

### 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 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/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 To a maintained introugnout aosing. 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. Tofacitinb 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**

mg Tablets

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 Switching from Tofacitinib 5 mg Tablet to Tofacitinib 11

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
- Coadministration of potent inducers of CYP3A4 with Tofacitinib is not recommended. Dosage Modifications in Patients with Renal or Hepatic

### Impairment In patients with:

## Moderate

to Tofacitinib.

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

# CONTRAINDICATIONS

# WARNINGS AND PRECAUTIONS

Moderate or severe renal insufficiency, or

Avoid use of Tofacitinib in patients with an active, serious infection, including localized infections. The risks and benefits of treatment

- with chronic or recurrent infection
- should be considered prior to initiating Tofacitinib in patients:
- who have been exposed to tuberculosis
- 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

with a history of a serious or an opportunistic infection

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

Azathioprine, Tacrolimus, Cyclosporine). Combined use of multiple-dose Tofacitinib with potent immunosuppressants has not been studied in rheumatoid arthritis. Use of Tofacitinib in been studied in rheumatoid arthritis. Use of Tofacitinib in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

### **USE IN SPECIFIC POPULATIONS**

Pregnancy

### **Pregnancy Exposure Registry**

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Tofacitinib during pregnancy.

### **Risk Summary**

There are no adequate and well-controlled studies of Tofacitinib use in pregnant women.

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. The background risks in the U.S. general population of major birth defects and miscarriages are 2–4% and 15–20% of clinically recognized pregnancies, respectively.

Based on animal studies, Tofacitinib has the potential to affect a developing fetus. Fetocidal and teratogenic effects were noted when

developing tetus. Fetocidal and teratogenic effects were noted when pregnant rats and rabbits received Tofacitinib during the period of organogenesis at exposures multiples of 146 times and 13 times the human dose of 5 mg twice daily, respectively. Further, in a peri and post-natal study in rats, Tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73 times the human dose of 5 mg twice daily.

### Human Data

In the Tofacitinib clinical development program in rheumatoid arthritis, birth defects and miscarriages were reported.

### **Animal Data**

In a rat embryofetal developmental study, in which pregnant rats received Tofacitinib during organogenesis, Tofacitinib was teratogenic at exposure levels approximately 146 times the human dose of 5 mg twice daily (on an AUC basis at oral doses of 100 mg/kg/day in rats). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular mg/kg/day in rats). Ieratogenic errects consisted or external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively; and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). In addition, there was an increase in post-implantation loss, consisting of early and late resorptions, resulting in a reduced number of viable fetuses. Mean fetal body weight was reduced. No developmental toxicity was observed in rats at exposure levels approximately 58 times the human dose of 5 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in pregnant rats).

In a rabbit embryofetal developmental study in which pregnant rabbits received Tofacitinib during the period of organogenesis, Tofacitinib was teratogenic at exposure levels approximately 13 times the MRHD human dose of 5 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, amphaloceles membranous ventricular septal defects and omphalocele, membranous ventricular septal defects, cranial/skeletal malformations Imicrosta and microphthalmia), cranial/skeletal malformations (microstomia, microphthalmimid-line and tail defects. In addition, there was an increase post-implantation loss associated with late resorptions. 1 mid-line and fall defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3 times the human dose of 5 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in pregnant rabbits).

In a peri- and postnatal development study in pregnant rats received Tofacitinib from gestation day 6 through day 20 lactation, there were reductions in live litter size, postnatal surv 20 and pup body weights at exposure levels approximately 73 times the human dose of 5 mg twice daily (on an AUC basis at oral doses of 50 mg/kg/day in rats). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels approximately 17 times the human dose of 5 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in rats). Pregnancy Category C.

Lactation

### Risk Summary

It is not known whether Tofacitinib is excreted in human milk. Additionally, there are no data to assess the effects of the drug on the breastfed child. However, Tofacitinib is excreted in rat milk at concentrations higher than in maternal serum. Women should not breastfeed while treated with Tofacitinib. A decision should be made whether to discontinue breastfeeding or to discontinue Tofacitinib.

Human Data

There are no adequate and well-controlled studies of Tofacitinib use during breastfeeding. **Animal Data** 

Following administration of Tofacitinib to lactating rats, concentrations of Tofacitinib in milk over time paralleled those in serum, and were approximately 2 times higher in milk relative to maternal serum at all time points measured. Females and Males of Reproductive Potential

Contraception Females

### Embryofetal toxicity including malformations occurred in embryofetal development studies in rats and rabbits.

Females of reproductive potential should be advised to use effective contraception during treatment with Tofacitinib and for at least 4 weeks after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with Tofacitinib.

Infertility

## **Pediatric Use**

Based on findings in rats, treatment with Tofacitinib may result in reduced fertility in females of reproductive potential.

The safety and effectiveness of Tofacitinib in pediatric patients have not been established.

Geriatric Use

Of the 3315 patients who enrolled in Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among Tofacitinib -treated subjects 65 years of age and older was higher than among those under the age of 65. As there is a higher incidence of infections in the elderly population in general,

caution should be used when treating the elderly. **Use in Diabetics** 

As there is a higher incidence of infection in diabetic population in general, caution should be used when treating patients with general, diabetes. **Hepatic Impairment** 

Tofacitinib -treated patients with moderate hepatic impairment had greater Tofacitinib levels than Tofacitinib -treated patients with normal hepatic function. Higher blood levels may increase the risk of some adverse reactions; therefore, the recommended dose is Tofacitinib 5 mg once daily in patients with moderate hepatic impairment. Tofacitinib has not been studied in patients with severe hepatic impairment; therefore, use of Tofacitinib in patients with severe hepatic impairment is not recommended. No dose adjustment is required in patients with mild hepatic impairment. The safety and

efficacy of Tofacitinib have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology. Renal Impairment Tofacitinib treated patients with moderate and severe renal impairment had greater Tofacitinib blood levels than Tofacitinib

# treated patients with normal renal function; therefore, the recommended dose is Tofacitinib 5 mg once daily in patients with moderate and severe renal impairment. In clinical trials, Tofacitinib **Tofacitinib**

## was not evaluated in rheumatoid arthritis patients with baseline creatinine clearance values (estimated by the Cockroft-Gault equation) less than 40 mL/min. No dose adjustment is required in patients with mild renal impairment. **OVERDOSAGE**

Signs, Symptoms, and Laboratory Findings of Acute Overdosage in Humans There is no experience with overdose of Tofacitinib. Treatment or Management of Overdose

There is no specific antidote for overdose with Tofacitinib. In case an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate treatment.

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

# PHARMACEUTICAL INFORMATION

Storage Conditions Store in a cool and dry place, away from light. Keep out of the reach of children.

Presentation and Packaging:

Tofacinix Tablet: Each commercial box contains 30 tablets in Alu-Alu blister pack.



