Tofacinix

Tofacitinib Citrate INN

COMPOSITION

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

Tofacinix 11 Tablet: Each film coated tablet contains Tofacitinib citrate equivalent to Tofacitinib 11 mg.

Therapeutic Class: Antirheumatic drug.

PHARMACOLOGICAL ACTION

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

Tofacitinib 5 mg

The absolute oral bioavailability of Tofacitinib is 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 meals.

Tofacitinib XR 11 mg

Coadministration of Tofacitinib XR with a high-fat meal resulted in no changes in AUC while C_{max} was increased by 27% and T_{max} was extended by approximately 1 hour.

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 α1-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.

CLINICAL INFORMATION

Indication

Rheumatoid Arthritis

• Tofacitinib/Tofacitinib XR 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).

• Limitations of Use: Use of Tofacitinib/Tofacitinib XR in combination with biologic DMARDs or with potent immunosuppressants such as Azathioprine and Cyclosporine is not recommended.

Dosage in Rheumatoid Arthritis

Tofacitinib/Tofacitinib XR 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 XR is 11 mg once daily.

Switching from Tofacitinib Tablet to Tofacitinib XR Tablets

Patients treated with Tofacitinib 5 mg twice daily may be switched to Tofacitinib XR 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 / Tofacitinib XR not be initiated in patients with an absolute lymphocyte count less than 500 cells/mm3, an absolute neutrophil count (ANC) less than 1000 cells/mm3or who have hemoglobin levels less than 9 g/dL.

• Dose interruption is recommended for management of lymphopenia, neutropenia and anemia

• Avoid use of Tofacitinib / Tofacitinib XR 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 / Tofacitinib XR may result in loss of or reduced clinical response to Tofacitinib / Tofacitinib XR.

• Coadministration of potent inducers of CYP3A4 with Tofacitinib / Tofacitinib XR 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 / Tofacitinib XR in patients with severe hepatic impairment is not recommended.

USE IN SPECIFIC POPULATIONS

All information provided in this section is applicable to Tofacitinib / Tofacitinib XR as they contain the same active ingredient (Tofacitinib).

Pregnancy Category C.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

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

SIDE EFFECTS

• 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.

PHARMACEUTICAL INFORMATION

Storage Conditions

Store Tofacitinib / Tofacitinib XR at 20°C to 25°C (68°F to 77°F) dry place, away from light. keep out of reach of children.

Presentation and packaging:

Tofacinix 5 Tablet: Each commercial box contains (3x10's) 30 tablets in Alu-Alu blister pack.

Tofacinix 11 mg Tablet: Each commercial box contains (3x10's) 30 tablets in Alu-Alu blister pack

Only for Export

LF00000

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

Marketed By
BEACON®
Medicare Limited