214 mm

17.0" (W)

Width: 17.0”
Length: 24.0”
Fold: 1.25” x 1.25”

26 mm

21 mm

9826-01-256

Tofacitinib
Extended-Release Tablets

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 XELJANZ vs. TNF blockers in rheumatoid arthritis (RA) patients. (5.2)**
- **Malignancies have occurred in patients treated with XELJANZ. Higher rate of lymphomas and lung cancers with XELJANZ vs. TNF blockers in RA patients. (5.3)**
- **Higher rate of major adverse CV events (defined as CV death, myocardial infarction, and stroke) with XELJANZ vs. TNF blockers in RA patients. (5.4)**
- **Thrombosis has occurred in patients treated with XELJANZ. Increased incidence of pulmonary embolism, venous and arterial thrombosis with XELJANZ vs. TNF blockers in RA patients. (5.5)**

---------- RECENT MAJOR CHANGES ----------

Boxed Warning	10/2025
Indications and Usage, Psoriatic Arthritis (1.2)	10/2025
Warnings and Precautions, Serious Infections (5.1)	03/2026
Warnings and Precautions, Hypoglycemia in Patients with Diabetes (5.8)	6/2026

---------- INDICATIONS AND USAGE ----------

Tofacitinib extended-release tablets are Janus kinase (JAK) inhibitors.
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.
- **Moderately to severely active ulcerative colitis (UC),** 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)
- Use of tofacitinib extended-release tablets for UC in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1.5)

---------- DOSAGE AND ADMINISTRATION ----------

Recommended Evaluations and Immunization Prior to Treatment Initiation

- Prior to initiating tofacitinib extended-release tablets, consider 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^3, an absolute neutrophil count (ANC) < 1,000 cells/mm^3 or hemoglobin < 9 g/dL. (2.1)

Important Administration Instructions

- Tofacitinib extended-release tablets are not substitutable with XELJANZ (tablets and oral solution). (2.2)
- Switching between XELJANZ 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)

Adult Patients with UC

- Induction: Tofacitinib extended-release tablets 22 mg once daily for 8 weeks; evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed, continue tofacitinib extended-release tablets 22 mg once daily for a maximum of 16 weeks. Discontinue tofacitinib extended-release tablets 22 mg once daily after 16 weeks if adequate therapeutic response is not achieved. (2.5)
- Maintenance: Tofacitinib extended-release tablets 11 mg once daily. For patients with loss of response during maintenance treatment, tofacitinib extended-release tablets 22 mg once daily may be considered and limited to the shortest duration, with careful consideration of the benefits and risks for the individual patient. Use the lowest effective dose needed to maintain response. (2.5)

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, 2.5, 8.7)
- See full prescribing information (FPI) for recommended dosage in patients with moderate or severe RI or moderate HI. (2.3, 2.5, 8.6, 8.7)

Dosage Modification
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, 2.5, 7)

---------- DOSAGE FORMS AND STRENGTHS ----------

- Tofacitinib extended-release tablets: 11 mg (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)
- Hypoglycemia in Patients with Diabetes: Consider increased monitoring of blood glucose; advise patients with diabetes to notify their healthcare provider if they develop signs or symptoms of hypoglycemia. (5.8)
- Laboratory Monitoring: Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.9)
- Vaccinations: Avoid use of live vaccines concurrently with tofacitinib extended-release tablets. (5.10)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions are:

- RA, PsA, and AS: Reported in ≥ 2% of adult patients treated with XELJANZ tablets monotherapy or in combination with DMARDs: upper respiratory tract infection (URI), nasopharyngitis, diarrhea, and headache. (6.1)
- UC: Reported in ≥ 5% of adult patients treated with either XELJANZ tablets and ≥1% greater than reported in patients treated with placebo: nasopharyngitis, elevated cholesterol levels, headache, URI, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ScieGen Pharmaceuticals, Inc. at 1-855-724-3436 or FDA at 1-800-FDA-1088 or *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.

Revised: 7/2026

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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 taking 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, including herpes zoster, and other infections due to opportunistic pathogens.**

The risks and benefits of tofacitinib extended-release tablets treatment 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 infection during and after tofacitinib extended-release tablets treatment, including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy. If a serious infection develops, interrupt tofacitinib extended-release tablets until the infection is controlled *[see Warnings and Precautions (5.1)]*.

MORTALITY

In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular (CV) risk factor comparing XELJANZ tablets 5 mg or 10 mg twice a day to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden CV death, was observed with XELJANZ tablets 5 mg or 10 mg twice a day *[see Warnings and Precautions (5.2)]*. XELJANZ 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 XELJANZ 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 XELJANZ tablets 5 mg or 10 mg twice a day compared with TNF blockers *[see Warnings and Precautions (5.3)]*.

Lymphomas and lung cancers were observed at a higher rate in patients treated with XELJANZ 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

RA patients 50 years of age and older with at least one cardiovascular risk factor, treated with XELJANZ 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 that 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 XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death. RA patients 50 years of age and older with at least one cardiovascular risk factor treated with XELJANZ tablets 5 mg or 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these events. Avoid tofacitinib extended-release tablets in patients at risk. Discontinue tofacitinib extended-release tablets and promptly evaluate patients with symptoms of thrombosis *[see Warnings and Precautions (5.5)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis
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.

Limitations of 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.

1.2 Psoriatic Arthritis
Tofacitinib extended-release tablets are indicated for the treatment of adults with active PsA who have had an inadequate response or intolerance to one or more TNF blockers.

Limitations of Use
Use of tofacitinib extended-release tablets in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

1.3 Ankylosing Spondylitis
Tofacitinib extended-release tablets are indicated for the treatment of adult patients with 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 in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

1.5 Ulcerative Colitis
Tofacitinib extended-release tablets are indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have an inadequate response or intolerance to one or more TNF blockers.

Limitations of Use
Use of tofacitinib extended-release tablets in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

2 DOSAGE AND ADMINISTRATION

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, treat for 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)]*.
- A complete blood count: Avoid initiation of tofacitinib extended-release tablets treatment in patients with a lymphocyte count less than 500 cells/mm^3, absolute neutrophil count less than 1000 cells/mm^3, or hemoglobin level less than 9 g/dL *[see Warnings and Precautions (5.9)]*.
- Baseline hepatic function evaluation: Tofacitinib extended-release tablets are 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 vaccinations and initiation of tofacitinib extended-release tablets should be in accordance with current vaccination guidelines regarding immunosuppressive agents *[see Warnings and Precautions (5.10)]*.

2.2 Important Administration Instructions

- Tofacitinib extended-release tablets are not substitutable with XELJANZ (tablets and oral solution). Switching between XELJANZ 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 (5.9) 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)]*.
- Take tofacitinib extended-release tablets with or without food *[see Clinical Pharmacology (12.3)]*.
- 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)]*, and patients with lymphopenia, neutropenia, or anemia.

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[a]	11 mg once daily
Recommended Dosage in Patients with Renal Impairment (RI)[b]	
Mild RI (CLcr > 50 and ≤ 80 mL/min)	11 mg once daily
Moderate RI (CLcr ≥ 30 and ≤ 50 mL/min)	XELJANZ tablets 5 mg once daily
Severe RI (CLcr < 30 mL/min)	XELJANZ 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 after dialysis
Recommended Dosage in Patients with Hepatic Impairment (HI)	
Mild HI (Child-Pugh A)	11 mg once daily
Moderate HI (Child-Pugh B)	XELJANZ tablets 5 mg once daily
Severe HI (Child-Pugh C)	Use of XELJANZ tablets/tofacitinib extended-release tablets is not recommended.
Dosage Modifications with Concomitant Use of CYP3A4 and/or CYP2C19 Inhibitor(s)	
Strong CYP2C19 inhibitor(s)	11 mg once daily
Moderate CYP2C19 inhibitor(s)	
Moderate CYP3A4 inhibitor(s)	
Moderate CYP3A4 inhibitor(s) with strong CYP2C19 inhibitor(s) (e.g., fluconazole)	XELJANZ tablets 5 mg once daily
Strong CYP3A4 inhibitor(s)	
Dosage Modifications for Lymphopenia, Neutropenia, or Anemia	
Patients with lymphocyte count less than 500 cells/mm^3, confirmed by repeat testing	Discontinue dosing.
Patients with ANC less than 500 cells/mm^3	Discontinue dosing.
Patients with ANC 500 to 1,000 cells/mm^3	Interrupt dosing. When ANC is greater than 1,000, resume 11 mg once daily.
Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL	Interrupt dosing until hemoglobin values have normalized.

[a] Excludes patients who concomitantly use XELJANZ tablets/tofacitinib extended-release tablets with strong CYP3A4 inhibitor(s) or moderate CYP3A4 inhibitor(s) and strong CYP2C19 inhibitor(s), as well as patients with lymphocyte count less than 500 cells/mm^3, ANC < 1,000 cells/mm^3, or hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL.

[b] Tofacitinib PK was evaluated in subjects with varying degrees of renal impairment, where the severity of renal impairment was defined based on creatinine clearance (CLcr) estimated using the Cockcroft-Gault equation: CLcr > 80 mL/min (normal renal function); CLcr > 50 and ≤ 80 mL/min (mild renal impairment); ≥ 30 and ≤ 50 mL/min (moderate renal impairment); < 30 mL/min (severe renal impairment).

Switching from XELJANZ Tablets to Tofacitinib extended-release tablets
Patients treated with XELJANZ tablets 5 mg twice daily may be switched to tofacitinib extended-release tablets 11 mg once daily the day following the last dose of XELJANZ tablets 5 mg.

2.5 Recommended Dosage in Adults with Ulcerative Colitis
Table 3 displays the recommended dosage of tofacitinib extended-release tablets in adult patients with ulcerative colitis (UC) *[see Indications and Usage (1.5)]* with and without renal impairment (including those who are undergoing hemodialysis) or hepatic impairment *[see Use in Specific Populations (8.6, 8.7)]*. Table 4 displays the recommended dosage modification for patients concomitantly using CYP2C19 and/or CYP3A4 inhibitors *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*, and patients with lymphopenia, neutropenia, or anemia.

Table 3: Recommended Dosage of Tofacitinib Extended-Release Tablets in Adults with Ulcerative Colitis With and Without Renal Impairment or Hepatic Impairment

Adults	Tofacitinib Extended Release Tablets
Patients with Normal Renal and Hepatic Function[a]	**Induction:** 22 mg once daily for at least 8 weeks; evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed continue 22 mg once daily for a maximum of 16 weeks. Discontinue 22 mg once daily after 16 weeks if adequate therapeutic response is not achieved. **Maintenance:** 11 mg once daily. For patients with loss of response during maintenance treatment, may consider a dosage of 22 mg once daily (limited to the shortest duration), with careful consideration of the benefits and risks for the individual patient. Use the lowest effective dose needed to maintain response.
Recommended Dosage in Patients with Renal Impairment (RI)[b]	
Mild RI (CLcr > 50 and ≤ 80 mL/min)	Same as patients with normal renal function.
Moderate RI (CLcr ≥ 30 and ≤ 50 mL/min)	**Induction:** 11 mg once daily for atleast 8 weeks; evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed continue 11 mg once daily for a maximum of 16 weeks. Discontinue 11 mg once daily after 16 weeks if adequate therapeutic response is not achieved. **Maintenance:** Tofacitinib extended release tablets is not recommended. See Maintenance Dosage for XELJANZ tablets for Moderate or Severe RI. 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 after dialysis.
Severe RI (CLcr < 30 mL/min)	XELJANZ 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 after dialysis
Recommended Dosage in Patients with Hepatic Impairment (HI)	
Mild HI (Child-Pugh A)	11 mg once daily
Moderate HI (Child-Pugh B)	XELJANZ tablets 5 mg once daily
Severe HI (Child-Pugh C)	Use of XELJANZ tablets/tofacitinib extended-release tablets is not recommended.
Dosage Modifications with Concomitant Use of CYP3A4 and/or CYP2C19 Inhibitor(s)	
Strong CYP2C19 inhibitor(s)	11 mg once daily
Moderate CYP2C19 inhibitor(s)	
Moderate CYP3A4 inhibitor(s)	
Moderate CYP3A4 inhibitor(s) with strong CYP2C19 inhibitor(s) (e.g., fluconazole)	XELJANZ tablets 5 mg once daily
Strong CYP3A4 inhibitor(s)	
Dosage Modifications for Lymphopenia, Neutropenia, or Anemia	
Patients with lymphocyte count less than 500 cells/mm^3, confirmed by repeat testing	Discontinue dosing.
Patients with ANC less than 500 cells/mm^3	Discontinue dosing.
Patients with ANC 500 to 1,000 cells/mm^3	Interrupt dosing. When ANC is greater than 1,000, resume 11 mg once daily.
Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL	Interrupt dosing until hemoglobin values have normalized.

Switching from XELJANZ Tablets to Tofacitinib extended-release tablets
Patients treated with XELJANZ tablets:

- 5 mg twice daily may be switched to tofacitinib extended-release tablets 11 mg once daily the day following the last dose of XELJANZ tablets 5 mg.
- 10 mg twice daily may be switched to tofacitinib extended-release tablets 22 mg once daily the day following the last dose of XELJANZ tablets 10 mg.

3 DOSAGE FORMS AND STRENGTHS
Tofacitinib extended-release tablets:

- 11 mg of tofacitinib: Pink, oval, film coated extended release tablet debossed with “567” on one side and plain on other side.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections
Serious and sometimes fatal infections may occur with tofacitinib extended-release tablets. Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, urinary tract infection, cellulitis, herpes zoster, bronchitis, septic shock, diverticulitis, gastroenteritis, appendicitis, and sepsis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystosis, multi–dermatomal herpes zoster, cytomegalovirus infections, BK virus infection, and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids.

In the UC population, treatment with XELJANZ tablets 10 mg twice daily was associated with greater risk of serious infections compared to 5 mg twice daily. Additionally, opportunistic herpes zoster infections (including meningoencephalitis, ophthalmologic, and disseminated cutaneous) were seen in patients who were treated with XELJANZ tablets 10 mg twice daily.

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

Avoid use 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.

Closely monitor 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 during treatment with tofacitinib extended-release tablets, promptly complete diagnostic testing appropriate for an immunocompromised patient; initiate appropriate antimicrobial therapy, and monitor the patients closely.

Caution is also recommended in patients with a history of chronic lung disease, or in those who develop interstitial lung disease, as they may be more prone to infections.

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Discontinuation and monitoring criteria for lymphopenia are recommended *[see Dosage and Administration (2.3, 2.5)]*.

Tuberculosis
Evaluate and test patients for latent or active tuberculosis (TB) infection prior to and per applicable guidelines during administration of tofacitinib extended-release tablets.

Consider anti-TB therapy prior to administration of tofacitinib extended-release tablets in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection.

Consultation with a physician with expertise in the treatment of TB is recommended to aid in the decision about whether initiating anti-TB therapy is appropriate for an individual patient.

Monitor patients closely for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Treat patients with latent TB with standard antimycobacterial therapy before administering tofacitinib extended-release tablets**.**

Viral Reactivation
Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with XELJANZ. Postmarketing cases of hepatitis B reactivation have been reported in patients treated with XELJANZ. The impact of tofacitinib extended-release tablets on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Perform screening for viral hepatitis in accordance with clinical guidelines before starting therapy with tofacitinib extended-release tablets. The risk of herpes zoster is increased in patients treated with tofacitinib extended-release tablets and appears to be higher in patients treated with XELJANZ in Japan and Korea.

5.2 Increased Risk of Mortality
Increased risk of mortality may occur with tofacitinib extended-release tablets. Adult patients with rheumatoid arthritis (RA), 50 years of age and older, with at least one cardiovascular risk factor treated with XELJANZ 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 in a large, randomized, postmarketing safety study (RA Safety Study 1). The incidence rate of all-cause mortality per 100 patient-years was 1.23 for XELJANZ tablets 10 mg twice a day, 0.88 for XELJANZ tablets 5 mg twice a day, and 0.69 for TNF blockers *[see Clinical Studies (14.6)]*. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with tofacitinib extended-release tablets.

XELJANZ 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)]*.

For the treatment of UC, use tofacitinib extended-release tablets at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response *[see Dosage and Administration (2.5)]***.**

5.3 Malignancy and Lymphoproliferative Disorders
Malignancies and lymphoproliferative disorders may occur with tofacitinib extended-release tablets. Malignancies, including lymphomas and solid cancers, were observed in clinical studies of XELJANZ. *[see Adverse Reactions (6.1)]*.

Other malignancies were observed in XELJANZ clinical studies and the postmarketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

In RA Safety Study 1, a higher rate of malignancies (excluding non-melanoma skin cancer (NMSC)) was observed in patients treated with XELJANZ tablets 5 mg or 10 mg twice a day compared with TNF blockers. The incidence rate of malignancies (excluding NMSC) per 100 patient-years was 1.13 for XELJANZ tablets 10 mg twice a day, 1.13 for XELJANZ tablets 5 mg twice a day, and 0.77 for TNF blockers. Patients who are current or past smokers are at additional increased risk *[see Clinical Studies (14.6)]*.

Lymphomas and lung cancers, which are a subset of all malignancies in RA Safety Study 1, were observed at a higher rate in patients treated with XELJANZ tablets 5 mg twice a day and XELJANZ tablets 10 mg twice a day compared to those treated with TNF blockers. The incidence rate of lymphomas per 100 patient-years was 0.11 for XELJANZ tablets 10 mg twice a day, 0.07 for XELJANZ tablets 5 mg twice a day, and 0.02 for TNF blockers. The incidence rate of lung cancers per 100 patient-years among current and past smokers was 0.59 for XELJANZ tablets 10 mg twice a day, 0.48 for XELJANZ tablets 5 mg twice a day, and 0.27 for TNF blockers *[see Clinical Studies (14.6)]*.

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. XELJANZ 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)]*.

Non-Melanoma Skin Cancer
Non-melanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ tablets. Periodic skin examination is recommended for patients who are at increased risk for skin cancer. In the UC population, treatment with XELJANZ tablets 10 mg twice daily was associated with greater risk of NMSC than treatment with placebo.

5.4 Major Adverse Cardiovascular Events
Major adverse cardiovascular events may occur with tofacitinib extended-release tablets. 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 XELJANZ 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 (MI), and non-fatal stroke, compared to those treated with TNF blockers. The incidence rate of MACE per 100 patient-years was 1.11 for XELJANZ tablets 10 mg twice a day, 0.91 for XELJANZ tablets 5 mg twice a day, and 0.79 for TNF blockers. The incidence rate of fatal or non-fatal myocardial infarction per 100 patient-years was 0.39 for XELJANZ tablets 10 mg twice a day, 0.36 for XELJANZ tablets 5 mg twice a day, and 0.2 for TNF blockers *[see Clinical Studies (14.6)]*. 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 who are current or past smokers and patients with other cardiovascular risk factors. Inform patients about the symptoms of serious cardiovascular events and the steps to take if they occur. Discontinue tofacitinib extended-release tablets in patients that have experienced a MI or stroke. XELJANZ 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)]*.

5.5 Thrombosis
Thrombosis may occur with tofacitinib extended-release tablets. Thrombosis, including pulmonary embolism (PE), deep venous thrombosis (DVT), and arterial thrombosis, have occurred in patients treated with XELJANZ 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 (5.2)]*.

Patients with RA 50 years of age and older with at least one cardiovascular risk factor treated with XELJANZ tablets 5 mg or 10 mg twice daily compared to TNF blockers in RA Safety Study 1 had an observed increase in incidence of these thrombotic events. The incidence rate of DVT per 100 patient-years was 0.28 for XELJANZ tablets 10 mg twice a day, 0.22 for XELJANZ tablets 5 mg twice a day, and 0.16 for TNF blockers. The incidence rate of PE per 100 patient-years was 0.49 for XELJANZ tablets 10 mg twice a day, 0.18 for XELJANZ tablets 5 mg twice a day, and 0.05 for TNF blockers *[see Clinical Studies (14.6)]*.

XELJANZ 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)]*.

In a long-term extension study in patients with UC, five cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one death in a patient with advanced cancer.

Promptly evaluate patients with symptoms of thrombosis and discontinue tofacitinib extended-release tablets in patients with symptoms of thrombosis.

Avoid tofacitinib extended-release tablets in patients that may be at increased risk of thrombosis. For the treatment of UC, use tofacitinib extended-release tablets at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response *[see Dosage and Administration (2.5)]*.

5.6 Gastrointestinal Perforations
Gastrointestinal perforations may occur with tofacitinib extended-release tablets. Events of gastrointestinal perforation have been reported in clinical studies with XELJANZ tablets, although the role of JAK inhibition in these events is not known. In these studies, many patients with RA received background therapy with nonsteroidal anti-inflammatory drugs (NSAIDs).

There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ tablets treatment groups in clinical trials of patients with UC, and many of them were receiving background corticosteroids.

Promptly evaluate patients treated with tofacitinib extended-release tablets who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis or taking NSAIDs

17.0" (W)

24.0" (L)

SIO-07-2026

Tofacitinib
Extended-Release Tablets

Hepatitis B or C Serology
The safety and efficacy of tofacitinib extended-release tablets have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

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

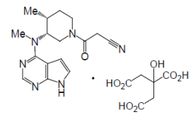
In a study in patients with end-stage renal disease (ESRD) undergoing hemodialysis, plasma tofacitinib concentrations declined more rapidly during the period of hemodialysis and dialyzer efficiency, calculated as dialyzer clearance/blood flow entering the dialyzer, was high [mean (SD) = 0.73 (0.15)]. 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 extended-release tablets.

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

11 DESCRIPTION
Tofacitinib extended-release tablets are 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)-ß-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

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 $C_{16}H_{20}N_6O \bullet C_6H_8O_7$. The chemical structure of tofacitinib citrate is:



Tofacitinib extended-release tablets are supplied for oral administration as a 11 mg pink, oval, extended-release film coated tablet debossed with "567" on one side and plain on other side. Each tablet contains 11 mg of tofacitinib (equivalent to 17.77 mg tofacitinib citrate) and the following inactive ingredients: colloidal silicon dioxide, ferrosoferric oxide/black iron oxide, hypromellose, lactose monohydrate, macrogol, magnesium stearate, polyvinyl alcohol, povidone, red iron oxide, talc and titanium dioxide.

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 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 IC_{50} of 406, 56, and 1377 nM, respectively. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known.

12.2 Pharmacodynamics
Treatment with XELJANZ 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 to 6 weeks after discontinuation of treatment. Treatment with XELJANZ was associated with dose-dependent increases in B cell counts. Changes in circulating 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 (RA) were lower than in patients who received placebo; however, changes were small and not dose-dependent.

After treatment with XELJANZ in patients with RA, rapid decreases in serum C-reactive protein (CRP) were observed and maintained throughout dosing. Changes in CRP observed with XELJANZ 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 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 8 describes the pharmacokinetic parameters of tofacitinib extended-release tablets.

Table 8 Pharmacokinetic Parameters of Tofacitinib Extended-Release Tablets Following Multiple Oral Dosing

PK Parameters[a] (CV%)	Tofacitinib extended-release tablets	
Dosing Regimen	**11 mg Once Daily**	**22 mg Once Daily**
AUC_{24} (ng.hr/mL)	269.0 (18)	596.6 (19)
C_{max} (ng/mL)	38.2 (15)	83.8 (25)
C_{min} (ng/mL)	1.07 (69)	3.11 (43)
T_{max} (hours)	4.0 (3.0 to 4.0)	4.0 (2.0 to 4.0)

Abbreviations: AUC_{24} = area under the concentration time profile from time 0 to 24 hours; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; T_{max} = time to C_{max}; CV = Coefficient of variation.
[a] Values represent the geometric mean, except T_{max}, for which is the median (range) is shown.

Absorption
XELJANZ
The absolute oral bioavailability of XELJANZ is 74%. Coadministration of XELJANZ with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. In clinical trials, XELJANZ was administered without regard to meals [see *Dosage and Administration (2.2)]*.

Tofacitinib Extended-Release Tablets
Coadministration of tofacitinib extended-release tablets 11 and 22 mg with a high-fat meal resulted in no changes in AUC while C_{max} was increased by 27% and 19% respectively. T_{max} was extended by approximately 1 hour for both tofacitinib extended-release tablets 11 and 22 mg.

Distribution
After intravenous administration, the volume of distribution was 87 L. The protein binding of tofacitinib is approximately 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 Excretion
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.

Pharmacokinetics in Patients with RA, PsA, AS, and UC
Population pharmacokinetic (PK) analyses indicated that PK characteristics were similar between patients with RA, PsA, ankylosing spondylitis, and UC. The coefficient of variation (%) in AUC of tofacitinib were generally similar across different disease patients, ranging from 22% to 34% (Table 9).

Table 9: Tofacitinib Exposure in Patients with RA, PsA, AS, and UC After Administration of XELJANZ 5 mg Twice Daily or 10 mg Twice Daily

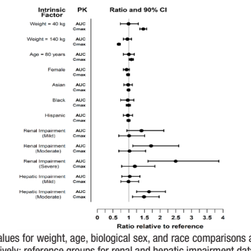
Pharmacokinetic Parameters[a] Geometric Mean (CV%)	XELJANZ 5 mg Twice Daily				XELJANZ 10 mg Twice Daily
	Rheumatoid Arthritis	Psoriatic Arthritis	Ankylosing Spondylitis	Ulcerative Colitis	Ulcerative Colitis
$AUC_{0\text{-}24,ss}$ (ng·h/mL)	504 (22.0%)	419 (34.1%)	381 (25.4%)	423 (22.6%)	807 (24.6%)

Abbreviations: $AUC_{0\text{-}24,ss}$ = area under the plasma concentration-time curve over 24 hours at steady state;
CV = coefficient of variation.
[a] Pharmacokinetic parameters estimated based on population pharmacokinetic analysis.

Specific Populations
Covariate evaluation as part of population PK analyses in adult patient populations indicated no clinically relevant change in tofacitinib exposure, after accounting for differences in renal function (i.e., creatinine clearance) between patients, based on age, weight, biological sex and race (Figure 1). An approximately linear relationship between body weight and volume of distribution was observed, resulting in higher peak (C_{max}) and lower trough (C_{min}) concentrations in lighter patients. However, this difference is not considered to be clinically relevant.

The effect of renal and hepatic impairment and other intrinsic factors on the PK of tofacitinib is shown in Figure 1.

Figure 1: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics



Note: Reference values for weight, age, biological sex, and race comparisons are 70 kg, 55 years, male, and white, respectively; reference groups for renal and hepatic impairment data are patients with normal renal and hepatic function. Renal function was estimated using creatinine clearance by Cockcroft-Gault method and hepatic function was estimated using Child-Pugh scoring method.

In patients with end-stage renal disease maintained on hemodialysis, mean AUC was approximately 40% 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, 2.5) and Use in Specific Populations (8.6)]*.

Drug Interaction Studies
Potential for Tofacitinib Extended-Release Tablets to Influence the PK of Other Drugs
In vitro studies indicate that tofacitinib does not significantly inhibit or induce the activity of the major human drug-metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations corresponding to the steady state C_{max} of a 10 mg twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the pharmacokinetics of midazolam, a highly sensitive CYP3A4 substrate, when concomitantly administered with XELJANZ.

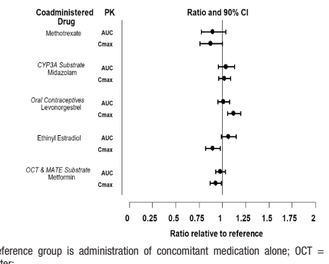
In vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug-metabolizing uridine 5'-diphospho-glucuronosyltransferases (UGTs) [UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7] at concentrations exceeding 250 times the steady state C_{max} of a 10 mg twice daily dose.

In patients with RA, the oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalize CYP enzyme activity in patients with RA. Therefore, concomitant use with tofacitinib extended-release tablets is not expected to result in clinically relevant increases in the metabolism of CYP substrates in patients with RA.

In vitro data indicate that the potential for tofacitinib to inhibit transporters such as P-glycoprotein, organic anionic or cationic transporters at therapeutic concentrations is low.

The impact of tofacitinib on the PK of other drugs for the concomitant drugs are shown in Figure 2.

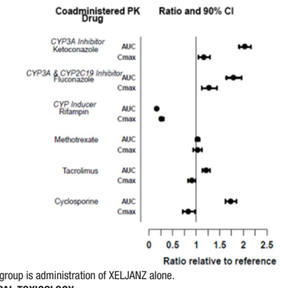
Figure 2: Impact of Tofacitinib on the Pharmacokinetics of Other Drugs



Note: Reference group is administration of concomitant medication alone; OCT = Organic Cationic Transporter;
MATE = Multidrug and Toxic Compound Extrusion

Potential for Other Drugs to Influence the Pharmacokinetics of Tofacitinib
Since tofacitinib is metabolized by CYP3A4, interaction with drugs that inhibit or induce CYP3A4 is likely. Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to substantially alter the pharmacokinetics of tofacitinib (see Figure 3).

Figure 3: Impact of Other Drugs on the Pharmacokinetics of Tofacitinib



Note: Reference group is administration of XELJANZ alone.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 39-week toxicology 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 6-month rasH2 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 200 mg/kg/day) was not carcinogenic in mice.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hibernomas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 30 mg/kg/day (approximately 42 times the exposure levels at the recommended dose of 5 mg twice daily, and approximately 21 times the 10 mg twice daily dose on an AUC basis). The relevance of benign Leydig cell tumors to human risk is not known.

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 in the absence of metabolic enzymes. Tofacitinib was negative in the *in vivo* rat micronucleus assay and in the *in vitro* CHO-HGPRT assay and the *in vivo* rat hepatocyte unscheduled DNA synthesis assay.

In rats, tofacitinib at 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 exposure levels of tofacitinib equal to 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 100 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 XELJANZ tablets (referred to as "XELJANZ" in this subsection of labeling) included six randomized controlled trials in adults with moderate to severe active RA.

Trial Design
- 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 XELJANZ 5 mg or 10 mg twice daily or placebo added to their background DMARD. At the Month 3 visit, all patients randomized to placebo treatment were switched in a blinded fashion to a second predetermined treatment of XELJANZ 5 mg or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in Health Assessment Questionnaire – Disability Index (HAQ-DI), and rates of Disease Activity Score DAS28-4(ESR) less than 2.6.
- 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 XELJANZ 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 in a blinded fashion to a second predetermined treatment of XELJANZ 5 mg or 10 mg twice daily. At the end of Month 6, all patients treated with placebo were switched to their second predetermined XELJANZ treatment in a blinded fashion. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3, and rates of DAS28-4(ESR) less than 2.6 at Month 6.
- 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 XELJANZ 5 mg or 10 mg orally twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. Patients treated with placebo were switched as in Study RA-II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.
- Study RA-IV (NCT00847613) was a 2-year trial with a planned analysis at 1 year in which 797 patients with moderate to severe active RA who had an inadequate response to MTX received XELJANZ 5 mg or 10 mg twice daily or placebo added to background MTX. Patients treated with placebo were switched as in Study RA-II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.
- Study RA-V (NCT00960440) was a 6-month trial in which 399 patients with moderate to severe active RA who had an inadequate response to at least one approved TNF blocking biological product received XELJANZ 5 mg or 10 mg twice daily or placebo added to background MTX. At the Month 3 visit, all patients randomized to placebo treatment were switched in a blinded fashion to a second predetermined treatment of XELJANZ 5 or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, HAQ-DI, and DAS28-4(ESR) less than 2.6.
- 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 XELJANZ 5 or 10 mg twice daily or MTX dose-titrated over 8 weeks to 20 mg weekly. The primary endpoints were mean change from baseline in van der Heijde-modified Total Sharp Score (mTSS) at Month 6 and the proportion of patients who achieved an ACR70 response at Month 6.

Although other dosages have been studied, the recommended dosage of XELJANZ is 5 mg twice daily. XELJANZ 10 mg twice daily is not recommended for the treatment of RA [see *Dosage and Administration (2.3)]*.

Clinical Response
The percentages of XELJANZ-treated patients who achieved ACR20, ACR50, and ACR70 responses in Studies RA-I, IV, and V are shown in Table 10. Similar results were observed with Studies RA-II and III. In trials RA-I through V, patients treated with 5 mg twice daily XELJANZ had higher ACR20, ACR50, and ACR70 response rates versus patients treated with placebo, with or without background DMARD treatment, at Month 3 and Month 6. Higher ACR20 response rates were observed within 2 weeks compared to placebo. In the 12-month trials, ACR response rates in XELJANZ-treated patients were consistent at 6 and 12 months.

Table 10: Proportion of Adults with Moderate to Severe Active RA with an ACR Response at Months 3 and 6 in Studies RA-I, IV, and V

	Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders[c]		MTX Inadequate Responders[d]		TNF Blocker Inadequate Responders[e]	
	Study RA-I		Study RA-IV		Study RA-V	
N[a]	Placebo + background DMARD 122	XELJANZ 5mg Twice Daily + background DMARD 243	Placebo + background MTX 160	XELJANZ 5mg Twice Daily + background MTX 321	Placebo + background MTX 132	XELJANZ 5mg Twice Daily + background MTX 133
ACR20						
Month 3	26%	59%	27%	55%	24%	41%
Month 6	Na[b]	69%	25%	50%	NA	51%
ACR50						
Month 3	12%	31%	8%	29%	8%	26%
Month 6	NA	42%	9%	32%	NA	37%
ACR70						
Month 3	6%	15%	3%	11%	2%	14%
Month 6	NA	22%	1%	14%	NA	16%

[a] N is number of randomized and treated patients.
[b] NA (not applicable), as data for placebo treatment is not available beyond 3 months in Studies RA-I and RA-V due to placebo advancement.
[c] Inadequate response to at least one DMARD (biologic or nonbiologic) due to lack of efficacy or toxicity.
[d] Inadequate response to MTX defined as the presence of sufficient residual disease activity to meet the entry criteria.
[e] Inadequate response to a least one TNF blocker due to lack of efficacy and/or intolerance.

In Study RA-IV, a greater proportion of patients treated with XELJANZ 5 mg twice daily plus MTX achieved a low level of disease activity as measured by a DAS28-4(ESR) less than 2.6 at 6 months compared to those treated with MTX alone (Table 11).

Table 11: Proportion and Numbers of Adults with Moderate to Severe Active RA with DAS28-4(ESR) Less Than 2.6 with Number of Residual Active Joints at Month 6 in Study RA-IV

	Study RA-IV	
DAS28-4(ESR) Less Than 2.6	**Placebo + MTX 160**	**XELJANZ 5 mg Twice Daily + MTX 321**
Proportion of responders at Month 6 (n)	1% (2)	6% (19)
Of responders, proportion with 0 active joints (n)	50% (1)	42% (8)
Of responders, proportion with 1 active joints (n)	0	5% (1)
Of responders, proportion with 2 active joints (n)	0	32% (6)
Of responders, proportion with 3 or more active joints (n)	50% (1)	21% (4)

The results of the components of the ACR response criteria for Study RA-IV are shown in Table 12. Similar results were observed for XELJANZ in Studies RA-I, II, III, V, and VI.

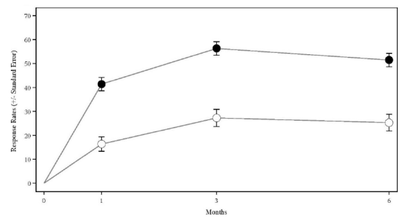
Table 12: Components of ACR Response in Adults with Moderate to Severe Active RA at Baseline and Month 3 in Study RA-IV

	Study RA-IV			
	Placebo + MTX N=160		**XELJANZ 5 mg Twice Daily + MTX N=321**	
Component (mean)[a]	Baseline	Month 3[a]	Baseline	Month 3[a]
Number of tender joints (0-68)	23 (13)	18 (14)	24 (14)	13 (14)
Number of swollen joints (0-66)	14 (9)	10 (9)	14 (8)	6 (8)
Pain[b]	55 (24)	47 (24)	58 (23)	34 (23)
Patient global assessment[b]	54 (23)	47 (24)	58 (24)	35 (23)
Disability index (HAQ-DI)[c]	1.32 (0.67)	1.19 (0.68)	1.41 (0.68)	0.99 (0.65)
Physician global assessment[b]	56 (18)	43 (22)	59 (16)	30 (19)
CRP (mg/L)	13.7 (14.9)	14.6 (18.7)	15.3 (19.0)	7.1 (19.1)

[a] Data shown is mean (Standard Deviation) at Month 3.
[b] Visual analog scale: 0 = best, 100 = worst.
[c] Health Assessment Questionnaire Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

The percent of ACR20 responders by visit for Study RA-IV is shown in Figure 4. Similar responses were observed for XELJANZ in Studies RA-I, II, III, V, and VI.

Figure 4: Percentage of ACR20 Responders by Visit Through Month 6 in Study RA-IV



Non-responder imputation was used. Patients who withdrew from the study were counted as failures, as were patients who failed to have at least a 20% improvement in joint counts at Month 3.

Radiographic Response
Two studies were conducted to evaluate the effect of XELJANZ on structural joint damage. In Study RA-IV and Study RA-VI, progression of structural joint damage was assessed radiographically and expressed as change from baseline in mTSS and its components, the erosion score and joint space narrowing score, at Months 6 and 12. The proportion of patients with no radiographic progression (mTSS change less than or equal to 0) was also assessed.

In Study RA-IV, XELJANZ 5 mg twice daily reduced the mean progression of structural damage (not statistically significant) as shown in Table 13. Analyses of erosion and joint space narrowing scores were consistent with the overall results.

In the placebo plus MTX group, 74% of patients experienced no radiographic progression at Month 6 compared to 84% of patients treated with XELJANZ plus MTX 5 mg twice daily.

In Study RA-VI, XELJANZ monotherapy inhibited the progression of structural damage compared to MTX at Months 6 and 12 as shown in Table 13. Analyses of erosion and joint space narrowing scores were consistent with the overall results.

In the MTX group, 55% of patients experienced no radiographic progression at Month 6 compared to 73% of patients treated with XELJANZ 5 mg twice daily.

Table 13: Radiographic Changes in Adults with Moderate to Severe Active RA at Months 6 and 12 in Studies RA-IV and VI

	Study RA-IV		
	Placebo N=139 Mean (SD)[a]	**XELJANZ 5 mg Twice Daily N=277 Mean (SD)[a]**	**XELJANZ 5 mg Twice Daily Mean Difference from Placebo[b] (CI)**
mTSS[c]			
Baseline	33 (42)	31 (48)	-
Month 6	0.5 (2.0)	0.1 (1.7)	-0.3 (-0.7, 0.0)
	Study RA-VI		
	MTX N=166 Mean (SD)[a]	**XELJANZ 5 mg Twice Daily N=346 Mean (SD)[a]**	**XELJANZ 5 mg Twice Daily Mean Difference from MTX[b] (CI)**
mTSS[c]			
Baseline	17 (29)	20 (40)	-
Month 6	0.8 (2.7)	0.2 (2.3)	-0.7 (-1.0, -0.3)
Month 12	1.3 (3.7)	0.4 (3.0)	-0.9 (-1.4, -0.4)

[a] SD = Standard Deviation
[b] Difference between least squares means XELJANZ minus placebo or MTX (95% CI = 95% confidence interval)
[c] Month 6 and Month 12 data are mean change from baseline.

Physical Function Response
Improvement in physical functioning was measured by the HAQ-DI. Patients who received XELJANZ 5 mg twice daily demonstrated greater improvement from baseline in physical functioning compared to patients who received placebo at Month 3.

The mean (95% CI) difference from placebo in HAQ-DI improvement from baseline at Month 3 in Study RA-III was -0.22 (-0.35, -0.10) in patients who received 5 mg XELJANZ twice daily. Similar results were obtained in Studies RA-I, II, IV and V. In the 12-month trials, HAQ-DI results in XELJANZ-treated patients were consistent at 6 and 12 months.

Other Health-Related Outcomes
General health status was assessed by the Short Form health survey (SF-36). In Studies RA-I, IV, and V, patients who received XELJANZ 5 mg twice daily demonstrated greater improvement from baseline compared to placebo in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 at Month 3.

14.2 Clinical Studies in Psoriatic Arthritis
The psoriatic arthritis (PsA) clinical development program with XELJANZ tablets (referred to as "XELJANZ" in this subsection of labeling) included 2 multicenter, randomized, double-blind, placebo-controlled trials in 816 adults with active PsA (Studies PsA-I and PsA-II).

Trial Designs and Population
All patients had active PsA for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender/painful joints and at least 3 swollen joints, and active plaque psoriasis. Patients randomized and treated across the 2 clinical trials represented different PsA subtypes at screening, including < 5 joints or asymmetric involvement (21%), ≥ 5 joints involved (90%), distal interphalangeal (DIP) joint involvement (61%), arthritis mutilans (8%), and spondylitis (19%). Patients in these clinical trials had a diagnosis of PsA for a mean (SD) of 7.7 (7.2) years. At baseline, 80% and 53% of patients had enthesitis and dactylitis, respectively. At baseline, all patients were required to receive treatment with a stable dose of a nonbiologic DMARD (79% received methotrexate, 13% received sulfasalazine, 7% received leflunomide, 1% received other nonbiologic DMARDs). In both clinical trials, the primary endpoints were the ACR20 response and the change from baseline in HAQ-DI at Month 3.

- Study PsA-I was a 12-month clinical trial in 422 patients who had an inadequate response to a nonbiologic DMARD (67% and 33% were inadequate responders to 1 nonbiologic DMARD and ≥2 nonbiologic DMARDs, respectively) and who were naïve to treatment with a TNF blocker. Although Study PsA-1 included patients who are TNF blocker-naïve, XELJANZ and tofacitinib extended-release tablets are not approved for use in TNF blocker-naive patients [*see Indications and Usage (1.2)]*. Patients were randomized in a 2:2:2:1:1 ratio to receive XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, adalimumab 40 mg subcutaneously once every 2 weeks, placebo to XELJANZ 5 mg twice daily treatment sequence, or placebo to XELJANZ 10 mg twice daily treatment sequence, respectively; study drug was added to background nonbiologic DMARD treatment. At the Month 3 visit, all patients randomized to placebo treatment were switched in a blinded fashion to a predetermined XELJANZ dosage of 5 mg or 10 mg twice daily.Study PsA-I was not designed to demonstrate non-inferiority or superiority to adalimumab.
- Study PsA-II was a 6-month clinical trial in 394 patients who had an inadequate response to at least 1 approved TNF blocker (66%, 19%, and 15% were inadequate responders to 1 TNF blocker, 2 TNF blockers and ≥ 3 TNF blockers, respectively). Patients were randomized in a 2:2:1:1 ratio to receive XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, placebo to XELJANZ 5 mg twice daily treatment sequence, or placebo to XELJANZ 10 mg twice daily treatment sequence, respectively; study drug was added to background nonbiologic DMARD treatment. At the Month 3 visit, placebo patients were switched in a blinded fashion to a predetermined XELJANZ dosage of 5 mg or 10 mg twice daily as in Study PsA-I.

Although other dosages have been studied, the recommended dosage of XELJANZ is 5 mg twice daily. XELJANZ 10 mg twice daily is not recommended for treatment of PsA *[see Dosage and Administration (2.3)]*.

Clinical Response
At Month 3, patients treated with XELJANZ 5 mg twice daily had higher ($p \leq 0.05$) response rates versus placebo for ACR20, ACR50, and ACR70 in Study PsA-I and for ACR20 and ACR50 in Study PsA-II; ACR70 response rates were also higher for XELJANZ 5 mg twice daily versus placebo in Study PsA-II, although the differences versus placebo were not statistically significant ($p > 0.05$)(Tables 14 and 15).

Table 14: Proportion of Adults with Active PsA with an ACR Response at Month 3 in Study PsA-I* [Nonbiologic DMARD Inadequate Responders (TNF Blocker- Naive)]**

Treatment Group	Placebo	XELJANZ 5 mg Twice Daily + Background Nonbiologic DMARD	
N[a]	105	107	
	Response Rate	Response Rate	Difference (%) 95% CI from Placebo
Month 3			
ACR20	33%	50%	17.1 (4.1, 30.2)
ACR50	10%	28%	18.5 (8.3, 28.7)
ACR70	5%	17%	12.1 (3.9, 20.2)

Patients with missing data were treated as non-responders.
* Patients received one concomitant nonbiologic DMARD.
** XELJANZ and Tofacitinib extended-release tablets are not approved for use in TNF blocker-naive patients *[see Indications and Usage (1.2)]*.
[a] N is number of randomized and treated patients.

Table 15: Proportion of Adults with Active PsA with an ACR Response at Month 3 in Study PsA-II* (TNF Blocker Inadequate Responders)

Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	
N[a]	131	131	
	Response Rate	Response Rate	Difference (%) 95% CI from Placebo
Month 3			
ACR20	24%	50%	26.0 (14.7, 37.2)
ACR50	15%	30%	15.3 (5.4, 25.2)
ACR70	10%	17%	6.9 (-1.3, 15.1)

Patients with missing data were treated as non-responders.
* Patients received one concomitant nonbiologic DMARD.
[a] N is number of randomized and treated patients.

Improvements from baseline in the ACR response criteria components for both studies are shown in Table 16.

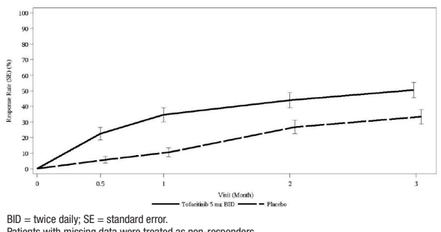
Table 16: Components of ACR Response in Adults with Active PsA at Baseline and Month 3 in Studies PsA-I and PsA-II

	Nonbiologic DMARD Inadequate Responders (TNF Blocker-Naïve)		TNF Blocker Inadequate Responders	
	Study PsA-I*,**		Study PsA-II*	
Treatment Group	**Placebo**	**XELJANZ 5 mg Twice Daily**	**Placebo**	**XELJANZ 5 mg Twice Daily**
N at Baseline	105	107	131	131
ACR Component[a]				
Number of tender/painful joints (0-68)				
Baseline	20.6	20.5	19.8	20.5
Month 3	14.6	12.2	15.1	11.5
Number of swollen joints (0-66)				
Baseline	11.5	12.9	10.5	12.1
Month 3	7.1	6.3	7.7	4.8
Patient assessment of arthritis pain[b]				
Baseline	53.2	55.7	54.9	56.4
Month 3	44.7	34.7	48.0	36.1
Patient global assessment of arthritis[b]				
Baseline	53.9	54.7	55.8	57.4
Month 3	44.4	35.5	49.2	36.9
HAQ-DI[c]				
Baseline	1.11	1.16	1.25	1.26
Month 3	0.95	0.81	1.09	0.88
Physician's Global Assessment of Arthritis[b]				
Baseline	53.8	54.6	53.7	53.5
Month 3	35.4	29.5	36.4	27.0
CRP (mg/L)				
Baseline	10.4	10.5	12.1	13.8
Month 3	8.6	4.0	11.4	7.7

* Patients received one concomitant nonbiologic DMARD.
** XELJANZ and Tofacitinib Extended-Release Tablets are not approved for use in TNF blocker-naïve patients *[see Indications and Usage (1.2)]*.
[a] Data shown are mean value at baseline and at Month 3.
[b] Visual analog scale (VAS): 0 = best, 100 = worst.
c HAQ-DI = Health Assessment Questionnaire – Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

The percentage of ACR20 responders by visit for Study PsA-I is shown in Figure 5. Similar responses were observed in Study PsA-II. In both studies, improvement in ACR20 response on XELJANZ was observed at the first visit after baseline (Week 2).

Figure 5: Percentage of ACR20 Responders by Visit Through Month 3 in Study PsA-I*,**



BID = twice daily; SE = standard error.
Patients with missing data were treated as non-responders.
* Subjects received one concomitant nonbiologic DMARD.
** XELJANZ and tofacitinib extended-release tablets are not approved for use in TNF blocker-naïve patients [see *Indications and Usage (1.2)]*.

In patients with active PsA evidence of benefit in enthesitis and dactylitis was observed with XELJANZ treatment.

Physical Function
Improvement in physical functioning