

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XELJANZ/XELJANZ XR safely and effectively. See full prescribing information for XELJANZ.

XELJANZ® (tofacitinib) tablets, for oral use

XELJANZ® XR (tofacitinib) extended release tablets, for oral use

Initial U.S. Approval: 2012

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ. (5.1)
- If a serious infection develops, interrupt XELJANZ/XELJANZ XR until the infection is controlled. (5.1)
- Prior to starting XELJANZ/XELJANZ XR, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ/XELJANZ XR. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)
- 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. (5.2)

RECENT MAJOR CHANGES

Indications and Usage, Psoriatic Arthritis (1.2)	12/2017
Dosage and Administration, Dosage in Psoriatic Arthritis (2.2)	12/2017
Warnings and Precautions, Serious Infections (5.1)	12/2017
Warnings and Precautions, Malignancy and Lymphoproliferative Disorders (5.2)	12/2017
Warnings and Precautions, Gastrointestinal Perforations (5.3)	12/2017
Warnings and Precautions, Vaccinations (5.5)	8/2017

INDICATIONS AND USAGE

- XELJANZ/XELJANZ XR is an inhibitor of Janus kinases (JAKs) indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). (1.1)
- XELJANZ/XELJANZ XR is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs). (1.2)
- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended. (1.1, 1.2)

DOSAGE AND ADMINISTRATION

Rheumatoid Arthritis

- Recommended dose of XELJANZ is 5 mg twice daily. (2.1)
- Recommended dose of XELJANZ XR is 11 mg once daily. (2.1)
- Recommended dose in patients with moderate and severe renal impairment and moderate hepatic impairment is XELJANZ 5 mg once daily. (2.5, 8.7, 8.8)
- Use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended. (2.5, 8.7)

Psoriatic Arthritis

- Recommended dose of XELJANZ is 5 mg twice daily, used in combination with nonbiologic DMARDs. (2.2)
- Recommended dose of XELJANZ XR is 11 mg once daily, used in combination with nonbiologic DMARDs. (2.2)
- Recommended dose in patients with moderate and severe renal impairment and moderate hepatic impairment is XELJANZ 5 mg once daily. (2.5, 8.7, 8.8)
- Use of XELJANZ/ XELJANZ XR in patients with severe hepatic impairment is not recommended. (2.5, 8.7)

DOSAGE FORMS AND STRENGTHS

XELJANZ Tablets: 5 mg (3)

XELJANZ XR Tablets: 11 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Avoid use of XELJANZ/XELJANZ XR during an active serious infection, including localized infections. (5.1)
- Gastrointestinal Perforations – Use with caution in patients that may be at increased risk. (5.3)
- Laboratory Monitoring – Recommended due to potential changes in lymphocytes, neutrophils, hemoglobin, liver enzymes and lipids. (5.4)
- Immunizations – Live vaccines: Avoid use with XELJANZ/XELJANZ XR. (5.5)

ADVERSE REACTIONS

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials (occurring in greater than or equal to 2% of patients treated with XELJANZ monotherapy or in combination with DMARDs) were upper respiratory tract infections, headache, diarrhea and nasopharyngitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer, Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., ketoconazole):
 - Recommended dose is XELJANZ 5 mg once daily. (2.4, 7.1)
- One or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole):
 - Recommended dose is XELJANZ 5 mg once daily. (2.4, 7.2)
- Potent CYP inducers (e.g., rifampin): May result in loss of or reduced clinical response. (2.4, 7.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2017

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

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FULL PRESCRIBING INFORMATION

WARNING: SERIOUS INFECTIONS AND MALIGNANCY

SERIOUS INFECTIONS

Patients treated with XELJANZ/XELJANZ XR are at increased risk for developing serious infections that may lead to hospitalization or death [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)*]. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ/XELJANZ XR 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/XELJANZ XR use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ/XELJANZ XR 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/XELJANZ XR 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/XELJANZ XR, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy [see *Warnings and Precautions (5.1)*].

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 *Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis

- XELJANZ/XELJANZ XR (tofacitinib) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs).
- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

1.2 Psoriatic Arthritis

- XELJANZ/XELJANZ XR (tofacitinib) is indicated for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other disease-modifying antirheumatic drugs (DMARDs).
- Limitations of Use: Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

2 DOSAGE AND ADMINISTRATION

- The recommended dose of XELJANZ is 5 mg twice daily and the recommended dose of XELJANZ XR is 11 mg once daily.
- XELJANZ/XELJANZ XR is given orally with or without food.
- Swallow XELJANZ XR tablets whole and intact. Do not crush, split, or chew.

Switching from XELJANZ Tablets to XELJANZ XR Tablets

Patients treated with XELJANZ 5 mg twice daily may be switched to XELJANZ XR 11 mg once daily the day following the last dose of XELJANZ 5 mg.

2.1 Dosage in Rheumatoid Arthritis

- XELJANZ/XELJANZ XR may be used as monotherapy or in combination with methotrexate or other nonbiologic disease-modifying antirheumatic drugs (DMARDs). The recommended dose of XELJANZ is 5 mg twice daily and the recommended dose of XELJANZ XR is 11 mg once daily.

2.2 Dosage in Psoriatic Arthritis

The recommended dose of XELJANZ is 5 mg twice daily, used in combination with nonbiologic DMARDs.

The recommended dose of XELJANZ XR is 11 mg once daily used in combination with nonbiologic DMARDs.

The efficacy of XELJANZ/XELJANZ XR as a monotherapy has not been studied in psoriatic arthritis.

2.3 Dosage Modifications due to Serious Infections and Cytopenias

(see [Tables 1, 2, and 3](#) below)

- It is recommended that XELJANZ/XELJANZ XR not be initiated in patients with an absolute lymphocyte count less than 500 cells/mm³, an absolute neutrophil count (ANC) less than 1000 cells/mm³ or who have hemoglobin levels less than 9 g/dL.
- Dose interruption is recommended for management of lymphopenia, neutropenia and anemia [see [Warnings and Precautions \(5.4\)](#) and [Adverse Reactions \(6.1\)](#)].
- Avoid use of XELJANZ/XELJANZ XR if a patient develops a serious infection until the infection is controlled.

2.4 Dosage Modifications due to Drug Interactions

- In patients receiving:
 - potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g., ketoconazole), or
 - one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole),the recommended dose is XELJANZ 5 mg once daily.
- Coadministration of potent inducers of CYP3A4 (e.g., rifampin) with XELJANZ/XELJANZ XR may result in loss of or reduced clinical response to XELJANZ/XELJANZ XR.
- Coadministration of potent inducers of CYP3A4 with XELJANZ/XELJANZ XR is not recommended.

2.5 Dosage Modifications in Patients with Renal or Hepatic Impairment

- In patients with:
 - moderate or severe renal insufficiency, or
 - moderate hepatic impairment,the recommended dose is XELJANZ 5 mg once daily.
- Use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended.

Table 1: Dose Adjustments for Lymphopenia

Low Lymphocyte Count [see Warnings and Precautions (5.4)]	
Lab Value (cells/mm ³)	Recommendation
Lymphocyte count greater than or equal to 500	Maintain dose
Lymphocyte count less than 500 (Confirmed by repeat testing)	Discontinue XELJANZ/XELJANZ XR

Table 2: Dose Adjustments for Neutropenia

Low ANC [see Warnings and Precautions (5.4)]	
Lab Value (cells/mm ³)	Recommendation
ANC greater than 1000	Maintain dose

Low ANC [see *Warnings and Precautions (5.4)*]

Lab Value (cells/mm ³)	Recommendation
ANC 500–1000	For persistent decreases in this range, interrupt dosing until ANC is greater than 1000 <ul style="list-style-type: none"> When ANC is greater than 1000, resume XELJANZ 5 mg twice daily/XELJANZ XR 11 mg once daily
ANC less than 500 (Confirmed by repeat testing)	Discontinue XELJANZ/XELJANZ XR

Table 3: Dose Adjustments for Anemia

Low Hemoglobin Value [see <i>Warnings and Precautions (5.4)</i>]	
Lab Value (g/dL)	Recommendation
Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Maintain dose
Greater than 2 g/dL decrease or less than 8.0 g/dL (Confirmed by repeat testing)	Interrupt the administration of XELJANZ/XELJANZ XR until hemoglobin values have normalized

3 DOSAGE FORMS AND STRENGTHS

XELJANZ is provided as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) tablets: White, round, immediate-release film-coated tablets, debossed with "Pfizer" on one side, and "JKI 5" on the other side.

XELJANZ XR is provided as 11 mg tofacitinib (equivalent to 17.77 mg tofacitinib citrate) tablets: Pink, oval, extended release film-coated tablets with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS**5.1 Serious Infections**

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcosis, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infection, and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localized disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids.

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

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

- with chronic or recurrent infection
- who have been exposed to tuberculosis
- with a history of a serious or an opportunistic infection

- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR. XELJANZ/XELJANZ XR 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/XELJANZ XR 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.

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

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Discontinuation and monitoring criteria for lymphopenia are discussed in Dosage Modifications due to Serious Infections and Cytopenias [see *Dosage and Administration (2.2)*].

Tuberculosis

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

Anti-tuberculosis therapy should also be considered prior to administration of XELJANZ/XELJANZ XR 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 physician with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating anti-tuberculosis 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.

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

Viral Reactivation

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were observed in clinical studies with XELJANZ. The impact of XELJANZ/XELJANZ XR 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/XELJANZ XR. The risk of herpes zoster is increased in patients treated with XELJANZ/XELJANZ XR and appears to be higher in patients treated with XELJANZ in Japan and Korea.

5.2 Malignancy and Lymphoproliferative Disorders

Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy. Malignancies were observed in clinical studies of XELJANZ [see *Adverse Reactions (6.1)*].

In the seven controlled rheumatoid arthritis clinical studies, 11 solid cancers and one lymphoma were diagnosed in 3328 patients receiving XELJANZ with or without DMARD, compared to 0 solid cancers and 0 lymphomas in 809 patients in the placebo with or without DMARD group during the first 12 months of exposure. Lymphomas and solid cancers have also been observed in the long-term extension studies in rheumatoid arthritis patients treated with XELJANZ.

In the 2 controlled Phase 3 clinical trials in patients with active psoriatic arthritis, 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.

In Phase 2B, controlled dose-ranging trials in *de-novo* renal transplant patients, all of whom received induction therapy with basiliximab, high-dose corticosteroids, and mycophenolic acid products, Epstein Barr Virus-associated post-transplant lymphoproliferative disorder was observed in 5 out of 218 patients treated with XELJANZ (2.3%) compared to 0 out of 111 patients treated with cyclosporine.

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.

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.

5.3 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical studies with XELJANZ, although the role of JAK inhibition in these events is not known.

XELJANZ/XELJANZ XR 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 [see *Adverse Reactions (6.1)*].

5.4 Laboratory Abnormalities

Lymphocyte Abnormalities

Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean absolute lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts less than 500 cells/mm³ were associated with an increased incidence of treated and serious infections.

Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm³). In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm³, treatment with XELJANZ/XELJANZ XR is not recommended.

Monitor lymphocyte counts at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts [see *Dosage and Administration (2.3)*].

Neutropenia

Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2000 cells/mm³) compared to placebo.

Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a low neutrophil count (i.e., ANC less than 1000 cells/mm³). For patients who develop a persistent ANC of 500–1000 cells/mm³, interrupt XELJANZ/XELJANZ XR dosing until ANC is greater than or equal to 1000 cells/mm³. In patients who develop an ANC less than 500 cells/mm³, treatment with XELJANZ/XELJANZ XR is not recommended.

Monitor neutrophil counts at baseline and after 4–8 weeks of treatment and every 3 months thereafter. For recommended modifications based on ANC results [see *Dosage and Administration (2.3)*].

Anemia

Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a low hemoglobin level (i.e. less than 9 g/dL).

Treatment with XELJANZ/XELJANZ XR should be interrupted in patients who develop hemoglobin levels less than 8 g/dL or whose hemoglobin level drops greater than 2 g/dL on treatment.

Monitor hemoglobin at baseline and after 4–8 weeks of treatment and every 3 months thereafter. For recommended modifications based on hemoglobin results [see *Dosage and Administration (2.3)*].

Liver Enzyme Elevations

Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation compared to placebo. Most of these abnormalities occurred in studies with background DMARD (primarily methotrexate) therapy.

Routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded.

Lipid Elevations

Treatment with XELJANZ was associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Assessment of lipid parameters should be performed approximately 4–8 weeks following initiation of XELJANZ/XELJANZ XR therapy.

Manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

5.5 Vaccinations

Avoid use of live vaccines concurrently with XELJANZ/XELJANZ XR. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

A patient experienced dissemination of the vaccine strain of varicella zoster virus, 16 days after vaccination with live attenuated (Zostavax) virus vaccine and 2 days after treatment start with tofacitinib 5 mg twice daily. The patient was varicella virus naïve, as evidenced by no previous history of varicella infection and no anti-varicella antibodies at baseline. Tofacitinib was discontinued and the patient recovered after treatment with standard doses of antiviral medication.

Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ/XELJANZ XR therapy.

5.6 General

Specific to XELJANZ XR

As with any other non-deformable material, caution should be used when administering XELJANZ XR to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other drugs utilizing a non-deformable extended release formulation.

6 ADVERSE REACTIONS

6.1 Clinical Trial 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 recommended dose for XELJANZ XR is 11 mg once 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 Warnings and Precautions (5.1)*].

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.

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).

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 *Warnings and Precautions (5.1)*].

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 *Warnings and Precautions (5.1)*].

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 *Warnings and Precautions (5.1)*].

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 *Warnings and Precautions (5.2)*].

Laboratory Abnormalities

Lymphopenia

In the controlled clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm³ 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/mm³ were associated with an increased incidence of treated and serious infections [see *Warnings and Precautions (5.4)*].

Neutropenia

In the controlled clinical trials, confirmed decreases in ANC below 1000 cells/mm³ 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/mm³ 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 *Warnings and Precautions (5.4)*].

Liver Enzyme Elevations

Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3× 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 3× 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 3× 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 3× ULN and bilirubin elevations greater than 2× ULN, which required hospitalizations and a liver biopsy.

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: Adverse Reactions Occurring in at Least 2% or More of Patients on 5 or 10 mg Twice Daily XELJANZ With or Without DMARD (0–3 months) and at Least 1% Greater Than That Observed in Rheumatoid Arthritis Patients on Placebo

	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg Twice Daily*	Placebo
Preferred Term	N = 1336 (%)	N = 1349 (%)	N = 809 (%)
Diarrhea	4.0	2.9	2.3
Nasopharyngitis	3.8	2.8	2.8
Upper respiratory tract infection	4.5	3.8	3.3
Headache	4.3	3.4	2.1
Hypertension	1.6	2.3	1.1

N reflects randomized and treated patients from the seven clinical trials

* The recommended dose of XELJANZ is 5 mg twice daily.

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 (some 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

Clinical Experience in Methotrexate-Naïve Patients

Study VI was an active-controlled clinical trial in methotrexate-naïve patients [see *Clinical Studies (14)*]. The safety experience in these patients was consistent with Studies I–V.

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).

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-inhibitor (TNFi). 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 TNFi. 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 psoriatic arthritis treated with XELJANZ was consistent with the safety profile observed in rheumatoid arthritis patients.

7 DRUG INTERACTIONS

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

7.1 Potent CYP3A4 Inhibitors

Tofacitinib exposure is increased when XELJANZ is coadministered with potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) [see *Dosage and Administration (2.4)* and *Figure 3*].

7.2 Moderate CYP3A4 and Potent CYP2C19 Inhibitors

Tofacitinib exposure is increased when XELJANZ is coadministered with medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole) [see *Dosage and Administration (2.4)* and *Figure 3*].

7.3 Potent CYP3A4 Inducers

Tofacitinib exposure is decreased when XELJANZ is coadministered with potent CYP3A4 inducers (e.g., rifampin) [see *Dosage and Administration (2.4)* and *Figure 3*].

7.4 Immunosuppressive Drugs

There is a risk of added immunosuppression when XELJANZ/XELJANZ XR is coadministered with potent immunosuppressive drugs (e.g., azathioprine, tacrolimus, cyclosporine). Combined use of multiple-dose XELJANZ/XELJANZ XR with potent immunosuppressants has not been studied in rheumatoid arthritis and psoriatic arthritis. Use of XELJANZ/XELJANZ XR in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

8 USE IN SPECIFIC POPULATIONS

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

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to XELJANZ/XELJANZ XR during pregnancy. Patients should be encouraged to enroll in the XELJANZ/XELJANZ XR pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call the toll free number 1-877-311-8972.

Risk Summary

There are no adequate and well-controlled studies of XELJANZ/XELJANZ XR use in pregnant women.

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

Based on animal studies, XELJANZ/XELJANZ XR has the potential to affect a developing fetus. Fetocidal and teratogenic effects were noted when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 146 times and 13 times the human dose of 5 mg twice daily, respectively [see *Data*]. Further, in a peri and post-natal study in rats, tofacitinib resulted in reductions in live litter size, postnatal survival, and pup body weights at exposure multiples of approximately 73 times the human dose of 5 mg twice daily.

Data

Human Data

In the tofacitinib clinical development programs, birth defects and miscarriages were reported.

Animal Data

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

In a rabbit embryofetal developmental study in which pregnant rabbits received tofacitinib during the period of organogenesis, tofacitinib was teratogenic at exposure levels approximately 13 times the human dose of 5 mg twice daily (on an AUC basis at oral doses of 30 mg/kg/day in rabbits) in the absence of signs of maternal toxicity. Teratogenic effects included thoracogastroschisis, 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 human dose of 5 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in pregnant rabbits).

In a peri- and postnatal development study in pregnant rats 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 human dose of 5 mg twice daily (on an AUC basis at oral doses of 50 mg/kg/day in rats). There was no effect on behavioral and learning assessments, sexual maturation or the ability of the F1 generation rats to mate and produce viable F2 generation fetuses in rats at exposure levels approximately 17 times the human dose of 5 mg twice daily (on an AUC basis at oral doses of 10 mg/kg/day in rats).

8.2 Lactation

Risk Summary

It is not known whether tofacitinib is excreted in human milk. Additionally, there are no data to assess the effects of the drug on the breastfed child. However, tofacitinib is excreted in rat milk at concentrations higher than in maternal serum [see [Data](#)]. Women should not breastfeed while treated with XELJANZ/XELJANZ XR. A decision should be made whether to discontinue breastfeeding or to discontinue XELJANZ/XELJANZ XR.

Data

Human Data

There are no adequate and well-controlled studies of XELJANZ/XELJANZ XR use during breastfeeding.

Animal Data

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

8.3 Females and Males of Reproductive Potential

Contraception

Females

Embryofetal toxicity including malformations occurred in embryofetal development studies in rats and rabbits [see [Use in Specific Populations \(8.1\)](#)].

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

Infertility

Females

Based on findings in rats, treatment with XELJANZ/XELJANZ XR may result in reduced fertility in females of reproductive potential [see [Nonclinical Toxicology \(13.1\)](#)].

8.4 Pediatric Use

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

8.5 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 XELJANZ-treated subjects 65 years of age and older was higher than among those under the age of 65.

As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

8.6 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.

8.7 Hepatic Impairment

XELJANZ-treated patients with moderate hepatic impairment had greater tofacitinib levels than XELJANZ-treated patients with normal hepatic function [see *Clinical Pharmacology (12.3)*]. Higher blood levels may increase the risk of some adverse reactions, therefore, the recommended dose is XELJANZ 5 mg once daily in patients with moderate hepatic impairment [see *Dosage and Administration (2.5)*]. XELJANZ/XELJANZ XR has not been studied in patients with severe hepatic impairment; therefore, use of XELJANZ/XELJANZ XR in patients with severe hepatic impairment is not recommended. No dose adjustment is required in patients with mild hepatic impairment. The safety and efficacy of XELJANZ/XELJANZ XR have not been studied in patients with positive hepatitis B virus or hepatitis C virus serology.

8.8 Renal Impairment

XELJANZ-treated patients with moderate and severe renal impairment had greater tofacitinib blood levels than XELJANZ-treated patients with normal renal function; therefore, the recommended dose is XELJANZ 5 mg once daily in patients with moderate and severe renal impairment [see *Dosage and Administration (2.5)*]. In clinical trials, XELJANZ/XELJANZ XR was not evaluated in rheumatoid arthritis patients with baseline creatinine clearance values (estimated by the Cockcroft-Gault equation) less than 40 mL/min (or in patients with active psoriatic arthritis with creatinine clearance values less than 50 mL/min). No dose adjustment is required in patients with mild renal impairment.

10 OVERDOSAGE

Signs, Symptoms, and Laboratory Findings of Acute Overdosage in Humans

There is no experience with overdose of XELJANZ/XELJANZ XR.

Treatment or Management of Overdose

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

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

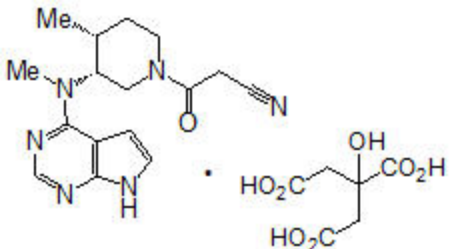
11 DESCRIPTION

XELJANZ/XELJANZ XR are formulated with the citrate salt of tofacitinib, a JAK inhibitor.

Tofacitinib citrate is a white to off-white powder with the following chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-β-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

The solubility of tofacitinib citrate in water is 2.9 mg/mL.

Tofacitinib citrate has a molecular weight of 504.5 Daltons (or 312.4 Daltons as the tofacitinib free base) and a molecular formula of C₁₆H₂₀N₆O·C₆H₈O₇. The chemical structure of tofacitinib citrate is:



XELJANZ is supplied for oral administration as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) white round, immediate-release film-coated tablet. Each tablet of XELJANZ contains the appropriate amount of tofacitinib as a citrate salt and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, HPMC 2910/Hypromellose 6cP, titanium dioxide, macrogol/PEG3350, and triacetin.

XELJANZ XR is supplied for oral administration as 11 mg tofacitinib (equivalent to 17.77 mg tofacitinib citrate) pink, oval, extended release film-coated tablet with a drilled hole at one end of the tablet band. Each tablet of XELJANZ XR contains the appropriate amount of tofacitinib as a citrate salt and the following inactive ingredients: sorbitol, hydroxyethyl cellulose, copovidone, magnesium stearate, cellulose acetate, hydroxypropyl cellulose, HPMC 2910/Hypromellose, titanium dioxide, triacetin, and red iron oxide. Printing ink contains shellac glaze, ammonium hydroxide, propylene glycol, and ferrous ferric oxide/black iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tofacitinib is a Janus kinase (JAK) inhibitor. JAKs are intracellular enzymes which transmit signals arising from cytokine or growth factor-receptor interactions on the cellular membrane to influence cellular processes of hematopoiesis and immune cell function. Within the signaling pathway, JAKs phosphorylate and activate Signal Transducers and Activators of Transcription (STATs) which modulate intracellular activity including gene expression. Tofacitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). Tofacitinib inhibited the *in vitro* activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC₅₀ of 406, 56, and 1377 nM, respectively. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known.

12.2 Pharmacodynamics

Treatment with XELJANZ was associated with dose-dependent reductions of circulating CD16/56+ natural killer cells, with estimated maximum reductions occurring at approximately 8–10 weeks after initiation of therapy. These changes generally resolved within 2–6 weeks after discontinuation of treatment. Treatment with XELJANZ 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 XELJANZ in patients with rheumatoid arthritis, rapid decreases in serum C-reactive protein (CRP) were observed and maintained throughout dosing. Changes in CRP observed with XELJANZ treatment do not reverse fully within 2 weeks after discontinuation, indicating a longer duration of pharmacodynamic activity compared to the pharmacokinetic half-life.

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

12.3 Pharmacokinetics

XELJANZ

Following oral administration of XELJANZ, peak plasma concentrations are reached within 0.5–1 hour, elimination half-life is ~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.

XELJANZ XR

Following oral administration of XELJANZ XR, peak plasma concentrations are reached at 4 hours and half-life is ~6 hours. Steady state concentrations are achieved within 48 hours with negligible accumulation after once daily administration. AUC and C_{\max} of tofacitinib for XELJANZ XR 11 mg administered once daily are equivalent to those of XELJANZ 5 mg administered twice daily.

Absorption

XELJANZ

The absolute oral bioavailability of XELJANZ is 74%. Coadministration of XELJANZ with a high-fat meal resulted in no changes in AUC while C_{\max} was reduced by 32%. In clinical trials, XELJANZ was administered without regard to meals.

XELJANZ XR

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

Distribution

After intravenous administration, the volume of distribution is 87 L. The protein binding of tofacitinib is ~40%. Tofacitinib binds predominantly to albumin and does not appear to bind to α 1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

Metabolism and Elimination

Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged tofacitinib, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of tofacitinib is attributed to the parent molecule.

Pharmacokinetics in Rheumatoid Arthritis Patients

Population PK analysis in rheumatoid arthritis patients 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 between-subject variability (% coefficient of variation) in AUC of tofacitinib is estimated to be approximately 27%.

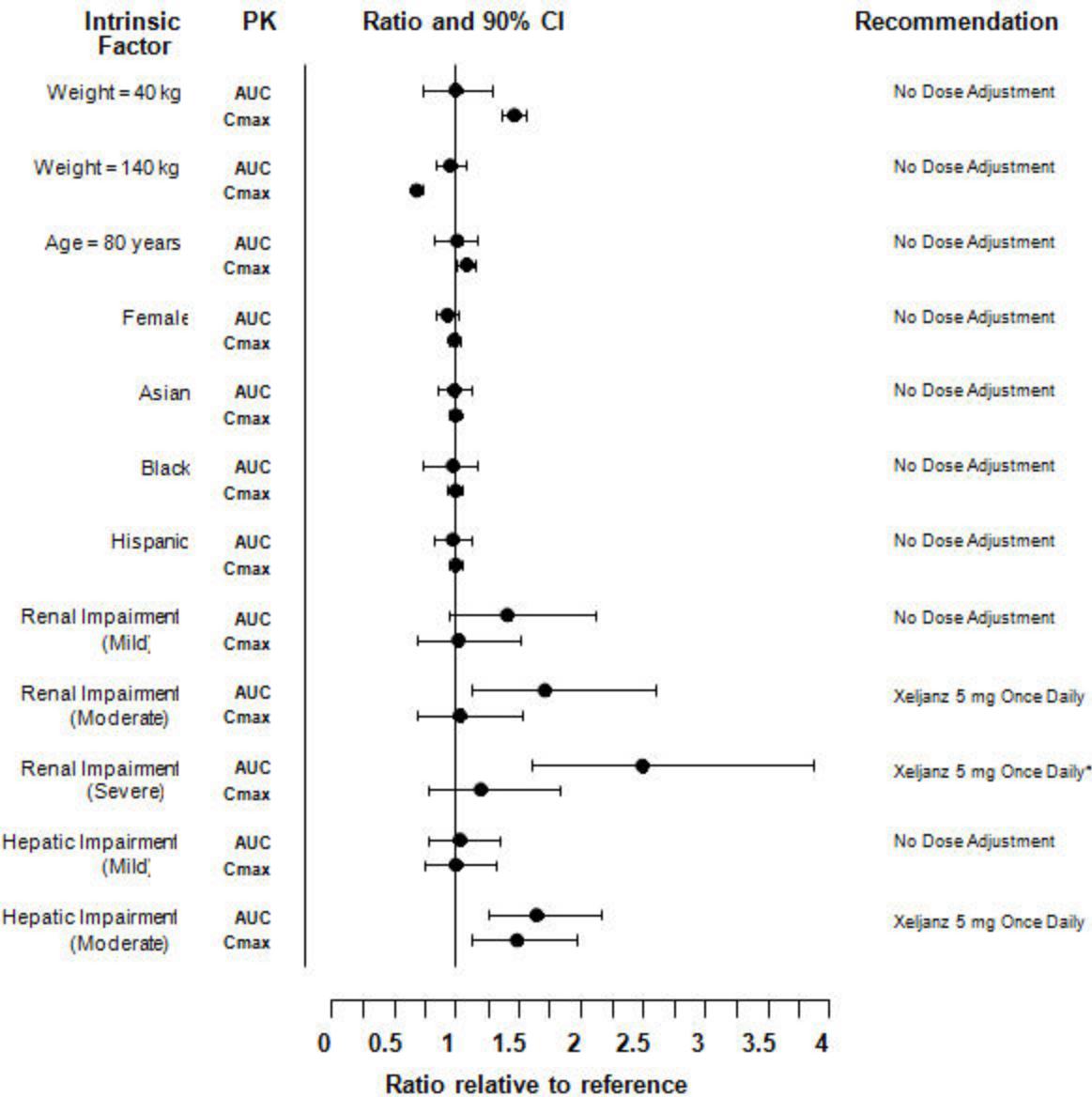
Pharmacokinetics in Patients with Active Psoriatic Arthritis

Results from population PK analysis in patients with active psoriatic arthritis were consistent with those in patients with rheumatoid arthritis.

Specific Populations

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



* Supplemental doses are not necessary in patients after dialysis. 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.

Drug Interactions

Potential for XELJANZ/XELJANZ XR 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 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 PK of midazolam, a highly sensitive CYP3A4 substrate, when coadministered with XELJANZ.

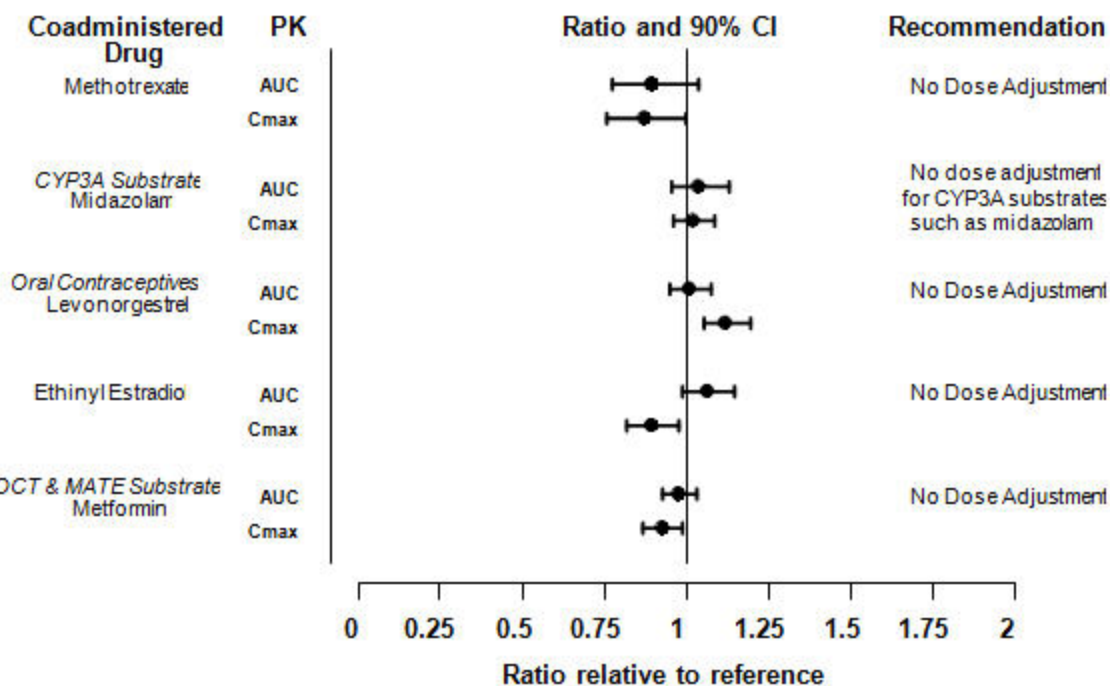
In vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug-metabolizing uridine 5'-diphospho-glucuronosyltransferases (UGTs) [UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7] at concentrations exceeding 250 times the steady state C_{max} of a 5 mg twice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

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, coadministration with XELJANZ/XELJANZ XR 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 coadministered drugs following administration with XELJANZ/XELJANZ XR are shown in Figure 2.

Figure 2. Impact of Tofacitinib on PK of Other Drugs

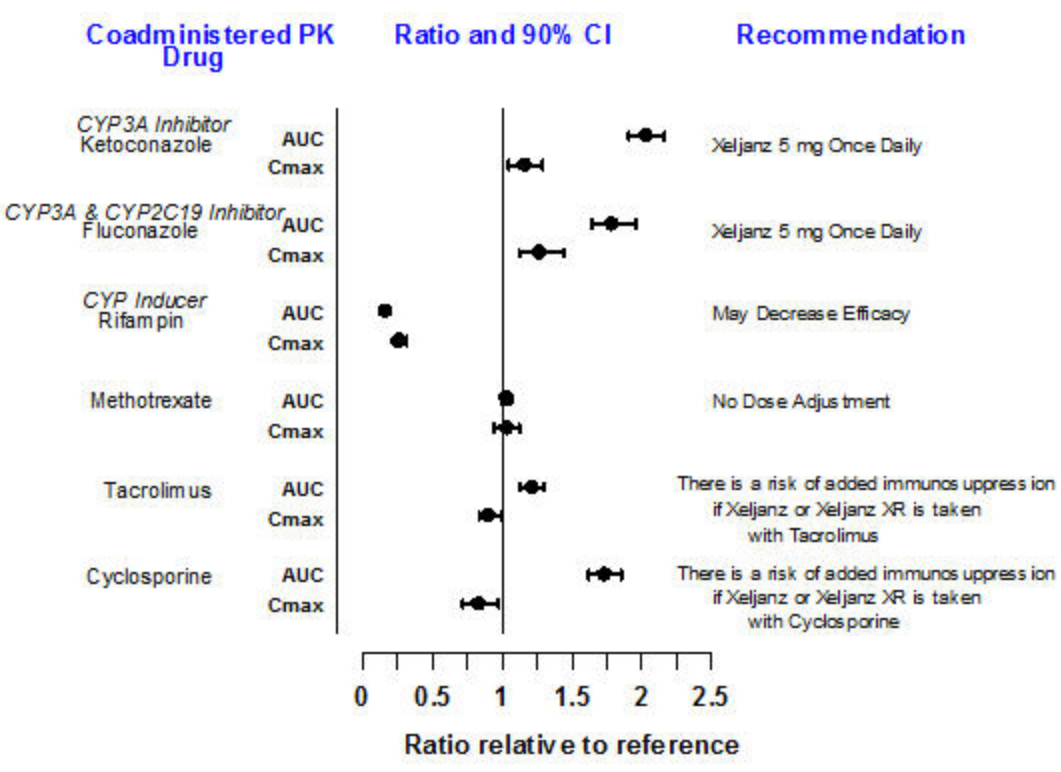


Note: Reference group is administration of concomitant medication alone; OCT = Organic Cationic Transporter; MATE = Multidrug and Toxic Compound Extrusion

Potential for Other Drugs to Influence the PK 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 PK of tofacitinib. Dosing recommendations for XELJANZ/XELJANZ XR for administration with CYP inhibitors or inducers are shown in Figure 3.

Figure 3. Impact of Other Drugs on PK of Tofacitinib



Note: Reference group is administration of tofacitinib alone

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 39-week toxicology study in monkeys, tofacitinib at exposure levels approximately 6 times the human dose (on an AUC basis at oral doses of 5 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1 times the human dose (on an AUC basis at oral doses of 1 mg/kg twice daily).

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib, at exposure levels approximately 34 times the human dose (on an AUC basis at oral doses of 200 mg/kg/day) was not carcinogenic in mice.

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

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

In rats, tofacitinib at exposure levels approximately 17 times the human dose (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the human dose (on an AUC basis at oral doses of 1 mg/kg/day). Tofacitinib exposure levels at approximately 133 times the human dose (on an AUC basis at oral doses of 100 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The XELJANZ clinical development program included two dose-ranging trials and five confirmatory trials. Although other doses have been studied, the recommended dose of XELJANZ is 5 mg twice daily.

Dose-Ranging Trials

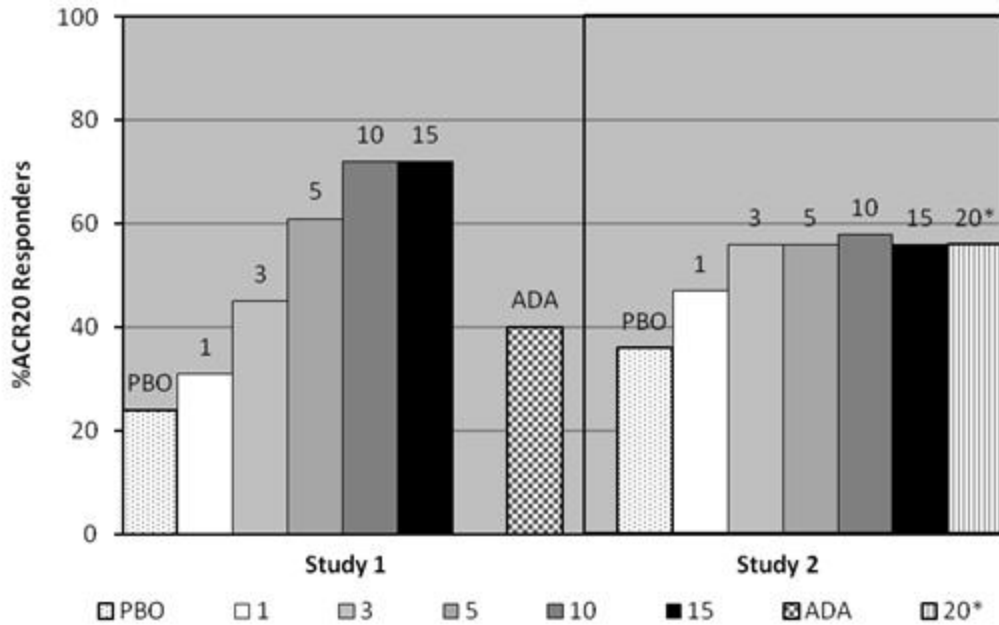
Dose selection for XELJANZ was based on two pivotal dose-ranging trials.

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: XELJANZ 1, 3, 5, 10 or 15 mg twice daily, adalimumab 40 mg subcutaneously every other week for 10 weeks followed by XELJANZ 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 XELJANZ (20 mg once daily; 1, 3, 5, 10 or 15 mg twice daily), or placebo added to background MTX.

The results of XELJANZ-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 XELJANZ 1 mg groups compared to patients treated with the other XELJANZ doses. However, there was no difference in the proportion of responders among patients treated with XELJANZ 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 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 XELJANZ 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 XELJANZ 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 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 XELJANZ 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 XELJANZ 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 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 XELJANZ 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 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 XELJANZ 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 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-inhibiting biologic agent received XELJANZ 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 XELJANZ 5 or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, HAQ-DI, and DAS28-4(ESR) less than 2.6.

Study VI (NCT01039688) was a 2-year monotherapy trial with a planned analysis at 1 year in which 952 MTX-naïve patients with moderate to severe active rheumatoid arthritis received XELJANZ 5 or 10 mg twice daily or MTX dose-titrated over 8

weeks to 20 mg. The primary end points were mean change from baseline in van der Heijde-modified Total Sharp Score (mTSS) at Month 6 and the proportion of patients who achieved an ACR70 response at Month 6.

Clinical Response

The percentages of XELJANZ-treated patients achieving ACR20, ACR50, and ACR70 responses in Studies I, IV, and V are shown in Table 5. Similar results were observed with Studies II and III. In trials I–V, patients treated with either 5 or 10 mg twice daily XELJANZ 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 XELJANZ-treated patients were consistent at 6 and 12 months.

Table 5: Proportion of Patients with an ACR Response

	Percent of Patients								
	Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders*			MTX Inadequate Responders†			TNF Inhibitor Inadequate Responders‡		
	Study I			Study IV			Study V		
N§	PBO	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg Twice Daily¶	PBO + MTX	XELJANZ 5 mg Twice Daily + MTX¶	XELJANZ 10 mg Twice Daily + MTX¶	PBO + MTX	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX¶
	122	243	245	160	321	316	132	133	134
ACR20									
Month 3	26%	59%	65%	27%	55%	67%	24%	41%	48%
Month 6	NA#	69%	70%	25%	50%	62%	NA	51%	54%
ACR50									
Month 3	12%	31%	36%	8%	29%	37%	8%	26%	28%
Month 6	NA	42%	46%	9%	32%	44%	NA	37%	30%
ACR70									
Month 3	6%	15%	20%	3%	11%	17%	2%	14%	10%
Month 6	NA	22%	29%	1%	14%	23%	NA	16%	16%

* Inadequate response to at least one DMARD (biologic or nonbiologic) due to lack of efficacy or toxicity.

† Inadequate response to MTX defined as the presence of sufficient residual disease activity to meet the entry criteria.

‡ Inadequate response to a least one TNF inhibitor due to lack of efficacy and/or intolerance.

§ N is number of randomized and treated patients.

¶ The recommended dose of XELJANZ is 5 mg twice daily.

NA Not applicable, as data for placebo treatment is not available beyond 3 months in Studies I and V due to placebo advancement.

In Study IV, a greater proportion of patients treated with XELJANZ 5 mg or 10 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 6).

Table 6: 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	XELJANZ 5 mg Twice Daily + MTX	XELJANZ 10 mg Twice Daily + MTX*
	160	321	316
Proportion of responders at Month 6 (n)	1% (2)	6% (19)	13% (42)

*

Study IV			
DAS28-4(ESR) Less Than 2.6	Placebo + MTX 160	XELJANZ 5 mg Twice Daily + MTX 321	XELJANZ 10 mg Twice Daily + MTX 316
Of responders, proportion with 0 active joints (n)	50% (1)	42% (8)	36% (15)
Of responders, proportion with 1 active joint (n)	0	5% (1)	17% (7)
Of responders, proportion with 2 active joints (n)	0	32% (6)	7% (3)
Of responders, proportion with 3 or more active joints (n)	50% (1)	21% (4)	40% (17)

* The recommended dose of XELJANZ is 5 mg twice daily.

The results of the components of the ACR response criteria for Study IV are shown in Table 7. Similar results were observed for XELJANZ in Studies I, II, III, V, and VI.

Table 7: Components of ACR Response at Month 3

	Study IV					
	XELJANZ 5 mg Twice Daily + MTX N=321		XELJANZ 10 mg* Twice Daily + MTX N=316		Placebo + MTX N=160	
	Baseline	Month 3[†]	Baseline	Month 3[†]	Baseline	Month 3[†]
Component (mean)[†]						
Number of tender joints (0–68)	24 (14)	13 (14)	23 (15)	10 (12)	23 (13)	18 (14)
Number of swollen joints (0–66)	14 (8)	6 (8)	14 (8)	6 (7)	14 (9)	10 (9)
Pain [‡]	58 (23)	34 (23)	58 (24)	29 (22)	55 (24)	47 (24)
Patient global assessment [‡]	58 (24)	35 (23)	57 (23)	29 (20)	54 (23)	47 (24)
Disability index (HAQ-DI) [§]	1.41 (0.68)	0.99 (0.65)	1.40 (0.66)	0.84 (0.64)	1.32 (0.67)	1.19 (0.68)
Physician global assessment [‡]	59 (16)	30 (19)	58 (17)	24 (17)	56 (18)	43 (22)
CRP (mg/L)	15.3 (19.0)	7.1 (19.1)	17.1 (26.9)	4.4 (8.6)	13.7 (14.9)	14.6 (18.7)

* The recommended dose of XELJANZ is 5 mg twice daily.

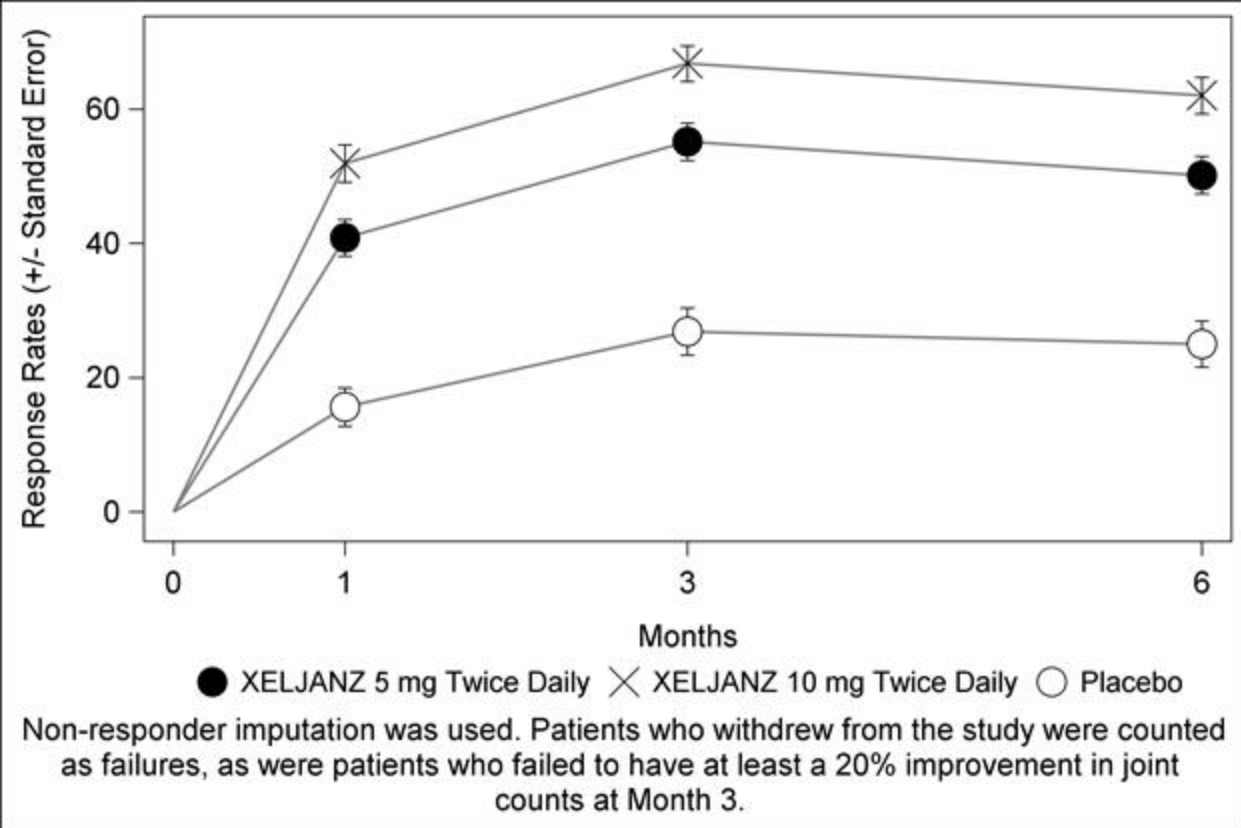
[†] Data shown is mean (Standard Deviation) at Month 3.

[‡] Visual analog scale: 0 = best, 100 = worst.

[§] 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 IV is shown in Figure 5. Similar responses were observed for XELJANZ in Studies I, II, III, V, and VI.

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



Radiographic Response

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

In Study IV, XELJANZ 10 mg twice daily plus background MTX reduced the progression of structural damage compared to placebo plus MTX at Month 6. When given at a dose of 5 mg twice daily, XELJANZ exhibited similar effects on mean progression of structural damage (not statistically significant). These results are shown in Table 8. 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% and 79% of patients treated with XELJANZ plus MTX 5 or 10 mg twice daily.

In Study VI, XELJANZ monotherapy inhibited the progression of structural damage compared to MTX at Months 6 and 12 as shown in Table 8. Analyses of erosion and joint space narrowing scores were consistent with the overall results.

In the MTX group, 55% of patients experienced no radiographic progression at Month 6 compared to 73% and 77% of patients treated with XELJANZ 5 or 10 mg twice daily.

Table 8: Radiographic Changes at Months 6 and 12

	Study IV				
	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg Twice Daily*	XELJANZ 10 mg Twice Daily
	N=139 Mean (SD)†	N=277 Mean (SD) †	Mean Difference from Placebo‡ (CI)	N=290 Mean (SD) †	Mean Difference from Placebo‡ (CI)
mTSS§					

*

†

‡

§

Baseline	33 (42)	31 (48)	-	37 (54)	-
Month 6	0.5 (2.0)	0.1 (1.7)	-0.3 (-0.7, 0.0)	0.1 (2.0)	-0.4 (-0.8, 0.0)
Study VI					
	MTX	XELJANZ 5 mg Twice Daily	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg Twice Daily*	XELJANZ 10 mg Twice Daily
	N=166	N=346	Mean Difference from MTX‡	N=369	Mean Difference from MTX‡
	Mean (SD)†	Mean (SD) †	(CI)	Mean (SD) †	(CI)
mTSS§					
Baseline	17 (29)	20 (40)	-	19 (39)	-
Month 6	0.8 (2.7)	0.2 (2.3)	-0.7 (-1.0, -0.3)	0.0 (1.2)	-0.8 (-1.2, -0.4)
Month 12	1.3 (3.7)	0.4 (3.0)	-0.9 (-1.4, -0.4)	0.0 (1.5)	-1.3 (-1.8, -0.8)

* The recommended dose of XELJANZ is 5 mg twice daily.

† SD = Standard Deviation

‡ Difference between least squares means XELJANZ minus placebo or MTX (95% CI = 95% confidence interval)

§ 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 XELJANZ 5 and 10 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 III was -0.22 (-0.35, -0.10) in patients receiving 5 mg XELJANZ twice daily and -0.32 (-0.44, -0.19) in patients receiving 10 mg XELJANZ twice daily. Similar results were obtained in Studies I, II, IV and V. In the 12-month trials, HAQ-DI results in XELJANZ-treated patients were consistent at 6 and 12 months.

Other Health-Related Outcomes

General health status was assessed by the Short Form health survey (SF-36). In studies I, IV, and V, patients receiving XELJANZ 5 mg twice daily or XELJANZ 10 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. 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-inhibitor (TNFi). 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 TNFi (66%, 19%, and 15% were inadequate responders to 1 TNFi, 2 TNFi and ≥ 3 TNFi, 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 either XELJANZ 5 mg or 10 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 both XELJANZ 5 mg or 10 mg twice daily versus placebo in Study PsA-II, although the differences versus placebo were not statistically significant ($p > 0.05$) (Tables 9 and 10).

Table 9: Proportion of Patients with an ACR Response in Study PsA-I* [Nonbiologic DMARD Inadequate Responders (TNFi-Naïve)]

Treatment Group	Placebo	XELJANZ 5 mg Twice Daily		XELJANZ 10 mg [†] Twice Daily	
		Response Rate	Difference (%) 95% CI from Placebo	Response Rate	Difference (%) 95% CI from Placebo
N [‡]	105	107		104	
Month 3					
ACR20	33%	50%	17.1 (4.1, 30.2)	61%	27.2 (14.2, 40.3)
ACR50	10%	28%	18.5 (8.3, 28.7)	40%	30.9 (19.9, 41.8)
ACR70	5%	17%	12.1 (3.9, 20.2)	14%	9.7 (1.8, 17.6)

Subjects with missing data were treated as non-responders.

* Subjects received one concomitant nonbiologic DMARD.

[†] The recommended dose of XELJANZ is 5 mg twice daily.

[‡] N is number of randomized and treated patients.

Table 10: Proportion of Patients with an ACR Response in Study PsA-II* (TNFi Inadequate Responders)

Treatment Group	Placebo	XELJANZ 5 mg Twice Daily		XELJANZ 10 mg [†] Twice Daily	
		Response Rate	Difference (%) 95% CI from Placebo	Response Rate	Difference (%) 95% CI from Placebo
N [‡]	131	131		132	
Month 3					
ACR20	24%	50%	26.0 (14.7, 37.2)	47%	23.3 (12.1, 34.5)
ACR50	15%	30%	15.3 (5.4, 25.2)	28%	13.5 (3.8, 23.3)
ACR70	10%	17%	6.9 (-1.3, 15.1)	14%	4.5 (-3.4, 12.4)

Subjects with missing data were treated as non-responders.

* Subjects received one concomitant nonbiologic DMARD.

[†] The recommended dose of XELJANZ is 5 mg twice daily.

[‡] N is number of randomized and treated patients.

Improvements from baseline in the ACR response criteria components for both studies are shown in Table 11.

Table 11: Components of ACR Response at Baseline and Month 3 in Studies PsA-I and PsA-II

	Nonbiologic DMARD Inadequate Responders (TNFi-Naïve)			TNFi Inadequate Responders		
	Study PsA-I*			Study PsA-II*		
Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg [†] Twice Daily	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg [†] Twice Daily
N at Baseline	105	107	104	131	131	132
ACR Component [‡]						
Number of tender/painful joints (0–68)						
Baseline	20.6	20.5	20.3	19.8	20.5	25.5
Month 3	14.6	12.2	9.9	15.1	11.5	14.5
Number of swollen joints (0–66)						
Baseline	11.5	12.9	11.7	10.5	12.1	12.8
Month 3	7.1	6.3	4.3	7.7	4.8	6.1
Patient assessment of arthritis pain [§]						
Baseline	53.2	55.7	54.4	54.9	56.4	59.5
Month 3	44.7	34.7	28.5	48.0	36.1	38.1
Patient global assessment of arthritis [§]						
Baseline	53.9	54.7	53.6	55.8	57.4	58.5
Month 3	44.4	35.5	29.8	49.2	36.9	38.8
HAQ-DI [¶]						
Baseline	1.11	1.16	1.08	1.25	1.26	1.37
Month 3	0.95	0.81	0.71	1.09	0.88	1.03
Physician's Global Assessment of Arthritis [§]						
Baseline	53.8	54.6	55.2	53.7	53.5	55.8
Month 3	35.4	29.5	23.6	36.4	27.0	25.6
CRP (mg/L)						
Baseline	10.4	10.5	8.1	12.1	13.8	15.0
Month 3	8.6	4.0	2.7	11.4	7.7	7.3

* Subjects received one concomitant nonbiologic DMARD.

[†] The recommended dose of XELJANZ is 5 mg twice daily.

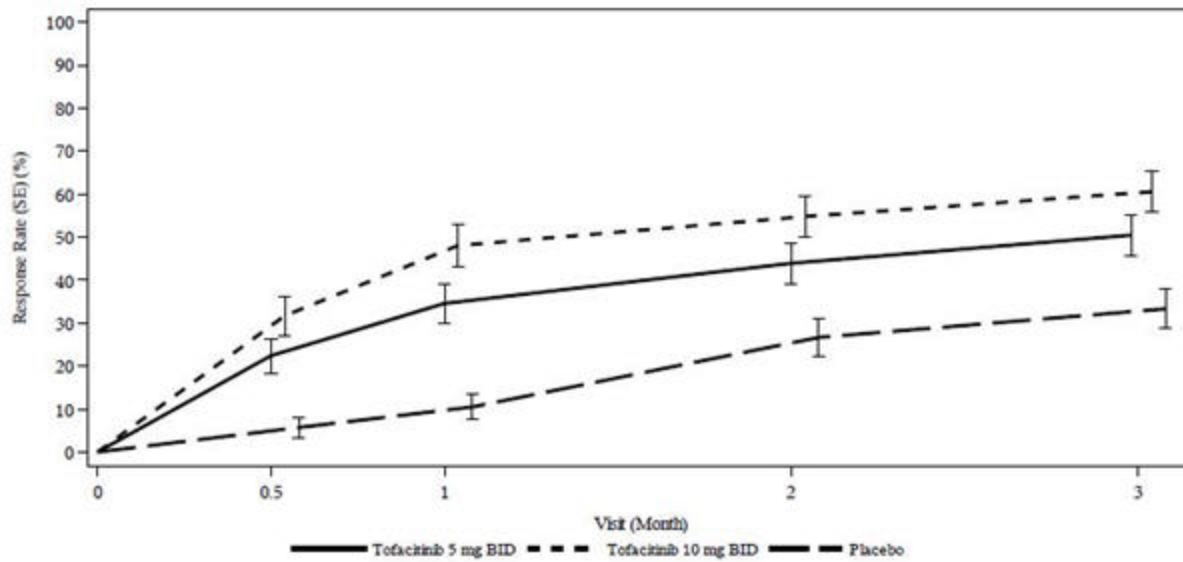
[‡] Data shown are mean value at baseline and at Month 3.

[§] Visual analog scale (VAS): 0 = best, 100 = worst.

[¶] 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-I¹



BID=twice daily; SE=standard error.

Subjects with missing data were treated as non-responders.

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

¹ Subjects received one concomitant nonbiologic DMARD.
The recommended dose of XELJANZ is 5 mg twice daily.

Physical Function

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg or 10 mg twice daily demonstrated significantly greater improvement ($p \leq 0.05$) from baseline in physical functioning compared to placebo at Month 3 (Table 12).

Table 12: 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* (TNFi-Naïve)			TNFi Inadequate Responders [†]		
	Study PsA-I [‡]			Study PsA-II [‡]		
Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg [§] Twice Daily	Placebo	XELJANZ 5 mg Twice Daily	XELJANZ 10 mg [§] Twice Daily
N [¶]	104	107	104	131	129	132
LSM Change from Baseline	-0.18	-0.35	-0.40	-0.14	-0.39	-0.35
Difference from Placebo (95% CI)	-	-0.17 (-0.29, -0.05)	-0.22 (-0.34, -0.10)	-	-0.25 (-0.38, -0.13)	-0.22 (-0.34, -0.09)

* Inadequate response to at least one nonbiologic DMARD due to lack of efficacy and/or intolerability.

[†] Inadequate response to at least one TNF inhibitor (TNFi) due to lack of efficacy and/or intolerability.

[‡] Subjects received one concomitant nonbiologic DMARD.

[§] The recommended dose of XELJANZ is 5 mg twice daily.

[¶] N is the total number of subjects in the statistical analysis.

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, 55% in patients receiving XELJANZ 10 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 or XELJANZ 10 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

XELJANZ is provided as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) tablets: White, round, immediate-release film-coated tablets, debossed with "Pfizer" on one side, and "JKI 5" on the other side, and available in:

XELJANZ

Bottles of 28:	NDC 0069-1001-03
Bottles of 60:	NDC 0069-1001-01
Bottles of 180:	NDC 0069-1001-02

XELJANZ XR is provided as 11 mg tofacitinib (equivalent to 17.77 mg tofacitinib citrate) tablets: Pink, oval, extended release tablet with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet:

XELJANZ XR

Bottles of 14:	NDC 0069-0501-14
Bottles of 30:	NDC 0069-0501-30

Storage and Handling

Store XELJANZ/XELJANZ XR at 20°C to 25°C (68°F to 77°F). [See USP Controlled Room Temperature].

XELJANZ/XELJANZ XR

Do not repackage.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Patient Counseling

Advise patients of the potential benefits and risks of XELJANZ/XELJANZ XR.

Serious Infection

Inform patients that XELJANZ/XELJANZ XR may lower the ability of their immune system to fight infections. Advise patients not to start taking XELJANZ/XELJANZ XR if they have an active infection. Instruct patients to contact their healthcare provider immediately during treatment if symptoms suggesting infection appear in order to ensure rapid evaluation and appropriate treatment [see *Warnings and Precautions (5.1)*].

Advise patients that the risk of herpes zoster, some cases of which can be serious, is increased in patients treated with XELJANZ [see *Warnings and Precautions (5.1)*].

Malignancies and Lymphoproliferative Disorders

Inform patients that XELJANZ/XELJANZ XR may increase their risk of certain cancers, and that lymphoma and other cancers have been observed in patients taking XELJANZ. Instruct patients to inform their healthcare provider if they have ever had any type of cancer [see *Warnings and Precautions (5.2)*].

Important Information on Laboratory Abnormalities

Inform patients that XELJANZ/XELJANZ XR may affect certain lab test results, and that blood tests are required before and during XELJANZ/XELJANZ XR treatment [see *Warnings and Precautions (5.4)*].

Pregnancy

Inform patients that XELJANZ/XELJANZ XR should not be used during pregnancy unless clearly necessary, and advise patients to inform their doctors right away if they become pregnant while taking XELJANZ/XELJANZ XR. Inform patients that Pfizer has a registry for pregnant women who have taken XELJANZ/XELJANZ XR during pregnancy. Advise patients to contact the registry at 1-877-311-8972 to enroll [see *Use in Specific Populations (8.1)*]. Women of reproductive potential should be advised to use effective contraception during treatment with XELJANZ/XELJANZ XR and for at least 4 weeks after the last dose [see *Use in Specific Populations (8.3)*]. Inform patients that they should not breastfeed while taking XELJANZ/XELJANZ XR [see *Use in Specific Populations (8.2)*].

Residual Tablet Shell

Patients receiving XELJANZ XR may notice an inert tablet shell passing in the stool or via colostomy. Patients should be informed that the active medication has already been absorbed by the time the patient sees the inert tablet shell.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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Medication Guide **XELJANZ (ZEL' JANS')** **XELJANZ XR (ZEL' JANS' EKS-AHR)** **(tofacitinib)**

What is the most important information I should know about XELJANZ/XELJANZ XR?

XELJANZ/XELJANZ XR may cause serious side effects including:

1. Serious infections.

XELJANZ/XELJANZ XR is a medicine that affects your immune system. XELJANZ/XELJANZ XR can lower the ability of your immune system to fight infections. Some people can have serious infections while taking XELJANZ/XELJANZ XR, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections.

- Your healthcare provider should test you for TB before starting XELJANZ/XELJANZ XR and during treatment.
- Your healthcare provider should monitor you closely for signs and symptoms of TB infection during treatment with XELJANZ/XELJANZ XR.

You should not start taking XELJANZ/XELJANZ XR if you have any kind of infection unless your healthcare provider tells you it is okay. You may be at a higher risk of developing shingles (herpes zoster).

Before starting XELJANZ/XELJANZ XR, tell your healthcare provider if you:

- think you have an infection or have symptoms of an infection such as:

- fever, sweating, or chills
- cough
- blood in phlegm
- warm, red, or painful skin or sores on your body
- burning when you urinate or urinating more often than normal

- muscle aches
- shortness of breath
- weight loss
- diarrhea or stomach pain
- feeling very tired

- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, chronic lung disease, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use XELJANZ/XELJANZ XR. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B or C.

After starting XELJANZ/XELJANZ XR, call your healthcare provider right away if you have any symptoms of an infection. XELJANZ/XELJANZ XR can make you more likely to get infections or make worse any infection that you have.

2. Cancer and immune system problems. XELJANZ/XELJANZ XR may increase your risk of certain cancers by changing the way your immune system works.

- Lymphoma and other cancers including skin cancers can happen in patients taking XELJANZ/XELJANZ XR. Tell your healthcare provider if you have ever had any type of cancer.
- Some people who have taken XELJANZ with certain other medicines to prevent kidney transplant rejection have had a problem with certain white blood cells growing out of control (Epstein Barr Virus-associated post-transplant lymphoproliferative disorder).

3. Tears (perforation) in the stomach or intestines.

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking XELJANZ/XELJANZ XR can get tears in their stomach or intestines. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.

Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

4. Changes in certain laboratory test results. Your healthcare provider should do blood tests before you start receiving XELJANZ/XELJANZ XR and while you take XELJANZ/XELJANZ XR to check for the following side effects:

- **changes in lymphocyte counts.** Lymphocytes are white blood cells that help the body fight off infections.
- **low neutrophil counts.** Neutrophils are white blood cells that help the body fight off infections.
- **low red blood cell count.** This may mean that you have anemia, which may make you feel weak and tired.

Your healthcare provider should routinely check certain liver tests.

You should not receive XELJANZ/XELJANZ XR if your lymphocyte count, neutrophil count, or red blood cell count is too low or your liver tests are too high.

Your healthcare provider may stop your XELJANZ/XELJANZ XR treatment for a period of time if needed because of changes in these blood test results.

You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving XELJANZ/XELJANZ XR, and as needed after that. Normal cholesterol levels are important to good heart health.

See "[What are the possible side effects of XELJANZ/XELJANZ XR?](#)" for more information about side effects.

What is XELJANZ/XELJANZ XR?

XELJANZ/XELJANZ XR is a prescription medicine called a Janus kinase (JAK) inhibitor.

XELJANZ/XELJANZ XR is used to treat adults with moderately to severely active rheumatoid arthritis in which methotrexate did not work well.

XELJANZ/XELJANZ XR is used to treat adults with active psoriatic arthritis in which methotrexate or other similar medicines called nonbiologic disease-modifying antirheumatic drugs (DMARDs) did not work well.

It is not known if XELJANZ/XELJANZ XR is safe and effective in people with Hepatitis B or C.

XELJANZ/XELJANZ XR is not recommended for people with severe liver problems.

It is not known if XELJANZ/XELJANZ XR is safe and effective in children.

What should I tell my healthcare provider before taking XELJANZ/XELJANZ XR?

Before taking XELJANZ/XELJANZ XR, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection. See "[What is the most important information I should know about XELJANZ/XELJANZ XR?](#)"
- have liver problems
- have kidney problems
- have any stomach area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines
- have had a reaction to tofacitinib or any of the ingredients in XELJANZ/XELJANZ XR
- have recently received or are scheduled to receive a vaccine. People who take XELJANZ/XELJANZ XR should not receive live vaccines. People taking XELJANZ/XELJANZ XR can receive non-live vaccines.
- plan to become pregnant or are pregnant. It is not known if XELJANZ/XELJANZ XR will harm an unborn baby. You should use effective birth control while you are taking XELJANZ/XELJANZ XR and for at least 4 weeks after you take your last dose.
 - **Pregnancy Registry:** Pfizer has a registry for pregnant women who take XELJANZ/XELJANZ XR. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking XELJANZ/XELJANZ XR, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.
- plan to breastfeed or are breastfeeding. You and your healthcare provider should decide if you will take XELJANZ/XELJANZ XR or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XELJANZ/XELJANZ XR and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- any other medicines to treat your rheumatoid arthritis or psoriatic arthritis. You should not take tocilizumab (Actemra[®]), etanercept (Enbrel[®]), adalimumab (Humira[®]), infliximab (Remicade[®]), rituximab (Rituxan[®]), abatacept (Orencia[®]), anakinra (Kineret[®]), certolizumab (Cimzia[®]), golimumab (Simponi[®]), ustekinumab (Stelara[®]), secukinumab (Cosentyx[®]), azathioprine, cyclosporine, or other immunosuppressive drugs while you are taking XELJANZ or XELJANZ XR. Taking XELJANZ or XELJANZ XR with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XELJANZ/XELJANZ XR?

- Take XELJANZ/XELJANZ XR exactly as your healthcare provider tells you to take it.
- Take XELJANZ 2 times a day with or without food.
- Take XELJANZ XR 1 time a day with or without food.
- Swallow XELJANZ XR tablets whole and intact. Do not crush, split, or chew.
- When you take XELJANZ XR, you may see something in your stool that looks like a tablet. This is the empty shell from the tablet after the medicine has been absorbed by your body.
- If you take too much XELJANZ/XELJANZ XR, call your healthcare provider or go to the nearest hospital emergency room right away.
- For the treatment of psoriatic arthritis, take XELJANZ/XELJANZ XR in combination with methotrexate, sulfasalazine or leflunomide as instructed by your healthcare provider.

Drug Administration
What are the possible side effects of XELJANZ/XELJANZ XR?

XELJANZ/XELJANZ XR may cause serious side effects, including:

- See "[What is the most important information I should know about XELJANZ/XELJANZ XR?](#)"
- **Hepatitis B or C activation infection** in people who carry the virus in their blood. If you are a carrier of the hepatitis B or C virus (viruses that affect the liver), the virus may become active while you use XELJANZ/XELJANZ XR. Your healthcare provider may do blood tests before you start treatment with XELJANZ and while you are using XELJANZ/XELJANZ XR. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B or C infection:
 - feel very tired
 - little or no appetite
 - clay-colored bowel movements
 - chills
 - muscle aches
 - skin rash
 - skin or eyes look yellow
 - vomiting
 - fevers
 - stomach discomfort
 - dark urine

Common side effects of XELJANZ/XELJANZ XR include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- diarrhea
- nasal congestion, sore throat, and runny nose (nasopharyngitis)

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of XELJANZ/XELJANZ XR. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Pfizer at 1-800-438-1985.

How should I store XELJANZ/XELJANZ XR?

- Store XELJANZ/XELJANZ XR at room temperature between 68°F to 77°F (20°C to 25°C).
- Safely throw away medicine that is out of date or no longer needed.

Keep XELJANZ/XELJANZ XR and all medicines out of the reach of children.

General information about the safe and effective use of XELJANZ/XELJANZ XR.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XELJANZ/XELJANZ XR for a condition for which it was not prescribed. Do not give XELJANZ/XELJANZ XR to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about XELJANZ/XELJANZ XR. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about XELJANZ/XELJANZ XR that is written for health professionals.

What are the ingredients in XELJANZ?

Active ingredient: tofacitinib citrate

Inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, HPMC 2910/Hypromellose 6cP, titanium dioxide, macrogol/PEG3350, and triacetin.

What are the ingredients in XELJANZ XR?

Active ingredient: tofacitinib citrate

Inactive ingredients: sorbitol, hydroxyethyl cellulose, copovidone, magnesium stearate, cellulose acetate, hydroxypropyl cellulose, HPMC 2910/Hypromellose, titanium dioxide, triacetin, and red iron oxide. Printing ink contains shellac glaze, ammonium hydroxide, propylene glycol, and ferrousferic oxide/black iron.

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