XELJANZ®
Tofacitinib citrate

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY AND THROMBOSIS

SERIOUS INFECTIONS
Patients treated with XELJANZ are at increased risk for developing serious infections that may lead to hospitalization or death *(see sections 4.4 and 4.7)*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ until the infection is controlled.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ 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 treatment with XELJANZ 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 treatment with XELJANZ, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *(see section 4.4)*.

MORTALITY
Rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular (CV) risk factor treated with XELJANZ 10 mg twice a day had a higher rate of all-cause mortality, including sudden CV death, compared to those treated with XELJANZ 5 mg given twice daily or TNF blockers in a large, ongoing, postmarketing safety study *(see section 4.4)*.

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications *(see section 4.4)*.

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. Rheumatoid arthritis patients who were 50 years of age and older with at least one CV risk factor treated with XELJANZ 10 mg twice daily compared to XELJANZ 5 mg twice daily or TNF blockers in a large, ongoing postmarketing safety study had an observed increase in incidence of these events. Many of these events were serious and some resulted in death. Discontinue XELJANZ and promptly evaluate patients with symptoms of thrombosis *(see section 4.4)*.

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mg film-coated tablet contains 8.078 mg of tofacitinib citrate equivalent to 5 mg of tofacitinib free base active pharmaceutical ingredient. Each 5 mg tablet also contains 61.307 mg lactose monohydrate.

For a full list of excipients, *see section 9.1*.

3. PHARMACEUTICAL FORM

Film-coated tablets:
Tofacitinib 5 mg film-coated tablets are white round immediate release film-coated tablet debossed with 'Pfizer' on one side and 'JKI 5' on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rheumatoid Arthritis

XELJANZ 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 methotrexate. It may be used as monotherapy or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs (DMARDs).

Limitations of Use: Use of XELJANZ in combination with biologic DMARDs or with potent immunosuppressants, such as azathioprine and cyclosporine is not recommended.

Psoriatic Arthritis

XELJANZ is indicated for the treatment of adult patients with active psoriatic arthritis (PsA) who have had an inadequate response or intolerance to methotrexate or other disease modifying antirheumatic drugs (DMARDs).

Limitations of Use: Use of XELJANZ in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ulcerative Colitis

XELJANZ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have an inadequate response or who are intolerant to TNF blockers.

Limitations of Use: Use of XELJANZ in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

4.2 Posology and method of administration

Important Administration Instructions

- Do not initiate XELJANZ in patients with an absolute lymphocyte count less than 500 cells/mm^3, an absolute neutrophil count (ANC) less than 1000 cells/mm^3 or who have hemoglobin levels less than 9 g/dL.
- Dose interruption is recommended for management of lymphopenia, neutropenia and anemia *(see sections 4.4 and 4.7)*.
- Interrupt use of XELJANZ if a patient develops a serious infection until the infection is controlled *(see section 4.4)*.
- Take XELJANZ with or without food *(see section 6.3)*.

Recommended Dosage in Rheumatoid Arthritis and Psoriatic Arthritis

Table 1 displays the recommended adult daily dosage of XELJANZ and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, in patients with moderate or severe renal impairment (including but not limited to those with severe insufficiency who are undergoing hemodialysis) or moderate hepatic impairment, with lymphopenia, neutropenia, or anemia.

Table 1: Recommended Dosage of XELJANZ in Patients with Rheumatoid Arthritis and Psoriatic Arthritis[1]

	XELJANZ
Adult patients	5 mg twice daily
Patients receiving: • strong CYP3A4 inhibitors (e.g., ketoconazole), or • a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole) *(see section 5)*	5 mg once daily
Patients with: • moderate or severe renal impairment • moderate hepatic impairment*	5 mg once daily For patients undergoing hemodialysis, dose should be administered after the dialysis session on dialysis days. If a dose was taken before the dialysis procedure, supplemental doses are not recommended in patients after dialysis.
Patients with lymphocyte count less than 500 cells/mm^3, confirmed by repeat testing	Discontinue dosing.
Patients with ANC 500 to 1000 cells/mm^3	Interrupt dosing. When ANC is greater than 1000, resume 5 mg twice daily.
Patients with ANC less than 500 cells/mm^3	Discontinue dosing.
Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/ dL	Interrupt dosing until hemoglobin values have normalized.

[1] XELJANZ is used in combination with nonbiologic disease modifying antirheumatic drugs (DMARDs) in psoriatic arthritis. The efficacy of XELJANZ as a monotherapy has not been studied in psoriatic arthritis.

* Use of XELJANZ in patients with severe hepatic impairment is not recommended.

Recommended Dosage in Ulcerative Colitis

Table 2 displays the recommended adult daily dosage of XELJANZ and dosage adjustments for patients receiving CYP2C19 and/or CYP3A4 inhibitors, with moderate or severe renal impairment (including

but not limited to those with severe insufficiency who are undergoing hemodialysis) or moderate hepatic impairment, with lymphopenia, neutropenia or anemia.

Table 2: Recommended Dosage of XELJANZ in Patients with UC

	XELJANZ tablet
Adult patients	**Induction:** 10 mg twice daily for at least 8 weeks *[see Clinical Studies (14.3)]*; evaluate patients and transition to maintenance therapy depending on therapeutic response. If needed continue 10 mg twice daily for a maximum of 16 weeks. Discontinue 10 mg twice daily after 16 weeks if adequate therapeutic response is not achieved. **Maintenance:** 5 mg twice daily. For patients with loss of response during maintenance treatment, a dosage of 10 mg twice 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.
Patients receiving: • Strong CYP3A4 inhibitors (e.g., ketoconazole), or • a moderate CYP3A4 inhibitor(s) with a strong CYP2C19 inhibitor(s) (e.g., fluconazole) *[see Drug Interactions (7)]*	If taking 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, reduce to 5 mg once daily.
Patients with: • moderate or severe renal impairment *[see Use in Specific Populations (8.7)]* • moderate hepatic impairment *[see Use in Specific Populations (8.8)]**	If taking 10 mg twice daily, reduce to 5 mg twice daily. If taking 5 mg twice daily, reduce to 5 mg once daily.
	For patients undergoing hemodialysis, dose should be administered after the dialysis session on dialysis days. If a dose was taken before the dialysis procedure, supplemental doses are not recommended in patients after dialysis.
Patients with lymphocyte count less than 500 cells/mm^3, confirmed by repeat testing	Discontinue dosing.

	XELJANZ tablet
Patients with ANC 500 to 1000 cells/mm^3	If taking 10 mg twice daily, reduce to 5 mg twice daily. When ANC is greater than 1000, increase to 10 mg twice daily based on clinical response. If taking 5 mg twice daily, interrupt dosing. When ANC is greater than 1000, resume 5 mg twice daily.
Patients with ANC less than 500 cells/mm^3	Discontinue dosing
Patients with hemoglobin less than 8 g/dL or a decrease of more than 2 g/dL	Interrupt dosing until hemoglobin values have normalized.

*Use of XELJANZ in patients with severe hepatic impairment is not recommended

Hepatic Impairment

Severe Impairment
XELJANZ has not been studied in patients with severe hepatic impairment; therefore, use of XELJANZ in patients with severe hepatic impairment is not recommended.

Moderate Impairment
XELJANZ-treated patients with moderate hepatic impairment had greater tofacitinib blood concentration than XELJANZ-treated patients with normal hepatic function *(see section 6.3)*. Higher blood concentrations may increase the risk of some adverse reactions. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate hepatic impairment *(see section 4.2)*.

Mild Impairment
No dosage adjustment of XELJANZ is required in patients with mild hepatic impairment.

Hepatitis B or C Serology
The safety and efficacy of XELJANZ have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

Renal Impairment

Moderate and Severe Impairment
XELJANZ-treated patients with moderate or severe renal impairment had greater tofacitinib blood concentrations than XELJANZ-treated patients with normal renal function. Therefore, dosage adjustment of XELJANZ is recommended in patients with moderate or severe renal impairment (including but not limited to those with severe insufficiency who are undergoing hemodialysis).

Mild Impairment
No dosage adjustment is required in patients with mild renal impairment.

Geriatric Use

Of the 3315 patients who enrolled in rheumatoid arthritis Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency

of serious infection among tofacitinib-treated subjects 65 years of age and older was higher than among those under the age of 65.

Of the 1156 XELJANZ treated patients in the UC program, a total of 77 patients (7%) were 65 years of age or older. The number of patients aged 65 years and older was not sufficient to determine whether they responded differently from younger patients.

As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly *(see section 4.4)*.

Pediatric Use

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

Use in Diabetics

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients *(see section 9.1)*.

4.4 Special warnings and precautions for use

Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving immunomodulatory agents, including biologic DMARDs and XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcus, histoplasmosis, esophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus infection, BK virus infections, and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localized disease, and rheumatoid arthritis patients were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids which, in addition to rheumatoid arthritis may predispose them to infections. Other serious infections that were not reported in clinical studies, may also occur (e.g., coccidioidomycosis).

In the UC population, XELJANZ treatment with 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 10 mg twice daily.

XELJANZ should not be initiated in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating XELJANZ in patients with chronic or recurrent infections, or those who have been exposed to tuberculosis, or with a history of a serious or an opportunistic infection, or have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or have underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. XELJANZ should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment

with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes *(see section 4.2)*. Caution is also recommended in patients with a history of chronic lung disease as they may be more prone to infections. Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with XELJANZ, a Janus-kinase (JAK) inhibitor, in clinical trials and in the post-marketing setting although the role of JAK inhibition in these events is not known.

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 discussed in *section 4.2*.

Tuberculosis

Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of XELJANZ.

Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before administering XELJANZ.

Antituberculosis therapy should also be considered prior to administration of XELJANZ in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a health care professional with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating antituberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Viral Reactivation

Viral reactivation has been reported with DMARD treatment and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. Post-marketing cases of hepatitis B reactivation have been reported in patients treated with XELJANZ. The impact of XELJANZ on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ. The risk of herpes zoster appears to be higher in Japanese and Korean patients treated with XELJANZ.

Venous Thromboembolism

Venous thromboembolism (VTE) has been observed in patients taking XELJANZ in clinical trials and post-marketing reporting. In one large ongoing randomized post authorization safety surveillance (PASS) study in RA patients who were 50 years or older with at least one cardiovascular risk factor, patients were treated with tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily or a TNF inhibitor. A dose dependent increase in pulmonary embolism (PE) events was observed in patients treated with tofacitinib compared to TNF inhibitors *(see section 4.8)*. Many of these PE events were serious and

some resulted in death. PE events were reported more frequently in this study in patients taking tofacitinib relative to other studies across the tofacitinib program *(see section 4.8)*.

Deep vein thrombosis (DVT) events were observed in all three treatment groups in this study *(see section 4.8)*.

Assess patients for VTE risk factors before starting treatment and periodically during treatment. Use XELJANZ with caution in patients in whom risk factors are identified *(see section 4.2)*. Urgently evaluate patients with signs and symptoms of VTE. Discontinue tofacitinib while evaluating suspected VTE, regardless of dose or indication.

Mortality

Rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular (CV) risk factor treated with XELJANZ 10 mg twice a day had a higher rate of all-cause mortality, including sudden CV death, compared to those treated with XELJANZ 5 mg given twice daily or TNF blockers in a large, ongoing, postmarketing safety study.

A dosage of XELJANZ 10 mg twice daily is not recommended for the treatment of RA or PsA *(see section 4.2)*.

For the treatment of UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response (*see section 4.2*).

Malignancy and Lymphoproliferative Disorder (Excluding Non-melanoma Skin Cancer [NMSC])

Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. The possibility exists for XELJANZ to affect host defenses against malignancies.

Lymphomas have been observed in patients treated with XELJANZ patients with rheumatoid arthritis, particularly those with highly active disease may be at a higher risk (up to several-fold) than the general population for the development of lymphoma. The role of XELJANZ, in the development of lymphoma is uncertain.

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

The role of treatment with XELJANZ on the development and course of malignancies is not known.

Recommendations for non-melanoma skin cancer are presented below.

Rheumatoid Arthritis

In controlled Phase 3 clinical studies in rheumatoid arthritis patients, 26 malignancies (excluding NMSC) including 5 lymphoma were diagnosed in 26 patients receiving XELJANZ/XELJANZ plus DMARD, compared to 0 malignancies (excluding NMSC) in patients in the placebo/placebo plus DMARD and 2 in 2 patients in the adalimumab group, 1 in 1 patient in the methotrexate group. 3800 patients (3942 patient-years of observation) were treated with XELJANZ for durations up to 2 years while 681 patients (203 patient-years of observation) were treated with placebo for a maximum of 6 months and 204 patients (179 patient-years of observation) were treated with adalimumab for 12 months. The exposure-adjusted incidence rate for malignancies and lymphoma was 0.66 and 0.13 events per 100 patient-years, respectively, in the XELJANZ groups.

In the long-term safety population (4867 patients), in rheumatoid arthritis studies, the rate of malignancies (excluding NMSC) and lymphoma was 0.97 and 0.09 events per 100 patient-years respectively, consistent with the rate observed in the controlled period.

Psoriatic Arthritis

During the 2 PsA controlled clinical studies there were 3 malignancies (excluding NMSC) in 474 patients receiving XELJANZ plus nonbiologic DMARD (6 to 12 months exposure) compared with 0 malignancies in 236 patients in the placebo plus nonbiologic DMARD group (3 months exposure) and 0 malignancies in 106 patients in the adalimumab plus nonbiologic DMARD group (12 months exposure). No lymphomas were reported. Malignancies have also been observed in the long term extension study in psoriatic arthritis patients treated with XELJANZ.

Ulcerative Colitis
All information provided in this section for the ulcerative colitis indication is applicable to XELJANZ 5 mg and 10 mg twice daily as they contain the same active ingredient (tofacitinib).

In the placebo-controlled induction and maintenance studies for ulcerative colitis, there were no malignancies (excluding NMSC) in any XELJANZ group. In the entire XELJANZ treatment experience for ulcerative colitis, malignancies (excluding NMSC) have been reported with an overall incidence rate of 0.5 events per 100 patient-years.

Non-melanoma Skin Cancer

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

Thrombosis

Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, have occurred in patients treated with XELJANZ and other Janus kinase (JAK) inhibitors used to treat inflammatory conditions. Patients with rheumatoid arthritis 50 years of age and older with at least one CV risk factor treated with XELJANZ 10 mg twice daily compared to XELJANZ 5 mg twice daily or TNF blockers in a large, ongoing postmarketing study had an observed increase in incidence of these events. Many of these events were serious and some resulted in death *(see section 4.4)*.

A dosage of XELJANZ 10 mg twice daily is not recommended for the treatment of RA *(see section 4.2)*.

In a long-term extension study in patients with UC, four 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 XELJANZ in patients with symptoms of thrombosis.

Avoid XELJANZ in patients that may be at increased risk of thrombosis. For the treatment of UC, use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response (*see section 4.2*)

Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials. The role of JAK inhibition in these events is not known. Events were primarily reported as diverticular perforation, peritonitis, abdominal abscess and appendicitis. In the rheumatoid arthritis clinical trials, the incidence rate of gastrointestinal perforation across all studies (Phase 1, Phase 2, Phase 3 and long term extension) for all treatments groups all doses was 0.11 events per 100 patient-years with XELJANZ therapy. Rheumatoid arthritis patients who developed gastrointestinal perforations were taking concomitant non-steroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. The relative contribution of these concomitant medications vs. XELJANZ to the development of gastrointestinal perforations is not known.

XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.
There was no discernable difference in frequency of gastrointestinal perforation between the placebo and the XELJANZ arms in clinical trials of patients with UC, and many of them were receiving background corticosteroids.

Hypersensitivity

Reactions such as angioedema and urticaria that may reflect drug hypersensitivity have been observed in patients receiving XELJANZ. Some events were serious. Many of these events occurred in patients that have a history of multiple allergies. If a serious hypersensitivity reaction occurs, promptly discontinue XELJANZ while evaluating the potential cause or causes of the reaction.

Laboratory Parameters

Lymphocytes: Lymphocyte counts <500 cells/mm^3 were associated with an increased incidence of treated and serious infections. It is not recommended to initiate XELJANZ treatment in patients with a low lymphocyte count (i.e., <500 cells/mm^3). In patients who develop a confirmed absolute lymphocyte count <500 cells/mm^3 treatment with XELJANZ is not recommended. Lymphocytes should be monitored at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts *(see section 4.2)*.

Neutrophils: Treatment with XELJANZ was associated with an increased incidence of neutropenia (<2000 cells/mm^3) compared to placebo. It is not recommended to initiate XELJANZ treatment in patients with a low neutrophil count (i.e., ANC <1000 cells/mm^3). For patients who develop a persistent

ANC of 500-1000 cells/mm^3, reduce XELJANZ dose or interrupt XELJANZ dosing until ANC is >1000 cells/mm^3. In patients who develop a confirmed absolute neutrophil count <500 cells/mm^3, treatment with XELJANZ is not recommended. Neutrophils should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter *(see sections 4.2 and 4.7)*.

Hemoglobin: It is not recommended to initiate XELJANZ treatment in patients with low hemoglobin values (i.e., <9 g/dL). Treatment with XELJANZ should be interrupted in patients who develop hemoglobin levels <8 g/dL or whose hemoglobin level drops >2 g/dL on treatment. Hemoglobin should be monitored at baseline and after 4 - 8 weeks of treatment and every 3 months thereafter *(see sections 4.2 and 4.7)*.

Lipids: Treatment with XELJANZ was associated with increases in lipid parameters such as total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. Assessment of lipid parameters should be performed approximately 4 - 8 weeks following initiation of XELJANZ therapy. Patients should be managed according to current local clinical guidelines for the management of hyperlipidemia. Increase in total and LDL cholesterol associated with XELJANZ may be decreased to pre-treatment levels with statin therapy.

In the clinical trials in psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis changes in lymphocytes, neutrophils, and lipids observed with XELJANZ treatment were similar to the changes observed in clinical trials in rheumatoid arthritis.

Vaccinations

No data are available on the secondary transmission of infection by live vaccines to patients receiving XELJANZ. It is recommended that live vaccines not be given concurrently with XELJANZ. It is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating XELJANZ therapy. The interval between live vaccinations and initiation of XELJANZ therapy should be in accordance with current vaccination guidelines regarding immunomodulatory agents. Consistent with these guidelines, if live zoster vaccine is administered, it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus. Vaccination should occur at least 2 weeks but preferably 4 weeks before initiating immunomodulatory agents such as XELJANZ.

A controlled study in patients with rheumatoid arthritis on background methotrexate evaluated the humoral and cell-mediated responses to immunization with a live attenuated virus vaccine (Zostavax) indicated for prevention of herpes zoster. The immunization occurred 2 to 3 weeks before initiating a 12-week treatment with XELJANZ 5 mg twice daily or placebo. Six weeks after immunization with the zoster vaccine, XELJANZ and placebo recipients exhibited similar humoral and cell-mediated responses (mean fold change of VZV IgG antibodies 2.11 in XELJANZ 5 mg twice daily and 1.74 in placebo twice daily; VZV IgG fold-rise ≥1.5 in 57% of XELJANZ recipients and in 43% of placebo recipients; mean fold change of VZV T-cell ELISPOT Spot Forming Cells 1.5 in XELJANZ 5 mg twice daily and 1.29 in placebo twice daily). These responses were similar to those observed in healthy volunteers aged 50 years and older.

In this study one patient experienced dissemination of the vaccine strain of varicella zoster virus, 16 days after vaccination. The patient was varicella virus naïve, as evidenced by no previous history of varicella infection and no anti-varicella antibodies at baseline. XELJANZ was discontinued and the subject recovered after treatment with standard doses of antiviral medication. Subsequent testing showed that this patient made robust anti-varicella T-cell and antibody responses to the vaccine

approximately 6 weeks post-vaccination, but not at 2 weeks post-vaccination, as expected for a primary infection.

4.5 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

Available data with XELJANZ use in pregnant women are insufficient to establish a drug associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and the fetus associated with rheumatoid arthritis and UC in pregnancy *(see section 4.5)*. In animal reproduction studies, fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73 times. Further, in a peri and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73 times the recommended dose of 5 mg twice daily *(see Data)*.

Women of reproductive potential should be advised to use effective contraception during treatment with tofacitinib and for at least 4 weeks after the last dose.

The estimated background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risks in the U.S. general population of major birth defects and miscarriages are 2 to 4% and 15 to 20% of clinically recognized pregnancies, respectively.

Clinical Considerations

Disease-associated Maternal and/or Embryo/Fetal Risk
Published data suggest that increased disease activity is associated with the risk of developing adverse pregnancy outcomes in women with rheumatoid arthritis or ulcerative colitis. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

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

In a rabbit embryofetal developmental study, in which pregnant rabbits received tofacitinib during the period of organogenesis, tofacitinib was teratogenic at exposure levels approximately 13 times the recommended dose of 5 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis,

omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. In addition, there was an increase in post-implantation loss associated with late resorptions. No developmental toxicity was observed in rabbits at exposure levels approximately 3 times the recommended dose of 5 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in pregnant rabbits).

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

Lactation

Risk Summary

There are no data on the presence of tofacitinib in human milk, the effects on a breastfed infant, or the effects on milk production. Tofacitinib is present in the milk of lactating rats (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk. Given the serious adverse reactions seen in patients treated with XELJANZ, such as increased risk of serious infections, advise patients that breastfeeding is not recommended during treatment and for at least 18 hours after the last dose of XELJANZ.

Data

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

Females and Males of Reproductive Potential

Contraception

Females
In an animal reproduction study, tofacitinib at AUC multiples of 13 times the recommended dose of 5 mg twice daily demonstrated adverse embryo-fetal findings *(see section 4.5).*

However, there is uncertainty as to how these animal findings relate to females of reproductive potential treated with the recommended clinical dose. Consider pregnancy planning and prevention for females of reproductive potential.

Infertility

Females
Based on findings in rats, treatment with XELJANZ may result in reduced fertility in females of reproductive potential. It is not known if this effect is reversible *(see section 8.1).*

4.6 Effects on ability to drive and use machines

No formal studies have been conducted on the effects on the ability to drive and use machines.

4.7 Adverse reactions

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Serious Infections *(see section 4.4)*
- Mortality *(see section 4.4)*
- Malignancy and Lymphoproliferative Disorders *(see section 4.4)*
- Thrombosis *(see section 4.4)*
- Gastrointestinal Perforations *(see section 4.4)*
- Hypersensitivity *(see section 4.4)*
- Laboratory Abnormalities *(see section 4.4)*

Clinical Trials Experience

Because clinical studies are 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.

Rheumatoid Arthritis

The clinical studies described in the following sections were conducted using XELJANZ. Although other doses of XELJANZ have been studied, the recommended dose of XELJANZ is 5 mg twice daily.

The following data includes two Phase 2 and five Phase 3 double-blind, controlled, multicenter trials. In these trials, patients were randomized to doses of XELJANZ 5 mg twice daily (292 patients) and 10 mg twice daily (306 patients) monotherapy, XELJANZ 5 mg twice daily (1044 patients) and 10 mg twice daily (1043 patients) in combination with DMARDs (including methotrexate) and placebo (809 patients). All seven protocols included provisions for patients taking placebo to receive treatment with XELJANZ at Month 3 or Month 6 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Therefore, some analyses that follow include patients who changed treatment by design or by patient response from placebo to XELJANZ in both the placebo and XELJANZ group of a given interval. Comparisons between placebo and XELJANZ were based on the first 3 months of exposure, and comparisons between XELJANZ 5 mg twice daily and XELJANZ 10 mg twice daily were based on the first 12 months of exposure.

The long-term safety population includes all patients who participated in a double-blind, controlled trial (including earlier development phase studies) and then participated in one of two long-term safety studies. The design of the long-term safety studies allowed for modification of XELJANZ doses according to clinical judgment. This limits the interpretation of the long-term safety data with respect to dose.

The most common serious adverse reactions were serious infections *(see section 4.4)*.

The proportion of patients who discontinued treatment due to any adverse reaction during the 0 to 3 months exposure in the double-blind, placebo-controlled trials was 4% for patients taking XELJANZ and 3% for placebo-treated patients.

Safety information from *ad hoc* interim analyses is also included for one large (N=4362), ongoing randomized post authorization safety surveillance (PASS) study in RA patients who were 50 years or older with at least one cardiovascular risk factor (CV risk factors defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence

of extra articular disease associated with RA, e.g. nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations), and were on a stable background dose of methotrexate.

Patients were randomized to open-label tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, or a TNF inhibitor (TNF inhibitor was either etanercept 50 mg once weekly or adalimumab 40 mg every other week) in a 1:1:1 ratio. The co-primary endpoints are adjudicated malignancy (excluding NMSC) and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessment of endpoints are blinded. The study is an event-powered study that also requires at least 1500 patients to be followed for 3 years. The study treatment of tofacitinib 10 mg twice daily has been stopped and the patients were switched to 5 mg twice daily because of a dose dependent signal of PE.

Overall Infections

In the seven controlled trials, during the 0 to 3 months exposure, the overall frequency of infections was 20% and 22% in the 5 mg twice daily and 10 mg twice daily groups, respectively, and 18% in the placebo group.

The most commonly reported infections with XELJANZ were upper respiratory tract infections, nasopharyngitis, and urinary tract infections (4%, 3%, and 2% of patients, respectively).

Ulcerative Colitis

In the randomized 8 week Phase 2/3 induction studies, the proportions of patients with infections were 21.1% for XELJANZ 10 mg twice daily compared with 15.2% for placebo. In the randomized 52-week Phase 3 maintenance study, the proportion of patients with infections were 35.9% for XELJANZ 5 mg twice daily, 39.8% for XELJANZ 10 mg twice daily, and 24.2% for placebo. In the entire treatment experience with XELJANZ in the ulcerative colitis program, the overall incidence rate of infection was 65.7 events per 100 patient years (involving 47.9% of patients). The most common infection was nasopharyngitis, occurring in 16.8% of patients.

Serious Infections

In the seven controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.5 events per 100 patient-years) who received placebo and 11 patients (1.7 events per 100 patient-years) who received XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 1.1 (-0.4, 2.5) events per 100 patient-years for the combined 5 mg twice daily and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, serious infections were reported in 34 patients (2.7 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 33 patients (2.7 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was -0.1 (-1.3, 1.2) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The most common serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infection *(see section 4.4)*.

Ulcerative Colitis

XELJANZ has been studied in patients with moderately to severely active UC in 4 randomized, double-blind, placebo-controlled trials (UC-I, UC-II, UC-III, and dose-ranging UC-V) and an open-label long-term extension study (UC-IV) (*see section 7.0)*.

Adverse reactions reported in ≥5% of patients treated with either 5 mg or 10 mg twice daily of XELJANZ and ≥1% greater than reported in patients receiving placebo in either the induction or maintenance clinical trials were: nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster.

Induction Trials (Study UC-I, UC-II, and UC-V):
Common adverse reactions reported in ≥2% of patients treated with XELJANZ 10 mg twice daily and ≥1% greater than that reported in patients receiving placebo in the 3 induction trials were: headache, nasopharyngitis, elevated cholesterol levels, acne, increased blood creatine phosphokinase, and pyrexia.

Maintenance Trial (Study UC-III)
Common adverse reactions reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported in patients receiving placebo are shown in Table 3.

Table 3: Common Adverse Reactions* in -UC Patients during the Maintenance Trial (Study UC-III)

	XELJANZ 5 mg Twice Daily	**XELJANZ 10 mg Twice Daily**	**Placebo**
Preferred Term	**N = 198 (%)**	**N = 196 (%)**	**N = 198 (%)**
Nasopharyngitis	10	14	6
Elevated cholesterol levels**	5	9	1
Headache	9	3	6
Upper respiratory tract infection	7	6	4
Increased blood creatine phosphokinase	3	7	2
Rash	3	6	4
Diarrhea	2	5	3
Herpes zoster	1	5	1
Gastroenteritis	3	4	3
Anemia	4	2	2
Nausea	1	4	3

* reported in ≥4% of patients treated with either dose of XELJANZ and ≥1% greater than reported for placebo.
** includes hypercholesterolemia, hyperlipidemia, blood cholesterol increased, dyslipidemia, blood triglycerides increased, low density lipoprotein increased, low density lipoprotein abnormal, or lipids increased.

Dose-dependent adverse reactions seen in patients treated with XELJANZ 10 mg twice daily, in comparison to 5 mg twice daily, include the following: herpes zoster infections, serious infections, and NMSC *(see section 4.4)*.

During the UC controlled clinical studies (8-week induction and 52-week maintenance studies), which included 1220 patients, 0 cases of solid cancer or lymphoma were observed in XELJANZ-treated patients.

In the long-term extension study, malignancies (including solid cancers, lymphomas and NMSC) were observed in patients treated with XELJANZ 5 mg and 10 mg twice daily *[see Warnings and Precautions (5.3)]*. Five cases of pulmonary embolism were reported in patients taking XELJANZ 10 mg twice daily, including one fatality in a patient with advanced cancer *(see section 4.4)*.

Tuberculosis

In the seven controlled trials, during the 0 to 3 months exposure, tuberculosis was not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven controlled trials, during the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg twice daily of XELJANZ and 6 patients (0.5 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.5 (0.1, 0.9) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

Cases of disseminated tuberculosis were also reported. The median XELJANZ exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days) *(see section 4.4)*.

Opportunistic Infections (excluding tuberculosis)

In the seven controlled trials, during the 0 to 3 months exposure, opportunistic infections were not reported in patients who received placebo, 5 mg twice daily of XELJANZ, or 10 mg twice daily of XELJANZ.

In the seven controlled trials, during the 0 to 12 months exposure, opportunistic infections were reported in 4 patients (0.3 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 4 patients (0.3 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0 (-0.5, 0.5) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

The median XELJANZ exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days) *(see section 4.4)*.

Malignancy

In the seven controlled trials, during the 0 to 3 months exposure, malignancies excluding NMSC were reported in 0 patients who received placebo and 2 patients (0.3 events per 100 patient-years) who received either XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (and the corresponding 95% confidence interval) was 0.3 (-0.1, 0.7) events per 100 patient-years for the combined 5 mg and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, malignancies excluding NMSC were reported in 5 patients (0.4 events per 100 patient-years) who received 5 mg twice daily of XELJANZ and 7 patients (0.6 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.2 (-0.4, 0.7) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ. One of these malignancies was a case of lymphoma that occurred during the 0 to 12 month period in a patient treated with XELJANZ 10 mg twice daily.

The most common types of malignancy, including malignancies observed during the long-term extension, were lung and breast cancer, followed by gastric, colorectal, renal cell, prostate cancer, lymphoma, and malignant melanoma *(see section 4.4)*.

Laboratory Abnormalities

<u>Lymphopenia</u>

In the controlled clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm^3 occurred in 0.04% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

Confirmed lymphocyte counts less than 500 cells/mm^3 were associated with an increased incidence of treated and serious infections *(see section 4.4)*.

Neutropenia

In the controlled clinical trials, confirmed decreases in ANC below 1000 cells/mm^3 occurred in 0.07% of patients for the 5 mg twice daily and 10 mg twice daily XELJANZ groups combined during the first 3 months of exposure.

There were no confirmed decreases in ANC below 500 cells/mm^3 observed in any treatment group.

There was no clear relationship between neutropenia and the occurrence of serious infections.

In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical trials *(see section 4.4)*.

Liver Enzyme Elevations

Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were observed in patients treated with XELJANZ. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of XELJANZ, or reduction in XELJANZ dose, resulted in decrease or normalization of liver enzymes.

In the controlled monotherapy trials (0-3 months), no differences in the incidence of ALT or AST elevations were observed between the placebo, and XELJANZ 5 mg and 10 mg twice daily groups.

In the controlled background DMARD trials (0-3 months), ALT elevations greater than 3x ULN were observed in 1.0%, 1.3% and 1.2% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. In these trials, AST elevations greater than 3x ULN were observed in 0.6%, 0.5% and 0.4% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively.

One case of drug-induced liver injury was reported in a patient treated with XELJANZ 10 mg twice daily for approximately 2.5 months. The patient developed symptomatic elevations of AST and ALT greater than 3x ULN and bilirubin elevations greater than 2x ULN, which required hospitalizations and a liver biopsy.

In the clinical trials in psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis, changes in liver enzyme tests observed with XELJANZ treatment were similar to the changes observed in clinical trials in rheumatoid arthritis where patients received background DMARDs.

Lipid Elevations

In the controlled clinical trials, dose-related elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were observed at one month of exposure and remained stable thereafter. Changes in lipid parameters during the first 3 months of exposure in the controlled clinical trials are summarized below:

- Mean LDL cholesterol increased by 15% in the XELJANZ 5 mg twice daily arm and 19% in the XELJANZ 10 mg twice daily arm.
- Mean HDL cholesterol increased by 10% in the XELJANZ 5 mg twice daily arm and 12% in the XELJANZ 10 mg twice daily arm.
- Mean LDL/HDL ratios were essentially unchanged in XELJANZ-treated patients.

In a controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy.

In the long-term safety population, elevations in lipid parameters remained consistent with what was seen in the controlled clinical trials.

Serum Creatinine Elevations

In the controlled clinical trials, dose-related elevations in serum creatinine were observed with XELJANZ treatment. The mean increase in serum creatinine was <0.1 mg/dL in the 12-month pooled safety analysis; however with increasing duration of exposure in the long-term extensions, up to 2% of patients were discontinued from XELJANZ treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 5 mg twice daily or 10 mg twice daily XELJANZ and at least 1% greater than that observed in patients on placebo with or without DMARD are summarized in Table 4.

Table 4: Common Adverse Reactions* in Clinical Trials of XELJANZ for the Treatment of Rheumatoid Arthritis with or without Concomitant DMARDs (0-3 Months)

	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg Twice Daily**	Placebo
Preferred Term	**N = 1336 (%)**	**N = 1349 (%)**	**N = 809 (%)**
Upper respiratory tract infection	4	4	3
Nasopharyngitis	4	3	3
Diarrhea	4	3	2
Headache	4	3	2
Hypertension	2	2	1

N reflects randomized and treated patients from the seven clinical trials

* Reported in ≥2% of patients treated with either dose of XELJANZ and ≥1% greater than that reported for placebo.

** The recommended dose of XELJANZ for the treatment of rheumatoid arthritis is 5 mg twice daily *(see section 4.2).*

Other adverse reactions occurring in controlled and open-label extension studies included:

Blood and lymphatic system disorders: Anemia
Infections and infestations: Diverticulitis
Metabolism and nutrition disorders: Dehydration
Psychiatric disorders: Insomnia
Nervous system disorders: Paresthesia
Respiratory, thoracic and mediastinal disorders: Dyspnea, cough, sinus congestion, interstitial lung disease (cases were limited to patients with rheumatoid arthritis and some were fatal)
Gastrointestinal disorders: Abdominal pain, dyspepsia, vomiting, gastritis, nausea
Hepatobiliary disorders: Hepatic steatosis
Skin and subcutaneous tissue disorders: Rash, erythema, pruritus

Musculoskeletal, connective tissue and bone disorders: Musculoskeletal pain, arthralgia, tendonitis, joint swelling
Neoplasms benign, malignant and unspecified (including cysts and polyps): Non-melanoma skin cancers
General disorders and administration site conditions: Pyrexia, fatigue, peripheral edema

Psoriatic Arthritis
XELJANZ 5 mg twice daily and 10 mg twice daily were studied in 2 double blind Phase 3 clinical trials in patients with active psoriatic arthritis (PsA). Although other doses of XELJANZ have been studied, the recommended dose of XELJANZ is 5 mg twice daily. A dosage of XELJANZ 10 mg twice daily is not recommended for the treatment of PsA *[see section 4.2)*.

Study PsA-I (NCT01877668) had a duration of 12 months and enrolled patients who had an inadequate response to a nonbiologic DMARD and who were naïve to treatment with a TNF blocker. Study PsA-I included a 3-month placebo-controlled period and also included adalimumab 40 mg subcutaneously once every 2 weeks for 12 months.

Study PsA-II (NCT01882439) had a duration of 6 months and enrolled patients who had an inadequate response to at least one approved TNF blocker. This clinical trial included a 3-month placebo controlled period.

In these combined Phase 3 clinical trials, 238 patients were randomized and treated with XELJANZ 5 mg twice daily and 236 patients were randomized and treated with XELJANZ 10 mg twice daily. All patients in the clinical trials were required to receive treatment with a stable dose of a nonbiologic DMARD [the majority (79%) received methotrexate]. The study population randomized and treated with XELJANZ (474 patients) included 45 (9.5%) patients aged 65 years or older and 66 (13.9%) patients with diabetes at baseline.

The safety profile observed in patients with active psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in rheumatoid arthritis patients.

Ulcerative Colitis
The following safety data were based on 4 randomized, double-blind, placebo-controlled studies: 2 Phase 3 induction studies of identical design (UC I and UC II), a Phase 3 maintenance study (UC III), and 1 dose-ranging Phase 2 induction study (UC V). Patients with moderately to severely active ulcerative colitis were enrolled in the Phase 2 and Phase 3 induction studies. In the induction studies, randomized patients received treatment with XELJANZ 10 mg twice daily (938 patients combined) or placebo (282 patients combined) for up to 8 weeks. Patients who completed either Study UC I or Study UC II and achieved clinical response entered Study UC III. In Study UC III, patients were re randomized, such that 198 patients received XELJANZ 5 mg twice daily, 196 patients received XELJANZ 10 mg twice daily, and 198 patients received placebo for up to 52 weeks. Concomitant use of immunosuppressants or biologics was prohibited during these studies. Concomitant stable doses of oral corticosteroids were allowed in the induction studies, with taper of corticosteroids to discontinuation mandated within 15 weeks of entering the maintenance study. In addition to the induction and maintenance studies, long-term safety was evaluated in an open label long term extension study (Study UC IV).

In induction and maintenance studies, across all treatment groups, the most common categories of serious adverse reactions were gastrointestinal disorders and infections, and the most common serious adverse reaction was worsening of ulcerative colitis.

In the controlled clinical studies for ulcerative colitis, 1 case of breast cancer was reported in a placebo-treated patient and no cases of solid cancers or lymphoma were observed in XELJANZ treated patients. Malignancies have also been observed in the long term extension study in patients with ulcerative colitis treated with XELJANZ, including solid cancers and lymphoma.

In induction and maintenance studies, the most frequent reason for study discontinuation was worsening of ulcerative colitis. Excluding discontinuations due to worsening of ulcerative colitis, the proportion of patients who discontinued due to adverse reactions was less than 5% in any of the XELJANZ or placebo treatment groups in these studies.

Overall, the safety profile observed in patients with ulcerative colitis treated with XELJANZ was consistent with the safety profile of XELJANZ across indications.

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of XELJANZ. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: Drug hypersensitivity (events such as angioedema and urticaria have been observed).

4.8 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 subjects 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 XELJANZ.

5. DRUG INTERACTIONS

Table 5 includes drugs with clinically important drug interactions when administered concomitantly with XELJANZ and instructions for preventing or managing them.

Table 5: Clinical Relevant Interactions Affecting XELJANZ When Co-administered with Other Drugs

Strong CYP3A4 Inhibitors (e.g., ketoconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ is recommended *(see sections 4.2, 6, Figure 3)*

Moderate CYP3A4 Inhibitors Co-administered with Strong CYP2C19 Inhibitors (e.g., fluconazole)	
Clinical Impact	Increased exposure to tofacitinib
Intervention	Dosage adjustment of XELJANZ is recommended *(see sections 4.2, 6, Figure 3)*
Strong CYP3A4 Inducers (e.g., rifampin)	
Clinical Impact	Decreased exposure to tofacitinib and may result in loss of or reduced clinical response
Intervention	Co-administration with XELJANZ is not recommended *(see section 6, Figure 3)*
Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)	
Clinical Impact	Risk of added immunosuppression; co-administration with biologic DMARDs or potent immunosuppressants has not been studied in patients with rheumatoid arthritis
Intervention	Co-administration with XELJANZ is not recommended *(see sections 4.1, 6, Figure 3)*

Interactions Affecting the Use of XELJANZ

Since tofacitinib is metabolized by CYP3A4, interaction with drugs that inhibit or induce CYP3A4 is likely. Tofacitinib exposure is increased when coadministered with potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) or when administration of one or more concomitant medications results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole).

Tofacitinib exposure is decreased when coadministered with potent CYP inducers (e.g., rifampin). Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to significantly alter the PK of tofacitinib.

Concomitant administration with methotrexate (15-25 mg MTX once weekly) had no effect on the PK of tofacitinib. Coadministration of ketoconazole, a strong CYP3A4 inhibitor, with a single dose of tofacitinib increased the AUC and C_{max} by 103% and 16%, respectively. Coadministration of fluconazole, a moderate inhibitor of CYP3A4 and a strong inhibitor of CYP2C19, increased the AUC and C_{max} of tofacitinib by 79% and 27%, respectively. Coadministration of tacrolimus (Tac), a mild inhibitor of CYP3A4, increased the AUC of tofacitinib by 21% and decreased the C_{max} of tofacitinib by 9%. Coadministration of cyclosporine (CsA), a moderate inhibitor of CYP3A4, increased the AUC of tofacitinib by 73% and decreased C_{max} of tofacitinib by 17%. The combined use of multiple-dose tofacitinib with these potent immunosuppressives has not been studied in patients with rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, or polyarticular course juvenile idiopathic arthritis. Coadministration of rifampin, a strong CYP3A4 inducer, decreased the AUC and C_{max} of tofacitinib by 84% and 74%, respectively.

Potential for XELJANZ 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 exceeding 80 times the steady state total C_{max} at 5 mg and 10 mg twice daily doses in rheumatoid arthritis, psoriatic arthritis, psoriasis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis patients. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the PK of midazolam, a highly sensitive CYP3A4 substrate, when coadministered with tofacitinib.

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 total C*max*

at 5 mg and 10 mg twice daily doses in rheumatoid arthritis, psoriatic arthritis, psoriasis patients, ulcerative colitis patients and polyarticular course juvenile idiopathic arthritis.

In rheumatoid arthritis patients, psoriasis patients, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis patients the oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalize CYP enzyme activity in these patients. Therefore, coadministration with tofacitinib is not expected to result in clinically relevant increases in the metabolism of CYP substrates in RA patients, psoriasis patients, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis patients.

6. CLINICAL PHARMACOLOGY

6.1 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.

6.2 Pharmacodynamics

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

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

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

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

6.3 Pharmacokinetics

XELJANZ

Following oral administration of tofacitinib, peak plasma concentrations are reached within 0.5-1 hour, elimination half-life is about 3 hours and a dose-proportional increase in systemic exposure was observed in the therapeutic dose range. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after twice daily administration.

Table 6: Pharmacokinetic Parameters of XELJANZ Following Multiple Oral Dosing

PK Parameters[a] (CV%)	XELJANZ
Dosing Regimen	**5 mg Twice Daily**
AUC_{24} (ng.h/mL)	263.4 (15)
C_{max} (ng/mL)	42.7 (26)
C_{min} (ng/mL)	1.41 (40)
T_{max} (hours)	1.0 (0.5 to 14.0[b])

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.

b Values beyond 12 hours were after the evening dose which was administered 12 hours after the morning dose of twice-daily XELJANZ.

Absorption

The absolute oral bioavailability of tofacitinib is 74%. Co-administration of tofacitinib with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. In clinical trials, tofacitinib was administered without regard to meals *(see section 4.2)*.

Distribution

After intravenous administration, the volume of distribution is 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.

Population Pharmacokinetics in Rheumatoid Arthritis Patients

Population pharmacokinetic analyses indicated that the coefficient of variation (%) in AUC of tofacitinib for patients with rheumatoid arthritis was 22.0% and psoriatic arthritis was 34% (Table 6).

Table 7. XELJANZ Exposure in Patient Populations at 5 mg Twice Daily Dose

Pharmacokinetic Parameters[a] Geometric Mean (CV%)	XELJANZ 5 mg Twice Daily
	Rheumatoid Arthritis
$AUC_{0\text{-}24,ss}$ (ng·h/mL)	504 (22.0%)
$AUC_{0\text{-}24,ss}$ (ng·h/mL)	419 (34.1%)

Abbreviations: $AUC_{0\text{-}24,ss}$=area under the plasma concentration-time curve over 24 hours at steady state; CV=coefficient of variation.

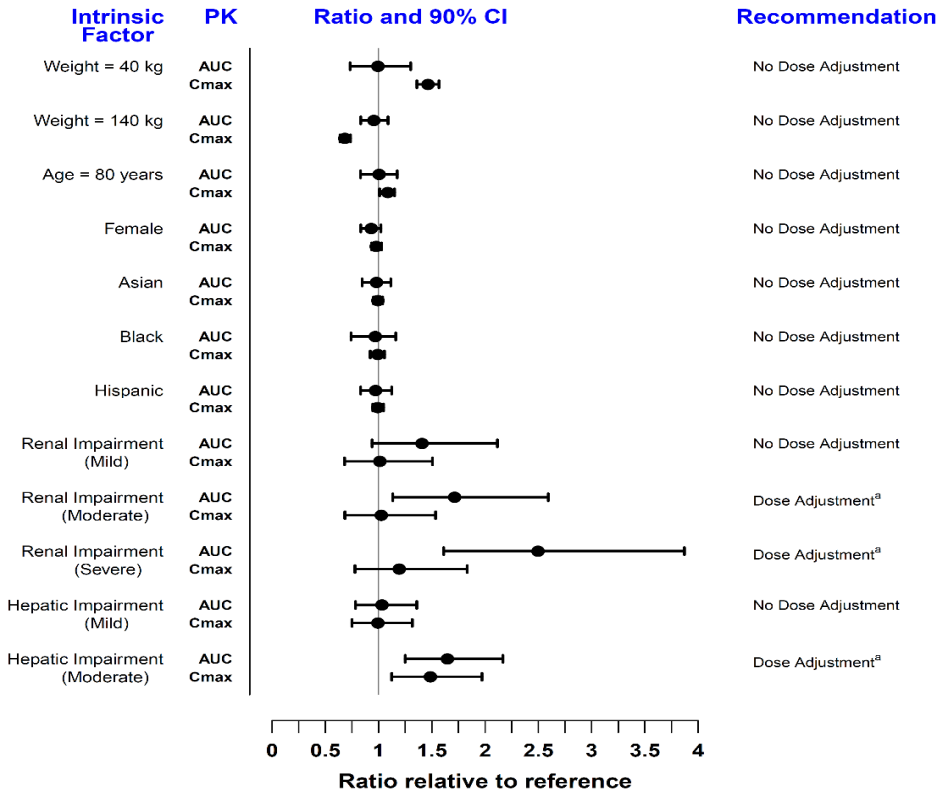
[a.] Pharmacokinetic parameters estimated based on population pharmacokinetic analysis.

Specific Populations

Covariate evaluation as part of population PK analyses in 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, gender 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 pharmacokinetics of tofacitinib is shown in Figure 1.

Figure 1: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics



Note: Reference values for weight, age, gender, and race comparisons are 70 kg, 55 years, male, and white, respectively; reference groups for renal and hepatic impairment data are subjects with normal renal and hepatic function.
[a] (*Refer to section 4.2)* for dosage adjustment in RA, PsA patients.

In subjects with ESRD 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. Dose adjustment is recommended in RA, PsA patients with ESRD maintained on hemodialysis *(see sections 4.2, 4.3, 4.4)*.

Pharmacokinetics in Patients with Active Ulcerative Colitis

Population PK analysis in ulcerative colitis patients indicated that there were no clinically relevant differences in tofacitinib exposure (AUC), based on age, weight, gender, and race. Exposure in women was 15% higher than in men, and Asian patients had 7.3% higher exposure than non Asian. Volume of distribution increased with body weight 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 between-subject variability (% coefficient of variation) in AUC of tofacitinib is estimated to be approximately 23% and 25% at the 5 mg twice daily dose and 10 mg twice daily dose, respectively, in ulcerative colitis patients.

Drug Interaction Studies

Potential for Tofacitinib to Influence the Pharmacokinetics 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 exceeding 160 times the steady state C_{max} of a 5 mg twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the

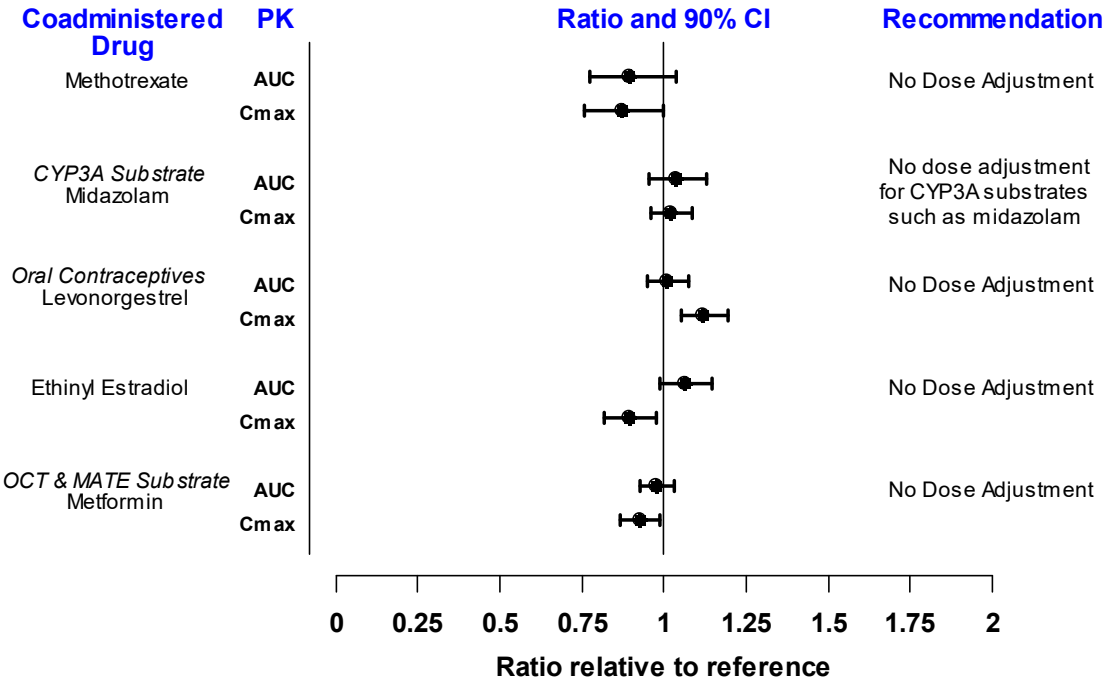
pharmacokinetics of midazolam, a highly sensitive CYP3A4 substrate, when co-administered with tofacitinib.

In rheumatoid arthritis patients, the oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalize CYP enzyme activity in rheumatoid arthritis patients. Therefore, co-administration with tofacitinib is not expected to result in clinically relevant increases in the metabolism of CYP substrates in rheumatoid arthritis patients.

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.

Dosing recommendations for co-administered drugs following administration with tofacitinib are shown in Figure 2.

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

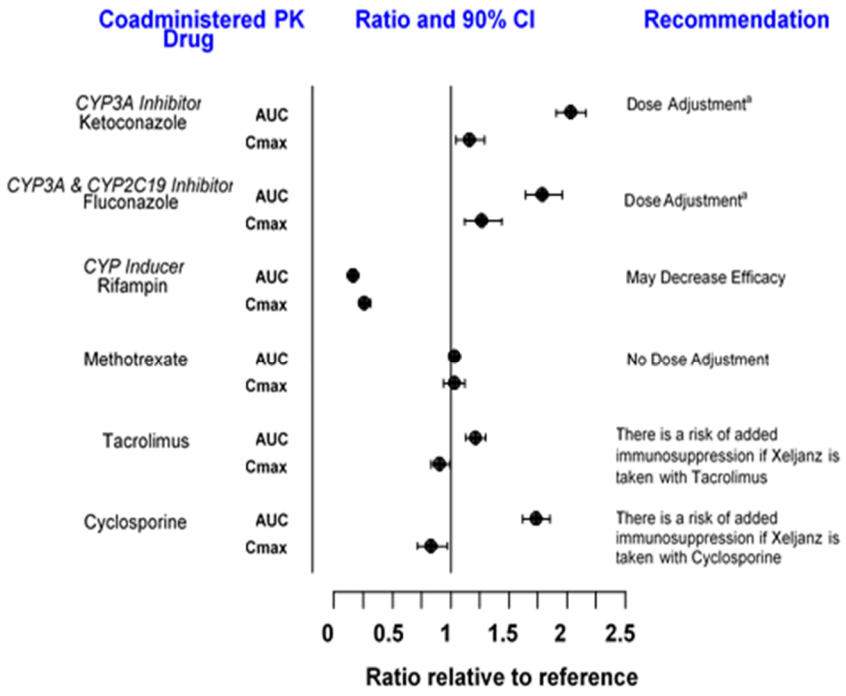


Note: Reference group is administration of concomitant medication alone; OCT = Organic Cationic Transporter; MATE = Multidrug and Toxic Compound Extrusion

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 tofacitinib alone
[a] *(see sections 4.2 and 5).*

7. CLINICAL STUDIES

The tofacitinib clinical development program included two dose-ranging trials and five confirmatory trials. Although other doses have been studied, the recommended dose of tofacitinib is 5 mg twice daily. Tofacitinib 10 mg twice daily is not recommended for the treatment of rheumatoid arthritis *(see section 4.2).*

Dose-Ranging Trials

Dose selection for tofacitinib was based on two pivotal dose-ranging trials.

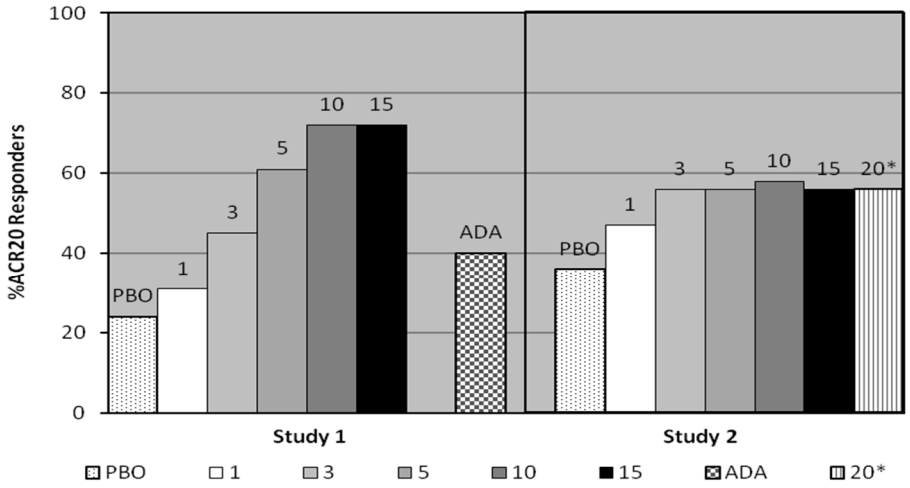
Dose-Ranging Study 1 was a 6-month monotherapy trial in 384 patients with active rheumatoid arthritis who had an inadequate response to a DMARD. Patients who previously received adalimumab therapy were excluded. Patients were randomized to 1 of 7 monotherapy treatments: tofacitinib 1, 3, 5, 10 or 15 mg twice daily, adalimumab 40 mg subcutaneously every other week for 10 weeks followed by tofacitinib 5 mg twice daily for 3 months, or placebo.

Dose-Ranging Study 2 was a 6-month trial in which 507 patients with active rheumatoid arthritis who had an inadequate response to MTX alone received one of 6 dose regimens of tofacitinib (20 mg once daily; 1, 3, 5, 10 or 15 mg twice daily), or placebo added to background MTX.

The results of tofacitinib-treated patients achieving ACR20 responses in Studies 1 and 2 are shown in Figure 4. Although a dose-response relationship was observed in Study 1, the proportion of patients with an ACR20 response did not clearly differ between the 10 mg and 15 mg doses. In Study 2, a smaller proportion of patients achieved an ACR20 response in the placebo and tofacitinib 1 mg groups

compared to patients treated with the other tofacitinib doses. However, there was no difference in the proportion of responders among patients treated with tofacitinib 3, 5, 10, 15 mg twice daily or 20 mg once daily doses.

Figure 4: Proportion of Patients with ACR20 Response at Month 3 in Dose-Ranging Studies 1 and 2



* XELJANZ twice daily dosing in mg, except for 20 mg which is once daily dosing in mg.
PBO is placebo; ADA is adalimumab 40 mg subcutaneous injection every other week.

Study 1 was a dose-ranging monotherapy trial not designed to provide comparative effectiveness data and should not be interpreted as evidence of superiority to adalimumab.

Confirmatory Trials

Study RA-I (NCT00814307) was a 6-month monotherapy trial in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic or biologic) received tofacitinib 5 or 10 mg twice daily or placebo. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 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 rheumatoid arthritis who had an inadequate response to a nonbiologic DMARD received tofacitinib 5 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 advanced in a blinded fashion to a second predetermined treatment of tofacitinib 5 or 10 mg twice daily. At the end of Month 6, all placebo patients were advanced to their second predetermined 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 rheumatoid arthritis who had an inadequate response to MTX. Patients received tofacitinib 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. Placebo patients were advanced as in Study 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 rheumatoid arthritis who had an inadequate response to MTX received tofacitinib 5 or 10 mg twice daily or placebo added to background MTX. Placebo patients were advanced as in Study 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 rheumatoid arthritis who had an inadequate response to at least one approved TNF-blocking biologic agent received tofacitinib 5 or 10 mg twice daily or placebo added to background MTX. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of tofacitinib 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.

Clinical Response

The percentages of tofacitinib-treated patients achieving ACR20, ACR50, and ACR70 responses in Studies RA-I, IV, and V are shown in Table 7. Similar results were observed with Studies RA-II and III. In trials RA-I through V, patients treated with 5 mg twice daily tofacitinib had higher ACR20, ACR50, and ACR70 response rates versus 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 tofacitinib-treated patients were consistent at 6 and 12 months.

Table 8: Proportion of Patients with an ACR Response

	Percent of Patients					
	Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders[c]		**MTX Inadequate Responders[d]**		**TNF Blocker Inadequate Responders[e]**	
	Study I		**Study IV**		**Study V**	
N[a]	PBO 122	Tofacitinib 5 mg Twice Daily 243	PBO + MTX 160	Tofacitinib 5 mg Twice Daily + MTX 321	PBO + MTX 132	Tofacitinib 5 mg Twice Daily + MTX 133
ACR20 Month 3 Month 6	 26% NA[b]	 59% 69%	 27% 25%	 55% 50%	 24% NA	 41% 51%
ACR50 Month 3 Month 6	 12% NA	 31% 42%	 8% 9%	 29% 32%	 8% NA	 26% 37%
ACR70 Month 3 Month 6	 6% NA	 15% 22%	 3% 1%	 11% 14%	 2% NA	 14% 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 I and 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 tofacitinib 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 8).

Table 9: Proportion of Patients with DAS28-4(ESR) Less Than 2.6 with Number of Residual Active Joints

Study IV		
DAS28-4(ESR) Less Than 2.6	**Placebo + MTX** **160**	**Tofacitinib 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 joint (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 9. Similar results were observed for tofacitinib in Studies RA-I, II, III and V.

Table 10: Components of ACR Response at Month 3

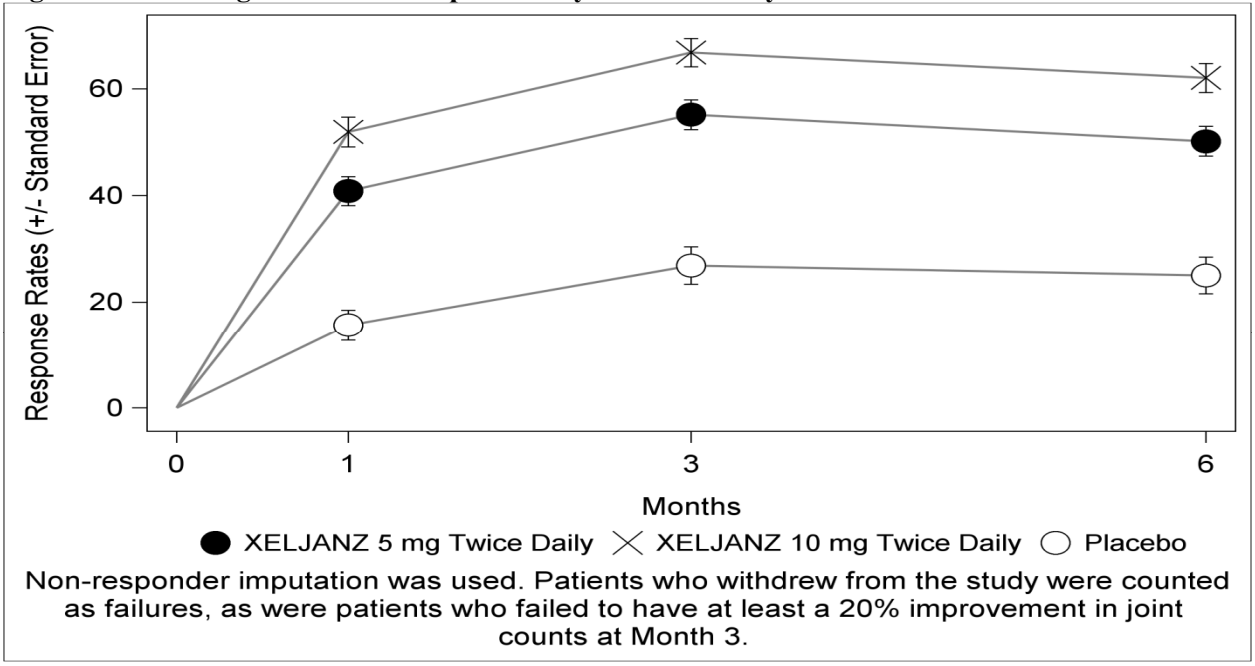
	Study IV			
	Tofacitinib **5 mg** **Twice Daily + MTX** **N=321**		**Placebo + MTX** **N=160**	
Component (mean)[a]	Baseline	Month 3[a]	Baseline	Month 3[a]
Number of tender joints (0-68)	24 (14)	13 (14)	23 (13)	18 (14)
Number of swollen joints (0-66)	14 (8)	6 (8)	14 (9)	10 (9)
Pain[b]	58 (23)	34 (23)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

CRP (mg/L)	15.3 (19.0)	7.1 (19.1)	13.7 (14.9)	14.6 (18.7)

[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 5. Similar responses were observed for tofacitinib in Studies RA-I, II, III and V.

Figure 5: Percentage of ACR20 Responders by Visit for Study RA-IV



Radiographic Response

One study was conducted to evaluate the effect of tofacitinib on structural joint damage. In Study RA-IV, 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, tofacitinib 5 mg twice daily reduced the mean progression of structural damage (not statistically significant) as shown in Table 11. 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 tofacitinib plus MTX 5 mg twice daily.

Table 11: Radiographic Changes at Months 6 and 12

	Study IV		
	Placebo N=139 Mean (SD)[a]	**Tofacitinib 5 mg Twice Daily N=277 Mean (SD)[a]**	**Tofacitinib 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)

[a] SD = Standard Deviation
[b] Difference between least squares means tofacitinib 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 receiving tofacitinib 5 mg twice daily demonstrated greater improvement from baseline in physical functioning compared to 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 receiving 5 mg tofacitinib twice daily. Similar results were obtained in Studies RA-I, II, IV and V. In the 12-month trials, HAQ-DI results in tofacitinib-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 receiving tofacitinib 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 Psoriatic Arthritis

The XELJANZ clinical development program to assess efficacy and safety included 2 multicenter, randomized, double-blind, placebo-controlled confirmatory trials in 816 patients 18 years of age and older (PsA-I and PsA-II). Although other doses have been studied, the recommended dose of XELJANZ is 5 mg twice daily. XELJANZ 10 mg twice daily is not recommended for the treatment of psoriatic arthritis [(*see section 4.2*)]. All patients had active psoriatic arthritis 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 psoriatic arthritis 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 psoriatic arthritis 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. 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 advanced in a blinded fashion to a predetermined XELJANZ dose of 5 mg or 10 mg twice daily. Study PsA-I was not designed to demonstrate noninferiority 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 advanced in a blinded fashion to a predetermined XELJANZ dose of 5 mg or 10 mg twice daily as in Study PsA-I.

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 12 and 13).

Table 12: Proportion of Patients with an ACR Response in Study PsA-I* [Nonbiologic DMARD Inadequate Responders (TNF Blocker-Naïve)]

Treatment Group	**Placebo**	**XELJANZ 5 mg Twice Daily**	
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)

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

Table 13: Proportion of Patients with an ACR Response 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)

Subjects with missing data were treated as non-responders.
[*] Subjects 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 14.

Table 14: Components of ACR Response 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

* Subjects received one concomitant nonbiologic DMARD.

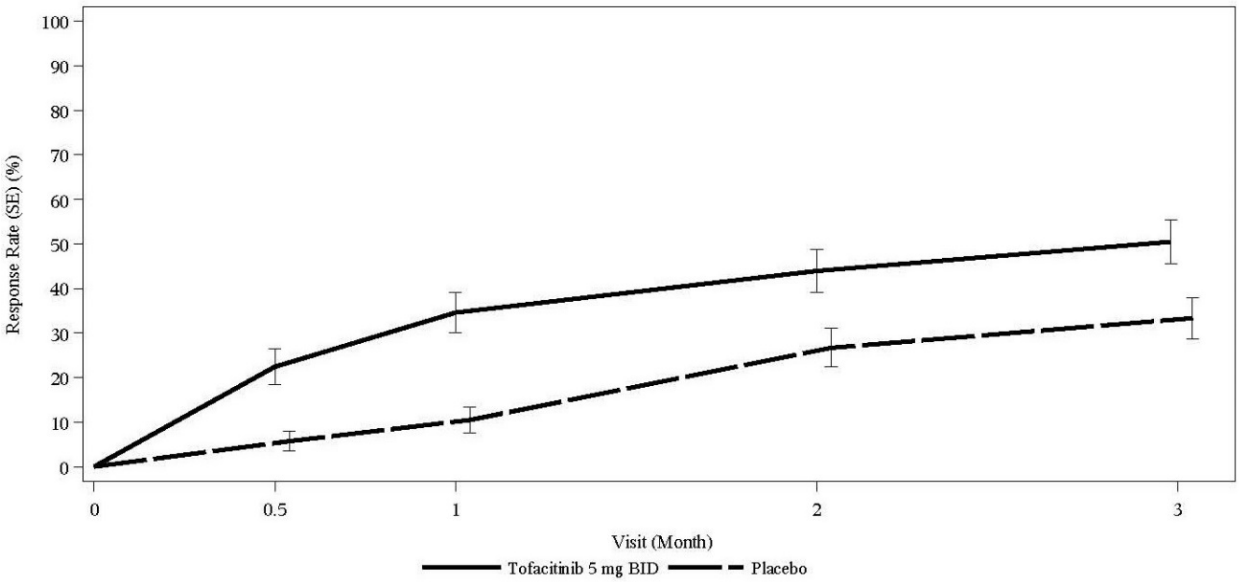
[a] Data shown are mean value at baseline and at Month 3.

[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 6. 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 6: Percentage of ACR20 Responders by Visit Through Month 3 in Study PsA-I*



BID=twice daily; SE=standard error.
Subjects with missing data were treated as non-responders.
* Subjects received one concomitant nonbiologic DMARD.

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

Physical Function

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg twice daily demonstrated significantly greater improvement ($p \leq 0.05$) from baseline in physical functioning compared to placebo at Month 3 (Table 15).

Table 15: Change from Baseline in HAQ-DI in Studies PsA-I and PsA-II

	Least Squares Mean Change from Baseline In HAQ-DI at Month 3			
	Nonbiologic DMARD Inadequate Responders[b] (TNF Blocker-Naïve)		**TNF Blocker Inadequate Responders[c]**	
	Study PsA-I*		**Study PsA-II***	
Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	Placebo	XELJANZ 5 mg Twice Daily
N[a]	104	107	131	129
LSM Change from Baseline	-0.18	-0.35	-0.14	-0.39
Difference from Placebo (95% CI)	-	-0.17 (-0.29, -0.05)	-	-0.25 (-0.38, -0.13)

* Subjects received one concomitant nonbiologic DMARD.
[a] N is the total number of subjects in the statistical analysis.
[b] Inadequate response to at least one nonbiologic DMARD due to lack of efficacy and/or intolerability.
[c] Inadequate response to at least one TNF blocker due to lack of efficacy and/or intolerability.

In Study PsA-I, the HAQ-DI responder rate (response defined as having improvement from baseline of ≥0.35) at Month 3 was 53% in patients receiving XELJANZ 5 mg twice daily and 31% in patients receiving placebo. Similar responses were observed in Study PsA-II.

Other Health-Related Outcomes
General health status was assessed by the Short Form health survey (SF-36). In Studies PsA-I and PsA-II, patients receiving XELJANZ 5 mg twice daily had greater improvement from baseline compared to placebo in Physical Component Summary (PCS) score, but not in Mental Component Summary (MCS) score at Month 3. Patients receiving XELJANZ 5 mg twice daily reported consistently greater improvement relative to placebo in the domains of Physical Functioning, Bodily Pain, Vitality, and Social Functioning, but not in Role Physical, General Health, Role Emotional, or Mental Health.

Radiographic Response
Treatment effect on inhibition of radiographic progression in psoriatic arthritis could not be established from the results of Study PsA-I.

Ulcerative Colitis
Induction Trials (Study UC-I [NCT01465763] and Study UC-II [NCT01458951])
In two identical induction trials (UC-I and UC-II), 1139 patients were randomized (598 and 541 patients, respectively) to XELJANZ 10 mg twice daily or placebo with a 4:1 treatment allocation ratio. These trials included adult patients with moderately to severely active UC (total Mayo score of 6 to 12, with an endoscopy subscore of at least 2, and rectal bleeding subscore of at least 1) and who had failed or were intolerant to at least 1 of the following treatments: oral or intravenous corticosteroids, azathioprine, 6-MP or TNF blocker. XELJANZ is indicated for patients who have an inadequate response or intolerance to one or more TNF blockers *(see section 4.1)*

The disease activity was assessed by Mayo scoring index (0 to 12) which consists of four subscores (0 to 3 for each subscore): stool frequency, rectal bleeding, findings on endoscopy, and physician global assessment. An endoscopy subscore of 2 was defined by marked erythema, absent vascular pattern, any friability, and erosions; an endoscopy subscore of 3 was defined by spontaneous bleeding and ulceration.

Patients were permitted to use stable doses of oral aminosalicylates and corticosteroids (prednisone daily dose up to 25 mg equivalent). Concomitant immunosuppressants (oral immunomodulators or biologic therapies) were not permitted for UC patients during these studies.

A total of 52%, 73% and 72% of patients had previously failed or were intolerant to TNF blockers (51% in Study UC-1 and 52% in Study UC-II), corticosteroids (75% in Study UC-I and 71% in Study UC-II), and/or immunosuppressants (74% in Study UC-I and 70% in Study UC-II), respectively.

Oral corticosteroids were received as concomitant treatment for UC by 47% of patients (45% in Study UC-I and 48% in Study UC-II) and 71% were receiving concomitant aminosalicylates as treatment for UC (71% in Study UC-I, and 72% in Study UC-II). The baseline clinical characteristics were generally similar between the XELJANZ treated patients and patients receiving placebo.

The primary endpoint of Study UC-I and Study UC-II was the proportion of patients in remission at Week 8, and the key secondary endpoint was the proportion of patients with improvement of endoscopic appearance of the mucosa at Week 8.

The efficacy results of Study UC-I and Study UC-II based on the centrally read endoscopy results are shown in Table 16.

Table 16: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 8 (Induction Study UC-I and Study UC-II, Central Endoscopy Read)

Study UC-I			
Endpoint	**Placebo**	**XELJANZ 10 mg Twice Daily**	**Treatment Difference versus Placebo (95% CI)**
Remission at Week 8[a]			
Total Population	N=122 8%	N=476 18%	10%* (4.3, 16.3)
With Prior TNF Blocker Failure[b]	N=64 2%	N=243 11%	
Without Prior TNF Blocker Failure[c]	N=58 16%	N=233 26%	
Improvement of endoscopic appearance of the mucosa at Week 8[d]			
Total Population	N=122 16%	N=476 31%	16%** (8.1, 23.4)
With Prior TNF Blocker Failure[b]	N=64 6%	N=243 23%	
Without Prior TNF Blocker Failure[c]	N=58 26%	N=233 40%	
Study UC-II			
Endpoint	**Placebo**	**XELJANZ 10 mg Twice Daily**	**Treatment Difference (95% CI)**
Remission at Week 8[a]			
Total Population	N=112 4%	N=429 17%	13%** (8.1, 17.9)
With Prior TNF Blocker Failure[b]	N=60 0%	N=222 12%	
Without Prior TNF Blocker Failure[c]	N=52 8%	N=207 22%	
Improvement of endoscopic appearance of the mucosa at Week 8[d]			
Total Population	N=112 12%	N-429 28%	17%** (9.5, 24.1)
With Prior TNF Blocker Failure[b]	N=60 7%	N=222 22%	
Without Prior TNF Blocker Failure[c]	N=52 17%	N=207 36%	

* p-value <0.01, ** p-value <0.001.
CI = Confidence interval; N = number of patients in the analysis set; TNF = tumor necrosis factor
[a] Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.
[b] Prior TNF blocker failure was defined in this program as inadequate response, loss of response, or intolerance to TNF blocker therapy.
[c] Patients in this group had failed one or more conventional therapies (corticosteroid, azathioprine, 6-mercaptopurine) but did not have history of prior failure of TNF blocker therapy.
[d] Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).

Clinical Response at Week 8
Clinical response was defined as a decrease from baseline in Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the subscore for rectal bleeding of ≥1 point or absolute subscore for rectal bleeding of 0 or 1.

Clinical response was observed in 60% of patients treated with XELJANZ 10 mg twice daily compared to 33% of placebo patients in Study UC-I and 55% compared to 29% in Study UC-II.

Normalization of the Endoscopic Appearance of the Mucosa at Week 8
Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0 and was observed in 7% of patients treated with XELJANZ 10 mg twice daily compared to 2% of placebo patients in both Studies UC-I and UC-II.

Rectal Bleeding and Stool Frequency
Decreases in rectal bleeding and stool frequency subscores were observed as early as Week 2 in patients treated with XELJANZ.

Maintenance Trial (Study UC-III [NCT01458574])
A total of 593 patients who completed the induction trials (UC-I or UC-II) and achieved clinical response were re-randomized with 1:1:1 treatment allocation ratio to XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, or placebo for 52 weeks in Study UC-III. XELJANZ 5 mg twice daily is the recommended dosage for maintenance therapy; limit use of XELJANZ 10 mg twice daily beyond induction to those with loss of response and should be used for the shortest duration *[see Dosage and Administration (2.3)]*. As in the induction trials, patients were permitted to use stable doses of oral aminosalicylates; however, corticosteroid tapering was required upon entrance into this study for patients who were receiving corticosteroids at baseline. Concomitant immunosuppressants (oral immunomodulators or biologic therapies) were not permitted.

At baseline of Study UC-III:

- 179 (30%) patients were in remission
- 289 (49%) patients were receiving oral corticosteroids
- 265 (45%), 445 (75%), and 413 (70%) patients had previously failed or were intolerant to TNF blocker therapy, corticosteroids, and immunosuppressants, respectively.

The primary endpoint was the proportion of patients in remission at Week 52. There were 2 key secondary endpoints: the proportion of patients with improvement of endoscopic appearance at Week 52, and the proportion of patients with sustained corticosteroid-free remission at both Week 24 and Week 52 among patients in remission at baseline of Study UC-III.

The efficacy results of Study UC-III based on the centrally read endoscopy results are summarized in Table 17.

Table 17: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints in Maintenance Study UC-III (Central Endoscopy Read)

				Treatment Difference versus Placebo (95% CI)	
Endpoint	**Placebo**	**XELJANZ 5 mg Twice Daily**	**XELJANZ 10 mg Twice Daily**	**XELJANZ 5 mg Twice Daily**	**XELJANZ 10 mg Twice Daily**
Remission at Week 52[a]					
Total Population	N=198 11%	N=198 34%	N=197 41%	23%* (15.3, 31.2)	30%* (21.4, 37.6)
With Prior TNF Blocker Failure[b]	N=89 11%	N=83 24%	N=93 37%		
Without Prior TNF Blocker Failure[c]	N=109 11%	N=115 42%	N=104 44%		
Improvement of endoscopic appearance of the mucosa at Week 52[d]					
Total Population	N=198 13%	N=198 37%	N=197 46%	24%* (16.0, 32.5)	33%* (24.2, 41.0)
With Prior TNF Blocker Failure[b]	N=89 12%	N=83 30%	N=93 40%		
Without Prior TNF Blocker Failure[c]	N=109 14%	N=115 43%	N=104 51%		
Sustained corticosteroid-free remission at both Week 24 and Week 52 among patients in remission at baseline[e]					
Total Population	N=59 5%	N=65 35%	N=55 47%	30%* (17.4, 43.2)	42%* (27.9, 56.5)
With Prior TNF Blocker Failure[b]	N=21 5%	N=18 22%	N=18 39%		
Without Prior TNF Blocker Failure[c]	N=38 5%	N=47 40%	N=37 51%		

* p-value <0.0001.
CI = Confidence interval; N = number of patients in the analysis set; TNF = tumor necrosis factor.
[a] Remission was defined as clinical remission (a Mayo score ≤2 with no individual subscore >1) and rectal bleeding subscore of 0.
[b] Prior TNF blocker failure was defined in this program as inadequate response, loss of response, or intolerance to TNF blocker therapy.
[c] Patients in this group had failed one or more conventional therapies (corticosteroid, azathioprine, 6-mercaptopurine) but did not have history of prior failure of TNF blocker therapy.
[d] Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).
[e] Sustained corticosteroid-free remission was defined as being in remission and not taking corticosteroids for at least 4 weeks prior to the visit at both Week 24 and Week 52.

Maintenance of Clinical Response

Maintenance of clinical response was defined as the proportion of patients who met the definition of clinical response (defined as a decrease from the induction study (UC-I, UC-II) baseline Mayo score of ≥3 points and ≥30%, with an accompanying decrease in the rectal bleeding subscore of ≥1 point or rectal bleeding subscore of 0 or 1) at both Baseline and Week 52 of Study UC-III.

Maintenance of clinical response was observed in 52% in the XELJANZ 5 mg twice daily group and 62% in the XELJANZ 10 mg twice daily group compared to 20% of placebo patients.

Maintenance of Remission (Among Patients in Remission at Baseline)
In the 179 patients who were in remission at baseline of Study UC-III (N = 59 for placebo, N = 65 for XELJANZ 5 mg twice daily, N = 55 for XELJANZ 10 mg twice daily), 46% in the XELJANZ 5 mg twice daily group and 56% in the XELJANZ 10 mg twice daily group maintained remission at Week 52 compared to 10% of placebo patients.

Normalization of the Endoscopic Appearance of the Mucosa
Normalization of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0 and was observed at Week 52 in 15% of patients in the XELJANZ 5 mg twice daily group and 17% of patients in the XELJANZ 10 mg twice daily group compared to 4% of placebo patients.

Open-label Extension Study (Study UC-IV [NCT01470612])
In Study UC-IV, 914 patients were treated of which 156 received 5 mg twice daily and 758 received 10 mg twice daily.

Of the 905 patients who were assigned to XELJANZ 10 mg twice daily in the 8-week induction studies (Study UC-I or Study UC-II), 322 patients completed the induction studies but did not achieve clinical response. Of these 322 patients, 291 continued to receive XELJANZ 10 mg twice daily (unblinded) and had available data after an additional 8 weeks in Study UC-IV. After 8 additional weeks (a total of 16 weeks treatment), 148 patients achieved clinical response, and 25 patients achieved remission (based on central endoscopy read). Among those 143 patients who achieved clinical response by 16 weeks and had available data at Week 52, 66 patients achieved remission (based on local endoscopy read) after continued treatment with XELJANZ 10 mg twice daily for 52 weeks.

8. NON-CLINICAL TOXICOLOGY

8.1 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 (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 (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 (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 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 (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 (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 (on an AUC basis at oral doses of 100 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration.

9. PHARMACEUTICAL PARTICULARS

9.1 List of excipients

Microcrystalline cellulose
Lactose monohydrate
Croscarmellose sodium
Magnesium stearate

Film Coat for 5 mg tablets: Opadry® II White (33G28523) containing:

HPMC 2910/Hypromellose 6cP
Titanium dioxide
Lactose monohydrate
Macrogol/PEG3350
Triacetin (glycerol triacetate)

9.2 Incompatibilities

Not applicable

9.3 Shelf-life

Observe “Expiry date” (month/year) imprinted on outer carton.

9.4 Special precautions for storage

Store below 30°C.

9.5 Nature and contents of container

Foil/foil blisters containing 14 and 56 film-coated tablets.
Some product strengths or pack sizes may not be available in your country.

9.6 Special precautions for disposal and other handling

No special requirements.

10. MANUFACTURER

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