action

Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). Tofacitinib inhibited the in vitro activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC50 of 406, 56, and 1377 nM, respectively. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known.

Pharmacokinetics

Absorption

The absolute oral bioavailability of Tofacitinib is 74%. Coadministration of Tofacitinib with a high-fat meal resulted in no changes in AUC while Cmax was reduced by 32%. In clinical trials, Tofacitinib was administered without regard to meals.

Distribution

After intravenous administration, the volume of distribution is 87 L. The protein binding of Tofacitinib is ~40%. Tofacitinib binds predominantly to albumin and does not appear to bind to 1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

Metabolism 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 radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged Tofacitinib, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of Tofacitinib is attributed to the parent molecule.

Pharmacodynamics

Treatment with Tofacitinib was associated with dose-dependent reductions of circulating CD16/56+ natural killer cells, with estimated maximum reductions occurring at approximately 8–10 weeks after initiation of therapy. These changes generally resolved within 2–6 weeks after discontinuation of treatment. Treatment with Tofacitinib was associated with dose-dependent increases in B cell counts. Changes in circulating T-lymphocyte counts and T-lymphocyte subsets (CD3+, CD4+ and CD8+) were small and inconsistent. The clinical significance of these changes is unknown.

Total serum IgG, IgM, and IgA levels after 6-month dosing in patients with rheumatoid arthritis were lower than placebo; however, changes were small and not dose-dependent.

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

INDICATIONS

- Tofacitinib is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).
- Tofacitinib is 5 mg twice daily.
- Tofacitinib is given orally with or without food.
- Limitations of Use: Use of Tofacitinib in combination with biologic DMARDs or with potent immunosuppressants such as Azathioprine and Cyclosporine is not recommended.

DOSAGE AND ADMINISTRATION

Tofacitinib may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). The recommended dose of Tofacitinib is 5 mg twice daily and the recommended dose of Tofacitinib is 11 mg once daily.

Switching from Tofacitinib 5 mg Tablet to Tofacitinib 11 mg Tablets

Patients treated with Tofacitinib 5 mg twice daily may be switched to Tofacitinib 11 mg once daily the day following the last dose of Tofacitinib 5 mg

Dosage Modifications due to Serious Infections and Cytopenias

- It is recommended that Tofacitinib not be initiated in patients with an absolute lymphocyte count less than 500 cells/mm³, an absolute neutrophil count (ANC) less than 1000 cells/mm³ or who have hemoglobin levels less than 9 g/dL.
- Dose interruption is recommended for management of lymphopenia, neutropenia and anemia
- Avoid use of Tofacitinib if a patient develops a serious infection until the infection is controlled.

Dosage Modifications due to Drug Interactions

In patients receiving:

- Potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., Ketoconazole), or
- One or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., Fluconazole), the recommended dose is Tofacitinib 5 mg once daily.
- Coadministration of potent inducers of CYP3A4 (e.g., Rifampin) with Tofacitinib may result in loss of or reduced clinical response to Tofacitinib.
- Coadministration of potent inducers of CYP3A4 with Tofacitinib is not recommended.

Dosage Modifications in Patients with Renal or Hepatic Impairment

In patients with:

- Moderate or severe renal insufficiency, or
- Moderate hepatic impairment, the recommended dose is Tofacitinib 5 mg once daily.
- Use of Tofacitinib in patients with severe hepatic impairment is not recommended.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Avoid use of Tofacitinib in patients with an active, serious infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating Tofacitinib in patients:

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection

ADVERSE REACTIONS

- upper respiratory tract infections (common cold, sinus infections)
- headache
- diarrhea
- nasal congestion, sore throat, and runny nose (nasopharyngitis)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

DRUG INTERACTIONS

- Potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., Ketoconazole): Recommended dose is Tofacitinib 5 mg once daily.
- One or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., Fluconazole): Recommended dose is Tofacitinib 5 mg once daily.
- Potent CYP inducers (e.g., Rifampin): May result in loss of or reduced clinical response.

Immunosuppressive Drugs

There is a risk of added immunosuppression when Tofacitinib is coadministered with potent immunosuppressive drugs (e.g., Azathioprine, Tacrolimus, Cyclosporine). Combined use of multiple-dose Tofacitinib with potent immunosuppressants has not been studied in rheumatoid arthritis. Use of Tofacitinib in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

