

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use **TOFACITINIB EXTENDED-RELEASE TABLETS** safely and effectively. See full prescribing information for **TOFACITINIB EXTENDED-RELEASE TABLETS**.

**TOFACITINIB** extended-release tablets, for oral use  
Initial U.S. Approval: 2012

### WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, and THROMBOSIS

- See full prescribing information for complete boxed warning.
- Increased risk of serious bacterial, fungal, viral, and opportunistic infections, including tuberculosis (TB), leading to hospitalization or death. Interrupt tofacitinib extended-release tablets treatment if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy; treat latent TB prior to use. Monitor all patients for active TB during treatment, even patients with initial negative latent TB test. (5.1)
  - Higher rate of all-cause mortality, including sudden cardiovascular (CV) death with tofacitinib vs. TNF blockers in rheumatoid arthritis (RA) patients. (5.2)
  - Malignancies have occurred in patients treated with tofacitinib. Higher rate of lymphomas and lung cancers with tofacitinib vs. TNF blockers in RA patients. (5.3)
  - Higher rate of major adverse CV events (defined as CV death, myocardial infarction, and stroke) with tofacitinib vs. TNF blockers in RA patients. (5.4)
  - Thrombosis has occurred in patients treated with tofacitinib. Increased incidence of pulmonary embolism, venous and arterial thrombosis with tofacitinib vs. TNF blockers in RA patients. (5.5)

### RECENT MAJOR CHANGES

Warnings and Precautions, Serious Infections (5.1) 04/2026

### INDICATIONS AND USAGE

Tofacitinib is a Janus kinase (JAK) inhibitor.  
Tofacitinib extended-release tablets are indicated for the treatment of adult patients with:

- Moderately to severely active rheumatoid arthritis (RA), who have had an inadequate response or intolerance to one or more TNF blockers.
  - Active psoriatic arthritis (PsA), who have had an inadequate response or intolerance to one or more TNF blockers.
  - Active ankylosing spondylitis (AS), who have had an inadequate response or intolerance to one or more TNF blockers.
- Limitations of Use:
- Use of tofacitinib extended-release tablets for RA, AS or PsA in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1.1, 1.2, 1.3)

### DOSAGE AND ADMINISTRATION

Recommended Evaluations and Immunization Prior to Treatment Initiation

- Prior to initiating tofacitinib extended-release tablets, consider

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### FULL PRESCRIBING INFORMATION

**WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, and THROMBOSIS**

**SERIOUS INFECTIONS**  
Patients treated with tofacitinib extended-release tablets are at increased risk for developing serious bacterial, fungal, viral, and opportunistic infections, including tuberculosis (TB), that may lead to hospitalization or death [see *Warnings and Precautions (5.1) and Adverse Reactions (6.1)*]. Most patients who developed these infections were being concomitant immunosuppressants such as methotrexate or corticosteroids. Reported infections included:

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

- Increased risk of mortality, including sudden cardiovascular (CV) death, compared to TNF blockers in RA patients.
- Malignancies, including lymphomas and solid tumors, have occurred in patients treated with tofacitinib and other Janus kinase inhibitors used to treat inflammatory conditions.
- In RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer [NMSC]) was observed in patients treated with tofacitinib compared to TNF blockers in RA patients. (5.3)
- Lymphomas and lung cancers were observed at a higher rate in patients treated with tofacitinib tablets 5 mg or 10 mg twice a day in RA patients compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.
- Major Adverse Cardiovascular Events  
In RA patients, a higher rate of major adverse cardiovascular events (MACE) was observed in patients treated with tofacitinib tablets 5 mg or 10 mg twice daily, had a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue tofacitinib extended-release tablets in patients who have experienced a myocardial infarction or stroke [see *Warnings and Precautions (5.4)*].
- Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with tofacitinib and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some were fatal. In RA patients 50 years of age and older, at least one cardiovascular risk factor treated with tofacitinib tablets 5 mg or 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid tofacitinib in patients at risk. Discontinue tofacitinib and promptly evaluate patients with symptoms of thrombosis [see *Warnings and Precautions (5.5)*].

### INDICATIONS AND USAGE

- 1.1 Rheumatoid Arthritis  
Tofacitinib extended-release tablets is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA), who have had an inadequate response or intolerance to one or more TNF blockers.
- 1.2 Psoriatic Arthritis  
Tofacitinib extended-release tablets is indicated for the treatment of adult patients with active PsA who have had an inadequate response or intolerance to one or more TNF blockers.
- 1.3 Ankylosing Spondylitis  
Tofacitinib extended-release tablets is indicated for the treatment of adult patients with active ankylosing spondylitis (AS), who have had an inadequate response or intolerance

performing an active and latent TB evaluation, viral hepatitis screening, a complete blood count, and updating immunizations. Avoid tofacitinib extended-release tablets initiation if absolute lymphocyte count <500 cells/mm<sup>3</sup>, an absolute neutrophil count (ANC) <1000 cells/mm<sup>3</sup> or hemoglobin <9 g/dL. (2.1)

### Important Administration Instructions

- Tofacitinib extended-release tablets is not substitutable with tofacitinib (tablets and oral solution). (2.2)
- Switching between tofacitinib tablets and tofacitinib extended-release tablets should be made by the healthcare provider. (2.2)

### Recommended Dosage

- Adult Patients with RA, PsA or AS
- Tofacitinib extended-release tablets 11 mg once daily. (2.3)
- Dosage in Patients with Renal Impairment or Hepatic Impairment
- Use of tofacitinib extended-release tablets in patients with severe HI is not recommended. (2.3, 8.7)
- See full prescribing information (FPI) for recommended dosage in patients with moderate or severe RI or moderate HI. (2.3, 8.6, 8.7)

See the full prescribing information for dosage modification by indication for patients who concomitantly use CYP2C19 and/or CYP3A4 inhibitors and patients with lymphopenia, neutropenia, or anemia. (2.3, 7.7)

### DOSAGE FORMS AND STRENGTHS

- Tofacitinib extended-release tablets: 11 mg tofacitinib (3)

### CONTRAINDICATIONS

None. (4)

### WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid use of tofacitinib extended-release tablets during an active serious infection, including localized infections. (5.1)
- Gastrointestinal Perforations: Promptly evaluate patients at increased risk for gastrointestinal perforation who present with new onset abdominal symptoms. (5.6)
- Laboratory Monitoring: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.8)
- Vaccinations: Avoid use of live vaccines concurrently with tofacitinib extended-release tablets. (5.9)

### ADVERSE REACTIONS

Most common adverse reactions are:

- RA, PsA, and AS: Reported in ≥2% of adult patients treated with tofacitinib tablets monotherapy or in combination with DMARDs: upper respiratory tract infection (URI), nasopharyngitis, diarrhea, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Edenbridge Pharmaceuticals, LLC BAA Dexcel Pharma USA at 1-877-381-3336 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- See FPI for clinically significant drug interactions. (2, 7)

### USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed. (8.2)

### See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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Tofacitinib 10 mg twice daily and tofacitinib extended-release tablets 22 mg once daily dosages are not recommended for the treatment of RA, psoriatic arthritis (PsA), or ankylosing spondylitis (AS) [see *Dosage and Administration (2.3)*].

**MALIGNANCIES**  
Malignancies, including lymphomas and solid tumors, have occurred in patients treated with tofacitinib and other Janus kinase inhibitors used to treat inflammatory conditions.

In RA patients, a higher rate of malignancies (excluding non-melanoma skin cancer [NMSC]) was observed in patients treated with tofacitinib compared to TNF blockers in RA patients. (5.3)

Lymphomas and lung cancers were observed at a higher rate in patients treated with tofacitinib tablets 5 mg or 10 mg twice a day in RA patients compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

**MAJOR ADVERSE CARDIOVASCULAR EVENTS**  
In RA patients, a higher rate of major adverse cardiovascular events (MACE) was observed in patients treated with tofacitinib tablets 5 mg or 10 mg twice daily, had a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue tofacitinib extended-release tablets in patients who have experienced a myocardial infarction or stroke [see *Warnings and Precautions (5.4)*].

**THROMBOSIS**  
Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with tofacitinib and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some were fatal. In RA patients 50 years of age and older, at least one cardiovascular risk factor treated with tofacitinib tablets 5 mg or 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid tofacitinib in patients at risk. Discontinue tofacitinib and promptly evaluate patients with symptoms of thrombosis [see *Warnings and Precautions (5.5)*].

to one or more TNF blockers.

- Limitations of Use  
Use of tofacitinib extended-release tablets in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
- Concomitant Use  
Use of tofacitinib extended-release tablets in combination with biologic disease-modifying antirheumatic drugs (DMARDs) or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
- 2.1 Recommended Evaluations and Immunization Prior to Treatment Initiation  
Prior to initiating tofacitinib extended-release tablets, consider performing the following:
- Active and latent tuberculosis (TB) infection evaluation: If the patient has latent TB, treatment for latent TB prior to tofacitinib extended-release tablets treatment [see *Warnings and Precautions (5.1)*].
  - Viral hepatitis screening in accordance with clinical guidelines [see *Warnings and Precautions (5.1)*].
  - Avoid initiation of tofacitinib extended-release tablets treatment in patients with a lymphocyte count less than 500 cells/mm<sup>3</sup>, absolute neutrophil count less than 1000 cells/mm<sup>3</sup>, or hemoglobin level less than 9 g/dL [see *Warnings and Precautions (5.8)*].
  - Baseline hepatic function evaluation: tofacitinib extended-release tablets is not recommended for patients with severe hepatic impairment [see *Use in Specific Populations*].

(8.7) and *Clinical Pharmacology (12.3)*.

- Update immunizations according to current immunization guidelines. The interval between live vaccination and initiation of tofacitinib extended-release tablets should be in accordance with current vaccination guidelines regarding immunosuppressive agents [see *Warnings and Precautions (5.9)*].

### 2.2 Important Administration Instructions

- Do not substitute tofacitinib extended-release tablets with tofacitinib (tablets and oral solution). Switching between tofacitinib and tofacitinib extended-release tablets should be made by the healthcare provider.
- Dose interruption is recommended for management of lymphopenia, neutropenia, and anemia [see *Warnings and Precautions (5.8) and Adverse Reactions (6.1)*].
- Interrupt use of tofacitinib extended-release tablets if a patient develops a serious infection until the infection is controlled [see *Warnings and Precautions (5.1)*].
- Consider the benefits and risks for therapy update prior to initiating or continuing therapy with tofacitinib extended-release tablets.
- Swallow tofacitinib extended-release tablets whole and intact. Do not crush, split, or chew the extended-release tablets [see *Clinical Pharmacology (12.3)*].

### 2.3 Recommended Dosage in Adults with Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

Table 1 displays the recommended dosage of tofacitinib extended-release tablets for adults with RA, PsA, and AS [see *Indication and Usage (1.1, 1.2, 1.3)*] with and without renal impairment (including those who are undergoing hemodialysis) or hepatic impairment [see *Use in Specific Populations (8.6, 8.7)*]. The table also displays the recommended dosage modifications for patients concomitantly using CYP2C19 and/or CYP3A4 inhibitors [see *Drug Interactions (7) and Clinical Pharmacology (12.3)*].

**Table 1: Recommended Dosage of Tofacitinib Extended-Release Tablets in Adults with Rheumatoid Arthritis, Psoriatic Arthritis, or Ankylosing Spondylitis**

Adults	Tofacitinib Extended-Release Tablets
Patients with Normal Renal and Hepatic Function	11 mg once daily
Recommended Dosage in Patients with Renal Impairment (RI)*	
Mild RI (CL <sub>CR</sub> ≥50 and ≤80 mL/min)	11 mg once daily
Moderate RI (CL <sub>CR</sub> ≥30 and ≤50 mL/min)	Tofacitinib tablets 5 mg once daily
Severe RI (CL <sub>CR</sub> <30 mL/min)	Tofacitinib tablets 5 mg once daily

For patients undergoing hemodialysis, administer the dose after the dialysis session on dialysis days. If a dose was taken before the dialysis procedure, supplemental doses are not recommended during dialysis.

**Recommended Dosage in Patients with Hepatic Impairment (HI)**

Mild HI (Child-Pugh A)	11 mg once daily
Moderate HI (Child-Pugh B)	Tofacitinib tablets 5 mg once daily
Severe HI (Child-Pugh C)	Use of tofacitinib tablets tofacitinib extended-release tablets is not recommended.

**Dosage Modifications with Concomitant Use of CYP3A4 and/or CYP2C19 Inhibitors**

Strong CYP2C19 inhibitor(s)	11 mg once daily
Moderate CYP2C19 inhibitor(s)	11 mg once daily
Moderate CYP3A4 inhibitor(s)	11 mg once daily
Moderate CYP3A4 inhibitor(s) with strong CYP2C19 inhibitor(s) (e.g., fluconazole)	Tofacitinib tablets 5 mg once daily
Strong CYP3A4 inhibitor(s)	5 mg once daily

**Dosage Modifications for Lymphopenia, Neutropenia, or Anemia**

Patients with lymphocyte count less than 500 cells/mm <sup>3</sup> confirmed by repeat testing	Discontinue dosing.
Patients with ANC less than 500 cells/mm <sup>3</sup>	Discontinue dosing.
Patients with ANC 500 to 1000 cells/mm <sup>3</sup>	Interrupt dosing. When ANC is greater than 1000, resume 11 mg once daily.
Patients with hemoglobin less than 6 g/dL or a decrease of more than 2 g/dL.	Interrupt dosing until hemoglobin values have normalized.

Switching from Tofacitinib Tablets to Tofacitinib Extended-Release Tablets  
Patients treated with tofacitinib tablets 5 mg twice daily may be switched to tofacitinib extended-release tablets 11 mg once daily the day following the last tofacitinib tablets 5 mg twice a day, and 0.02 for TNF blockers [see *Clinical Studies (14.4)*].

**3.3 DOSAGE FORMS AND STRENGTHS**  
Tofacitinib extended-release tablets:  
• 11 mg of tofacitinib: Brownish red, oval film coated tablets debossed with "11" on one side.

### CONTRAINDICATIONS

None.

### WARNINGS AND PRECAUTIONS

**5.1 Serious Infections**  
Serious and sometimes fatal infections may occur with tofacitinib extended-release tablets. Reported infections included:

- Invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving tofacitinib. The most common serious infections reported with tofacitinib included pneumonia, urinary tract infection, cellulitis, herpes zoster, bronchitis, sinusitis, diverticulitis, gastroenteritis, appendicitis, and sepsis.
- Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystosis, multi-dermalomal herpes zoster, cytomegalovirus infections, BK virus infection, and listeriosis were reported with tofacitinib. Some patients have presented with disseminated rather than localized infections.
- Immunomodulating agents such as methotrexate or corticosteroids.

Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

Avoid initiation of tofacitinib extended-release tablets in patients with an active, serious infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating tofacitinib extended-release tablets 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

Close monitoring of patients for the development of signs and symptoms of infection during and after treatment with tofacitinib extended-release tablets. Interrupt tofacitinib extended-release tablets if a patient develops a serious infection, an opportunistic infection, or sepsis. In patients who develop a new infection or sepsis, interrupt use of tofacitinib extended-release tablets until the infection is controlled and the patient is clinically stable.

**5.2 Malignancy and Lymphoproliferative Disorders**  
Malignancies, including lymphomas and solid tumors, have occurred in patients treated with tofacitinib and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some were fatal. In RA patients 50 years of age and older, at least one cardiovascular risk factor treated with tofacitinib tablets 5 mg or 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid tofacitinib in patients at risk. Discontinue tofacitinib and promptly evaluate patients with symptoms of thrombosis [see *Warnings and Precautions (5.5)*].

**5.3 Major Adverse Cardiovascular Events**  
In RA patients, a higher rate of major adverse cardiovascular events (MACE) was observed in patients treated with tofacitinib tablets 5 mg or 10 mg twice daily, had a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue tofacitinib extended-release tablets in patients who have experienced a myocardial infarction or stroke [see *Warnings and Precautions (5.4)*].

**5.4 Thrombosis**  
Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with tofacitinib and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some were fatal. In RA patients 50 years of age and older, at least one cardiovascular risk factor treated with tofacitinib tablets 5 mg or 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid tofacitinib in patients at risk. Discontinue tofacitinib and promptly evaluate patients with symptoms of thrombosis [see *Warnings and Precautions (5.5)*].

**5.5 Gastrointestinal Perforations**  
Patients at increased risk for gastrointestinal perforation who present with new onset abdominal symptoms should be promptly evaluated. Promptly evaluate patients at increased risk for gastrointestinal perforation who present with new onset abdominal symptoms.

**5.6 Hypersensitivity Reactions**  
Hypersensitivity reactions may occur with tofacitinib. Reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been reported in patients receiving tofacitinib extended-release tablets. Some events were serious. If a serious hypersensitivity reaction occurs, promptly discontinue tofacitinib extended-release tablets while evaluating the potential cause or causes of the reaction [see *Adverse Reactions (6.2)*].

**5.7 Laboratory Abnormalities**  
Laboratory abnormalities may occur with tofacitinib.

**Lymphocyte Abnormalities**  
Treatment with tofacitinib tablets was associated with a mild lymphocytosis at one month of tofacitinib tablets treatment followed by a gradual decrease in mean lymphocyte counts below the normal range during the 12-month period. Lymphocyte counts less than 500 cells/mm<sup>3</sup> in these patients were associated with an increased incidence of serious and infectious infections.

• Monitor lymphocyte counts at baseline and every 3 months thereafter.

• Avoid initiation of tofacitinib extended-release tablets treatment in patients with a low lymphocyte count (i.e., less than 9 g/dL). Interrupt treatment with tofacitinib extended-release tablets in patients who develop hemoglobin levels less than 9 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment until hemoglobin values have normalized.

**Liver Enzyme Elevations**  
Treatment with tofacitinib tablets was associated with an increased incidence of liver enzyme elevations in patients with tofacitinib. Most of these abnormalities occurred in studies with background DMARD therapy (primarily methotrexate).

The impact of tofacitinib on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Avoid use of tofacitinib extended-release tablets in patients with hepatitis B or C. Patients starting therapy with tofacitinib extended-release tablets. The risk of herpes zoster is increased in patients treated tofacitinib and appears to be higher in patients treated with tofacitinib in Japan and Korea.

### 5.8 Increased Risk of Mortality

In RA patients, a higher rate of mortality was observed in patients treated with tofacitinib 50 years of age and older, with at least one cardiovascular risk factor treated with tofacitinib tablets 5 mg or 10 mg twice a day had a higher observed rate of all-cause mortality, including sudden cardiovascular death, compared to those treated with TNF blockers. The incidence rate of CV death in RA patients was 0.28 for tofacitinib tablets 10 mg twice a day, 0.02 for tofacitinib tablets 5 mg twice a day, and 0.69 for TNF blockers [see *Clinical Studies (14.4)*].

**5.9 Vaccinations**  
Avoid use of live vaccines concurrently with tofacitinib extended-release tablets. Consider the benefits and risks for therapy update prior to initiating or continuing therapy with tofacitinib extended-release tablets. The interval between live vaccinations and initiation of tofacitinib extended-release tablets therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

**5.10 Risk of Gastrointestinal Obstruction with Tofacitinib Extended-Release Tablets - A Non-Deformable Extended-Release Formulation**  
Gastrointestinal obstruction may occur with tofacitinib extended-release tablets. Avoid use of tofacitinib extended-release tablets in patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drug utilizing a non-deformable extended-release formulation.

**5.11 Clinical Trials Experience**  
Because clinical trials were conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

**6 ADVERSE REACTIONS**  
The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections [see *Warnings and Precautions (5.1)*]
- Increased Risk of Mortality [see *Warnings and Precautions (5.2)*]
- Malignancy and Lymphoproliferative Disorders [see *Warnings and Precautions (5.3)*]
- Major Adverse Cardiovascular Events [see *Warnings and Precautions (5.4)*]
- Thrombosis [see *Warnings and Precautions (5.5)*]
- Gastrointestinal Perforations [see *Warnings and Precautions (5.6)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.7)*]
- Laboratory Abnormalities [see *Warnings and Precautions (5.8)*]

**6.1 Clinical Trials Experience**  
Because clinical trials were conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

**6.2 Common Adverse Reactions in Adults With or Without Concomitant DMARDs (0-3 Months)**

In RA Safety Study 1, 1,455 adults were treated with tofacitinib 5 mg twice daily, 1,456 adults were treated with tofacitinib 10 mg twice daily, and 1,456 adults were treated with TNF blockers. The incidence rate of tofacitinib 5 mg twice daily was 0.16 for tofacitinib tablets 5 mg twice a day, 0.02 for TNF blockers. The incidence rate of MACE per 100 patient-years was 1.11 for tofacitinib tablets 10 mg twice a day, 0.91 for tofacitinib tablets 5 mg twice a day, and 0.79 for TNF blockers. The incidence rate of thrombotic events per 100 patient-years was 0.39 for tofacitinib tablets 10 mg twice a day, 0.36 for tofacitinib tablets 5 mg twice a day, and 0.2 for TNF blockers [see *Clinical Studies (14.4)*].

Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with tofacitinib extended-release tablets, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy while on treatment, and patients who are current or past smokers. Tofacitinib 10 mg twice daily (or tofacitinib extended-release tablets 22 mg once daily) dosages are not recommended for the treatment of RA, PsA, or AS [see *Dosage and Administration (2.3)*].

**6.3 Thrombosis**  
Thrombosis may occur with tofacitinib. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis, have occurred in patients treated with tofacitinib and other Janus kinase (JAK) inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death [see *Warnings and Precautions (5.5)*].

**6.4 Major Adverse Cardiovascular Events**  
In RA Safety Study 1, patients with RA who were 50 years of age and older with at least one cardiovascular risk factor and treated with tofacitinib tablets 5 mg or 10 mg twice daily had a higher rate of major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction, and stroke, compared to those treated with TNF blockers. The incidence rate of MACE per 100 patient-years was 1.11 for tofacitinib tablets 10 mg twice a day, 0.91 for tofacitinib tablets 5 mg twice a day, and 0.79 for TNF blockers. The incidence rate of thrombotic events per 100 patient-years was 0.39 for tofacitinib tablets 10 mg twice a day, 0.36 for tofacitinib tablets 5 mg twice a day, and 0.2 for TNF blockers [see *Clinical Studies (14.4)*].

Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with tofacitinib extended-release tablets, particularly in patients with a known malignancy (other than a successfully treated NMSC), patients who develop a malignancy while on treatment, and patients who are current or past smokers. Tofacitinib 10 mg twice daily (or tofacitinib extended-release tablets 22 mg once daily) dosages are not recommended for the treatment of RA, PsA, or AS [see *Dosage and Administration (2.3)*].

**6.5 Gastrointestinal Perforations**  
Patients at increased risk for gastrointestinal perforation who present with new onset abdominal symptoms should be promptly evaluated. Promptly evaluate patients at increased risk for gastrointestinal perforation who present with new onset abdominal symptoms.

**6.6 Hypersensitivity Reactions**  
Hypersensitivity reactions may occur with tofacitinib. Reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been reported in patients receiving tofacitinib extended-release tablets. Some events were serious. If a serious hypersensitivity reaction occurs, promptly discontinue tofacitinib extended-release tablets while evaluating the potential cause or causes of the reaction [see *Adverse Reactions (6.2)*].

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V), a total of 505 patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among tofacitinib tablets-treated patients 65 years of age and older was higher than among those adults under the age of 65.

**1.7.3. Tofacitinib Tablet-Treated Patients in Clinical Trials of Patients with PsA.** A total of 72 (9.2%) patients were 65 years of age and older, including 2 (3.0%) patients 75 years and older. These clinical studies did not include sufficient numbers of patients aged 65 years and older with PsA to determine if they respond differently from younger adult patients.

**1.7.4. Tofacitinib Tablet-Treated Patients in Clinical Trials of Patients with AS.** A total of 12 (2.9%) patients were 65 years of age and older, including 1 (0.2%) patient 75 years and older. These clinical studies did not include sufficient numbers of patients aged 65 years and older with AS to determine if they respond differently from younger adult patients.

**1.7.5. Renal Impairment**  
**Moderate and Severe Renal Impairment**  
 Tofacitinib tablets with moderate renal impairment (RI) (CL<sub>CR</sub> ≥30 and <50 mL/minute) or severe RI (<30 mL/minute) had greater tofacitinib blood concentrations than tofacitinib-treated patients with normal renal function (CL<sub>CR</sub> >80 mL/minute). The recommended dosage of tofacitinib in patients with moderate or severe RI (including those with severe RI who are undergoing hemodialysis) is lower than the recommended dosage in patients with normal renal function (see *Dosage and Administration* (2.3)).

**1.7.6. Hepatic Impairment**  
**Moderate Hepatic Impairment**  
 Tofacitinib has not been studied in patients with severe hepatic impairment (HI) (Child-Pugh C); therefore, use of tofacitinib in patients with severe HI is not recommended. The recommended dosage of tofacitinib in patients with moderate hepatic impairment (Child-Pugh A) is the same as patients with normal hepatic function.

**1.7.7. Hepatic Impairment**  
**Severe Hepatic Impairment**  
 Tofacitinib has not been studied in patients with severe hepatic impairment (HI) (Child-Pugh C); therefore, use of tofacitinib in patients with severe HI is not recommended. The recommended dosage of tofacitinib in patients with moderate hepatic impairment (Child-Pugh A) is the same as patients with normal hepatic function.

**1.7.8. Hepatic Impairment**  
**Moderate Hepatic Impairment**  
 Tofacitinib-treated patients with moderate hepatic impairment (Child-Pugh B) had greater tofacitinib blood concentration than tofacitinib-treated patients with normal hepatic function (see *Clinical Pharmacology* (12.3)). Higher blood concentrations may increase the risk of adverse reactions. The recommended tofacitinib dosage in patients with moderate HI is lower than the recommended dosage in patients with normal hepatic function (see *Dosage and Administration* (2.3)).

**1.7.9. Hepatic Impairment**  
**Mild Hepatic Impairment**  
 The recommended dosage of tofacitinib in patients with mild hepatic impairment (Child-Pugh A) is the same as patients with normal hepatic function.

**1.7.10. Hepatic Impairment**  
**Severe Hepatic Impairment**  
 The safety and efficacy of tofacitinib have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

**1.8. OVERDOSAGE**  
 There is no specific antidote for overdose with tofacitinib. In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions.

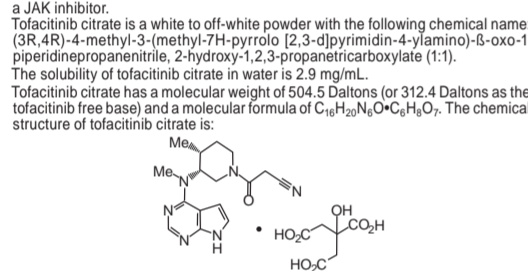
In a study in patients with end-stage renal disease (ESRD) undergoing hemodialysis, plasma tofacitinib concentrations declined more rapidly during the peritoneal dialysis, hemodialysis and dialyzer efficacy, calculated as dialyzer clearance/blood flow entering the dialyzer, was high (mean (SD) = 0.73 (0.15)). However, due to the significant non-renal clearance of tofacitinib, the fraction of total elimination occurring by hemodialysis was small, and thus, limits the value of hemodialysis for treatment of overdose with tofacitinib.

Consider contacting the Poison Help line (1-800-222-1222) or a medical toxicologist for additional overdose management recommendations.

**1.9. DESCRIPTION**  
 Tofacitinib extended-release tablets is formulated with the citrate salt of tofacitinib, a JAK inhibitor.

Tofacitinib citrate is a white to off-white powder with the following chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo[2,3-d]pyrimidin-4-ylamino)-6-oxo-1,6-dioxo-1,2,3,4-tetrahydro-2H-pyridin-2-one and the following molecular formula: (C<sub>23</sub>H<sub>26</sub>N<sub>6</sub>O<sub>5</sub>)<sub>n</sub>·xH<sub>2</sub>O. The solubility of tofacitinib citrate in water is 2.9 mg/mL.

Tofacitinib citrate has a molecular weight of 504.5 Daltons (or 312.4 Daltons as the tofacitinib free base) and a molecular formula of C<sub>23</sub>H<sub>26</sub>N<sub>6</sub>O<sub>5</sub>·xH<sub>2</sub>O. The chemical structure of tofacitinib citrate is:



Tofacitinib extended-release tablets is supplied for oral administration as a 11 mg brownish red, oval, extended-release film-coated tablet debossed with '11' on one side. Each 11 mg tablet of tofacitinib extended-release contains 11 mg tofacitinib (equivalent to 17.7 mg tofacitinib citrate) and higher compared with historical healthy subject data, consistent with approximately 30% contribution of renal clearance to the total clearance of tofacitinib (see *Dosage and Administration* (2.3)) and *Use in Specific Populations* (6.6)).

**12. CLINICAL PHARMACOLOGY**  
**12.1 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 cell membrane to intracellular signaling molecules and transcription factors in the cell nucleus. In 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 activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK2, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). Tofacitinib inhibited the *in vitro* activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC<sub>50</sub> of 406, 56, and 100 nM, respectively. However, the relative clearance of specific JAK combinations to therapeutic effectiveness is not known.

**12.2 Pharmacodynamics**  
 Treatment with tofacitinib was associated with dose-dependent reductions of circulating CD16<sup>+</sup> 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 CD4<sup>+</sup> (CD3<sup>+</sup>, CD4<sup>+</sup>, and CD8<sup>+</sup>) 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 (RA) were lower than in patients who received placebo; however, changes were small and not dose-dependent.

After treatment with tofacitinib in patients with RA, 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.

Similar changes in T cells, B cells, and serum CRP have been observed in patients with active psoriatic arthritis (PsA) although reversibility was not assessed. Total serum immunoglobulins were not assessed in patients with active PsA.

**12.3 Pharmacokinetics**  
 Following oral administration of tofacitinib, peak plasma concentrations were reached within 0.5 hour - 1 hour, elimination half-life was about 3 hours and a dose-dependent increase in systemic exposure was observed with increasing doses. Steady state concentrations were achieved in 24-48 hours with negligible accumulation after twice daily administration.

Following oral administration of tofacitinib extended-release tablets, peak plasma concentrations were reached at 4 hours and half-life was about 6 to 8 hours. Steady state concentrations were achieved within 48 hours with negligible accumulation after once daily administration.

Table 4 describes the pharmacokinetic parameters of tofacitinib and tofacitinib extended-release tablets.

**Table 4: Pharmacokinetic Parameters of Tofacitinib Tablets/Tofacitinib Extended-Release Tablets Following Multiple Oral Dosing**

Dosing Regimen	Tofacitinib Tablets		Tofacitinib Extended-Release Tablets	
	5 mg Twice Daily	10 mg Twice Daily	11 mg Once Daily	22 mg Once Daily
AUC <sub>0-24</sub> (ng·h/mL)	263.4 (15)	539.6 (22)	289.0 (15)	596.6 (19)
C <sub>max</sub> (ng/mL)	42.7 (28)	84.7 (19)	83.8 (25)	167.6 (19)
C <sub>min</sub> (ng/mL)	1.41 (40)	3.10 (54)	1.07 (69)	3.11 (43)
T <sub>max</sub> (hours)	1.0 (0.5 to 14.0)	0.8 (0.5 to 14.0)	4.0 (3.0 to 4.0)	2.0 (1.0 to 4.0)

Abbreviations: AUC<sub>0-24</sub> = area under the concentration time profile from time 0 to 24 hours; C<sub>max</sub> = maximum plasma concentration; C<sub>min</sub> = minimum plasma concentration; T<sub>max</sub> = time to C<sub>max</sub>; CV = Coefficient of variation.

Values represent the geometric mean, except T<sub>max</sub>, for which is the median (range) is shown.

<sup>a</sup> Values beyond 12 hours were after the evening dose which was administered 12 hours after the morning dose of twice-daily tofacitinib.

**Table 5: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics**

Pharmacokinetic Parameters*	Tofacitinib 5 mg Twice Daily			
	Rheumatoid Arthritis	Psoriatic Arthritis	Ankylosing Spondylitis	Non-inflammatory
AUC <sub>0-24</sub> (ng·h/mL)	504 (22.0%)	419 (34.1%)	381 (25.4%)	

Abbreviations: AUC<sub>0-24</sub> = area under the plasma concentration-time curve over 24 hours at steady state; CV = coefficient of variation.

\* Pharmacokinetic parameters estimated based on population pharmacokinetic analysis.

**13. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**  
**13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility**  
 In a 38-week carcinogenicity study in monkeys, tofacitinib at exposure levels approximately 6 times the recommended dose of 5 mg twice daily, and approximately 3 times

the 10 mg twice daily dose (on an AUC basis at oral doses of 5 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1 times the recommended dose of 5 mg twice daily, and approximately 0.5 times the 10 mg twice daily dose (on an AUC basis at oral doses of 1 mg/kg twice daily).

The carcinogenic potential of tofacitinib was assessed in 10 mg/kg twice daily transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib, at exposure levels approximately 34 times the recommended dose of 5 mg twice daily, and approximately 17 times the 10 mg twice daily dose (on an AUC basis at oral doses of 20 mg/kg twice daily) was not carcinogenic in any of the studies.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, fibromas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 30 mg/kg/day (approximately 15 times the recommended dose of 5 mg twice daily) and approximately 17 times the 10 mg twice daily dose (on an AUC basis at oral doses of 20 mg/kg twice daily). The incidence of these tumors was not statistically significant.

Tofacitinib was not mutagenic in the bacterial reverse mutation assay. It was positive for clastogenicity in the *in vitro* chromosome aberration assay with human lymphocytes in the presence of metabolic enzymes, but negative for the absence of metabolic enzymes. Tofacitinib was negative in the *in vivo* micronucleus assay and *in vitro* CHO-Chromosomal Aberration assay and the *in vivo* rat hepatocyte unscheduled DNA synthesis assay.

In rats, tofacitinib exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the 10 mg twice daily dose (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at approximately 17 times the recommended dose of 5 mg twice daily, and approximately 0.5 times the 10 mg twice daily dose (on an AUC basis at oral doses of 1 mg/kg/day). Tofacitinib exposure levels at approximately 133 times the recommended dose of 5 mg twice daily, and approximately 67 times the 10 mg twice daily dose (on an AUC basis at oral doses of 10 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration.

**14 CLINICAL STUDIES**  
**14.1 Clinical Studies in Rheumatoid Arthritis**  
 The rheumatoid arthritis (RA) clinical development program with tofacitinib included six randomized controlled trials in adults with moderate to severe active RA.

**14.1.1 Study RA-I (NCT00814307)** was a 6-month monotherapy trial in which 610 patients with moderate to severe active RA who had an inadequate response to a DMARD (nonbiologic or biologic) received tofacitinib 5 mg or 10 mg twice daily or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). At the Month 3 visit, nonresponding patients were switched to placebo in a second predetermined tofacitinib treatment group. At the Month 6 visit, all patients randomized to placebo treatment were switched in a blinded fashion to a second predetermined treatment of tofacitinib 5 mg or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, the change in Health Assessment Questionnaire - Disability Index (HAQ-DI), and rates of DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.2 Study RA-II (NCT00856544)** was a 12-month trial in which 792 patients with moderate to severe active RA who had an inadequate response to a nonbiologic DMARD received tofacitinib 5 mg or 10 mg twice daily or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). At the Month 3 visit, nonresponding patients were switched to placebo in a second predetermined tofacitinib treatment group. At the Month 6 visit, all patients randomized to placebo treatment were switched in a blinded fashion to a second predetermined treatment of tofacitinib 5 mg or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, the change in HAQ-DI, and rates of DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.3 Study RA-III (NCT00853385)** was a 12-month trial in 717 patients with moderate to severe active RA who had an inadequate response to methotrexate (MTX). Patients received tofacitinib 5 mg or 10 mg twice daily or MTX dose-titrated over 9 weeks to 10 mg twice daily. The primary endpoints at Month 6 and 12 were the proportion of patients who achieved an ACR20 response at Month 6, and the proportion of patients who achieved an ACR20 response at Month 12. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified Total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.4 Study RA-IV (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.5 Study RA-V (NCT01039688)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 952 MTX-naïve patients with moderate to severe active RA received tofacitinib 5 mg or 10 mg twice daily or MTX dose-titrated over 9 weeks to 10 mg twice daily. The primary endpoints at Month 6 and 12 were the proportion of patients who achieved an ACR20 response at Month 6, and the proportion of patients who achieved an ACR20 response at Month 12. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.6 Study RA-VI (NCT01039688)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 952 MTX-naïve patients with moderate to severe active RA received tofacitinib 5 mg or 10 mg twice daily or MTX dose-titrated over 9 weeks to 10 mg twice daily. The primary endpoints at Month 6 and 12 were the proportion of patients who achieved an ACR20 response at Month 6, and the proportion of patients who achieved an ACR20 response at Month 12. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.7 Study RA-VII (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.8 Study RA-VIII (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.9 Study RA-IX (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.10 Study RA-X (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.11 Study RA-XI (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.12 Study RA-XII (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.13 Study RA-XIII (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.14 Study RA-XIV (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.15 Study RA-XV (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.16 Study RA-XVI (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.17 Study RA-XVII (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.18 Study RA-XVIII (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.19 Study RA-XIX (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.20 Study RA-XX (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.21 Study RA-XXI (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.22 Study RA-XXII (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.23 Study RA-XXIII (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.24 Study RA-XXIV (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.25 Study RA-XXV (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.26 Study RA-XXVI (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.27 Study RA-XXVII (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.28 Study RA-XXVIII (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.29 Study RA-XXIX (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.30 Study RA-XXX (NCT00964713)** was a 2-year monotherapy trial with a planned analysis at 1 year in which 737 patients with moderate to severe active RA who had an inadequate response to MTX received tofacitinib 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched to tofacitinib 5 mg or 10 mg twice daily at Month 6. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heide-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

**14.1.31 Study RA-XXXI (NCT00**