PRODUCT MONOGRAPH

PrXELJANZ®
Tofacitinib tablets
5 mg tofacitinib (as tofacitinib citrate)

XELJANZ® XR
Tofacitinib extended-release tablets
11 mg tofacitinib (as tofacitinib citrate)

Tablets for oral administration
Anti-rheumatic, immunomodulator agent

Pfizer Canada Inc. 17,300 Trans-Canada Highway Kirkland, Quebec H9J 2M5	Date of Revision: 11 December 2017

TMPF PRISM C.V.
c/o Pfizer Manufacturing Holdings LLC
Pfizer Canada Inc., Licensee

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Table of Contents

PrXELJANZ®
XELJANZ® XR
Tofacitinib tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tofacitinib tablets / 5 mg tofacitinib (as tofacitinib citrate) Tofacitinib extended-release tablets / 11 mg tofacitinib (as tofacitinib citrate)	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

XELJANZ/XELJANZ XR (tofacitinib) in combination with methotrexate (MTX), is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA), in adult patients with moderately to severely active RA who have had an inadequate response to MTX.

In cases of intolerance to MTX, physicians may consider the use of XELJANZ/XELJANZ XR (tofacitinib) as monotherapy.

Limitations of use: Use of XELJANZ/XELJANZ XR in combination with biological disease-modifying anti-rheumatic drugs (bDMARDs) or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Pediatrics (<18 years of age)
The safety and effectiveness of XELJANZ/XELJANZ XR in pediatric patients have not been established. Therefore XELJANZ/XELJANZ XR should not be used in this patient population (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY** section).

Geriatrics (>65 years of age)
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. Therefore, Caution should be used when treating the elderly with XELJANZ/XELJANZ XR (see **WARNINGS and PRECAUTIONS**, **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**

section).

CONTRAINDICATIONS

XELJANZ/XELJANZ XR (tofacitinib) should not be administered to patients with known hypersensitivity to tofacitinib or any of its components. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING section of the product monograph.

WARNINGS AND PRECAUTIONS

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with XELJANZ/XELJANZ XR (tofacitinib) are at increased risk for developing serious infections that may lead to hospitalization or death. 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, and other infections due to opportunistic pathogens.**

Treatment with XELJANZ/XELJANZ XR should not be initiated in patients with active infections including chronic or localized 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 ADVERSE REACTIONS section).

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).

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.

Cardiovascular

Heart Rate Decrease and PR Interval Prolongation: XELJANZ causes a decrease in heart rate and a prolongation of the PR interval (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests, ADVERSE REACTIONS**, **ECG Findings**). Caution should be observed in patients with a low heart rate at baseline (< 60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Concomitant medications that result in a decrease in heart rate and/or PR interval prolongation should be avoided to the extent possible during treatment with XELJANZ/XELJANZ XR (see **DRUG INTERACTIONS**).

Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials with XELJANZ in rheumatoid arthritis patients, although the role of JAK inhibition in these events is not known. All patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. The relative contribution of these concomitant medications vs. XELJANZ to the development of gastrointestinal perforations is not known.

XELJANZ/XELJANZ XR should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., use of concomitant NSAIDs and/or corticosteroids, 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** section**).**

Hepatic

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.

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

The impact of XELJANZ/XELJANZ XR on chronic viral hepatitis reactivation is unknown. XELJANZ/XELJANZ XR has not been studied in patients with positive hepatitis B virus or hepatitis C virus serology, and should therefore not be used in these populations.

XELJANZ/XELJANZ XR has not been studied in patients with severe hepatic impairment, and should not be used in these patients. XELJANZ XR should not be used in patients with moderate to severe hepatic impairment Dose adjustment of XELJANZ is recommended for patients with moderate hepatic impairment (see **DOSAGE and ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY**).

Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in rheumatoid arthritis patients receiving immunomodulatory agents, including biologic DMARDs and XELJANZ. The most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcus, histoplasmosis, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus infections, BK virus infections, 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).

XELJANZ/XELJANZ XR should not be administered in patients with an active 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 infections,
- who have been exposed to tuberculosis,
- with a history of a serious or an opportunistic infection,
- who have resided or travelled 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.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes. Caution is also recommended in patients with a history of chronic lung disease as they may be more prone to infections. Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with XELJANZ in clinical trials and in the post-marketing setting.

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.
For discontinuation and monitoring criteria for lymphopenia see **Monitoring and Laboratory Tests**.

Treatment with XELJANZ was associated with increased rates of infections in Asian patients compared to other races (see **Special Populations** and **ADVERSE EVENTS**). XELJANZ/XELJANZ XR should be used with caution in this population.

Tuberculosis
Patients should be evaluated and tested for latent or active infection prior to administration of XELJANZ/XELJANZ XR and periodically (e.g. annually) while taking XELJANZ/XELJANZ XR.

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.

Antituberculosis 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 have risk factors for tuberculosis infection.

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.

Interstitial lung disease
Events of interstitial lung disease (ILD) have been reported in clinical trials with XELJANZ in rheumatoid arthritis patients, although the role of JAK inhibition in these events is not known. All patients who developed ILD were taking concomitant methotrexate, corticosteroids and/or sulfasalazine, which have been associated with ILD. Asian patients had an increased risk of ILD (see **Special Populations**).

XELJANZ/XELJANZ XR should be used with caution in patients with a risk or history of ILD.

Immune
XELJANZ/XELJANZ XR can increase the risk of infections and immunosuppression when co-administered with potent immunosuppressants such as cyclosporine, azathioprine and tacrolimus. Combined use of XELJANZ/XELJANZ XR with potent immunosuppressive drugs has not been studied in rheumatoid arthritis patients and is not recommended (see **DRUG INTERACTIONS** section).

Immunizations
No data are available on the secondary transmission of infection by live vaccines to patients receiving XELJANZ/XELJANZ XR. It is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating

XELJANZ/XELJANZ XR therapy and that live vaccines not be given concurrently with XELJANZ/XELJANZ XR. The interval between live vaccinations and initiation of tofacitinib therapy should be in accordance with current vaccination guidelines regarding immunomodulatory agents.

In patients being considered for XELJANZ/XELJANZ XR therapy, live zoster vaccine should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus. Vaccination should occur at least 2 weeks but preferably 4 weeks before initiating immunomodulatory agents such as XELJANZ/XELJANZ XR.

In a clinical trial, a varicella naïve patient treated with XELJANZ and methotrexate developed disseminated infection with the vaccine strain of the varicella zoster virus 16 days after vaccination. A satisfactory immune response to the vaccine was developed 6 weeks post-vaccination.

In a randomized, double-blind, placebo-controlled study in 200 adult rheumatoid arthritis patients treated with XELJANZ 10 mg BID or placebo, humoral responses to concomitant pneumococcal and influenza vaccines were assessed. The percentages of patients achieving a satisfactory humoral response to pneumococcal vaccines were lower for the XELJANZ group than the placebo group. This effect was more pronounced for patients receiving background methotrexate, a total of 31.6% XELJANZ-treated subjects and 61.8% placebo-treated subjects who received background methotrexate achieved a ≥ 2-fold increase in antibody concentrations to ≥6 of 12 pneumococcal antigens.

In the same study, the proportion of patients achieving protective antibody levels to the influenza antigens was lower in the XELJANZ group (64.9%) compared to the placebo group (92.7%) in patients receiving background methotrexate. However, the difference in humoral response to the influenza vaccine was small with 50.9% of patients in the XELJANZ group and 58.2% in the placebo group with background methotrexate achieving a ≥4-fold increase in antibody titers to ≥2 of 3 influenza antigens.

Malignancies and Lymphoproliferative Disorder

Malignancies have been observed in patients treated with XELJANZ. In patients treated with XELJANZ, malignancies were observed in clinical studies and the post marketing setting including but not limited to: lymphomas, lung cancer, breast cancer, colorectal cancer, gastric cancer, melanoma, prostate cancer, pancreatic cancer and renal cell carcinoma.

Consider the risks and benefits of XELJANZ/XELJANZ XR treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ/XELJANZ XR in patients who develop a malignancy. Recommendations for non-melanoma skin cancer are presented below.

In the controlled clinical studies, 5 malignancies (excluding NMSC) were diagnosed in patients receiving XELJANZ 5 mg BID, and 8 malignancies (excluding NMSC) were diagnosed in patients receiving XELJANZ 10 mg BID, compared to 0 malignancies (excluding NMSC) in

patients in the placebo/placebo plus DMARD group during the first 12 months. Lymphomas and solid cancers have also been observed in the long-term extension studies in patients treated with XELJANZ. Patients with rheumatoid arthritis, particularly those with highly active disease, may be at a higher risk (several fold) than the general population for the development of lymphoma.
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.

Non melanoma Skin Cancer
Nonmelanoma skin cancers (NMSCs) have been reported in patients treated with XELJANZ. Periodic skin examination is recommended.

Renal
XELJANZ XR is not recommended in patients with moderate (CLcr ≥30 and <60 mL/min), or severe renal insufficiency (CLcr ≥15 and <30 mL/min), including patients with ESRD undergoing dialysis.

Dosage adjustment of XELJANZ is recommended in patients with moderate and severe renal impairment (see **Special Populations, DOSAGE AND ADMINISTRATION,** and **ACTION and CLINICAL PHARMACOLOGY** section). In clinical trials, XELJANZ was not evaluated in rheumatoid arthritis patients with baseline creatinine clearance values (estimated by the Cockcroft-Gault equation) less than 40 mL/min.

Musculoskeletal
Treatment with XELJANZ was associated with increases in creatine kinase (CK). Maximum effects were generally observed within 6 months. Rhabdomyolysis was reported in one patient in the XELJANZ rheumatoid arthritis clinical trials. CK levels should be checked in patients with symptoms of muscle weakness and/or muscle pain to evaluate for evidence of rhabdomyolysis.

Special Populations
Pregnant Women
XELJANZ/XELJANZ XR should not be used during pregnancy. There are no adequate and well-controlled studies on the use of XELJANZ/XELJANZ XR in pregnant women. XELJANZ has been shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility, parturition, and peri/postnatal development. (see **TOXICOLOGY** section).

Women of reproductive potential should be advised to use effective contraception during XELJANZ/XELJANZ XR treatment and for 4 to 6 weeks after the last dose.

Nursing Women
XELJANZ was secreted in milk of lactating rats. It is not known whether XELJANZ/XELJANZ XR is excreted in human milk. Women should not breastfeed while being treated with XELJANZ/XELJANZ XR (see **TOXICOLOGY** section).

Pediatrics (<18 years of age)

The safety and effectiveness of XELJANZ/XELJANZ XR in pediatric patients have not been established. Therefore XELJANZ/XELJANZ XR should not be used in this patient population (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY** section).

Geriatrics (>65 years of age)

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. Caution should be used when treating the elderly with XELJANZ/XELJANZ XR (see **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY** section).

Asian patients

Asian patients have an increased risk of herpes zoster, opportunistic infections and interstitial lung disease. An increased incidence of some adverse events such as elevated transaminases (ALT, AST) and decreased WBCs were also observed. Therefore, XELJANZ/XELJANZ XR should be used with caution in Asian patients (see **ADVERSE EVENTS**).

Laboratory Parameters

Lymphopenia

Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts below the baseline of approximately 10% during 12 months of therapy. Lymphocyte counts less than 500 cells/mm^3 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/mm^3). In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm^3, XELJANZ/XELJANZ XR should be discontinued.

For recommended monitoring and dose modifications based on lymphocyte counts see **Monitoring and Laboratory Tests** and **DOSAGE AND ADMINISTRATION** section.

Neutropenia

Treatment with XELJANZ was associated with an increased incidence of neutropenia (< 2000/mm^3) compared to placebo.

Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with a low neutrophil count (i.e., ANC< 1000/mm^3). For patients who develop a persistent ANC of 500-1000/mm^3, interrupt dosing until ANC is >1000 cells/mm^3. In patients who develop an absolute neutrophil count < 500 cells/mm^3, discontinue treatment. For recommended monitoring and dose modification based on ANC, see **Monitoring and Laboratory Tests** and **DOSAGE AND ADMINISTRATION**.

Anemia

Avoid initiation of XELJANZ/XELJANZ XR treatment in patients with low hemoglobin values (i.e., <9 g/dL). Treatment with XELJANZ/XELJANZ XR should be interrupted in patients who develop hemoglobin levels <8 g/dL or whose hemoglobin level drops >2 g/dL on treatment.

For recommended monitoring and dose modification based on hemoglobin results, see **Monitoring and Laboratory Tests** and **DOSAGE AND ADMINISTRATION**.

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 enzymes and prompt investigation of the cause of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, XELJANZ/XELJANZ XR administration 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 at baseline and approximately 4-8 weeks following initiation of XELJANZ/XELJANZ XR therapy, and every 6 months thereafter. Patients should be managed according to local clinical guidelines for the management of hyperlipidemia.

Monitoring and Laboratory Tests

Lipid tests should be performed at baseline, approximately 4-8 weeks after initiation with XELJANZ/XELJANZ XR and every 6 months thereafter.

Liver enzymes tests are recommended. If drug-induced liver injury is suspected, the administration of XELJANZ/XELJANZ XR should be interrupted until this diagnosis has been excluded.

Assessment of renal function is recommended prior to initiation of XELJANZ/XELJANZ XR.

Lymphocytes, neutrophils and hemoglobin tests should be performed at baseline, approximately 4-8 weeks after initiation with XELJANZ/XELJANZ XR treatment, and every 3 months thereafter (see **DOSAGE and ADMINISTRATION** for recommended dose adjustment based on these laboratory tests).

Vital signs: Patients should be monitored for pulse rate and blood pressure at baseline and periodically during treatment with XELJANZ/XELJANZ XR (see **WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, ECG Findings; DRUG INTERACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

During controlled clinical trials, 8.0% (11.0 events/100 patient years) of patients in the 5 mg twice daily in the XELJANZ group were hospitalized due to serious adverse reactions compared to 7.8% (9.1 events/100 patient years) and 3.8% (13.0 events/100 patient years) of patients in the adalimumab and placebo group, respectively. Deaths occurred in 0.4% (0.6 events/100 patient years) of patients in the 5 mg twice daily XELJANZ group, compared to 0.5% (0.6 events/100 patient years) and 0.2% (0.5 events/100 patient years) of patients in the adalimumab and placebo groups, respectively.

The most common serious adverse reactions were serious infections, including pneumonia, cellulitis, herpes zoster, and urinary tract infection. During the first 3 months, serious infections (those requiring parenteral antibiotics or hospitalization) were reported in 0.7% (2.8 events/100 patient years) and 0.2% (0.6 events/100 patient years) of patients treated with XELJANZ or placebo, respectively. From 0-12 months, serious infections were reported in 2.4% (3.2 events/100 patient years) of XELJANZ treated patients (see **WARNINGS AND PRECAUTIONS**).

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials (occurring in ≥ 2% of patients treated with XELJANZ monotherapy or in combination with DMARDs) were upper respiratory tract infections (4.4% in the 5 mg twice daily group), headache (4.4% in the 5 mg twice daily group), nasopharyngitis (3.9% in the 5 mg twice daily group), and diarrhea (3.7% in the 5 mg twice daily group).

The proportion of patients who discontinued treatment due to any adverse reactions during the first 3 months in double-blind placebo-controlled studies was 7.8% for patients taking 5 mg twice daily of XELJANZ and 3.7% for placebo-treated patients. The most common adverse reactions that resulted in discontinuation of XELJANZ were infections. The most common infections resulting in discontinuation of therapy were herpes zoster and pneumonia.

Asian patients
Asian patients had higher rates of herpes zoster, opportunistic infections, interstitial lung disease, elevated transaminases (ALT, AST) and decreased WBCs. Therefore, XELJANZ/ XELJANZ XR should be used with caution in Asian patients.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information

from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 below lists the Adverse events (regardless of causality) occurring in ≥1% of patients treated with XELJANZ during the double-blind, placebo-controlled portion of the rheumatoid arthritis studies.

Table 1: : Summary of Adverse Events reported by ≥ 1 % of patients treated with XELJANZ (All Causalities) - All Phase 3 Studies (up to 3 months)

Body System/Adverse Event	XELJANZ 5mg BID (N=1216)	Placebo (N=681)	Adalimumab 40 mg SC q2w (N=204)
Infections and infestations			
Upper respiratory tract infection	53 (4.4)	23 (3.4)	7 (3.4)
Nasopharyngitis	48 (3.9)	19 (2.8)	7 (3.4)
Urinary tract infection	25 (2.1)	12 (1.8)	7 (3.4)
Bronchitis	14 (1.2)	10 (1.5)	4 (2.0)
Blood and lymphatic system disorders			
Anemia	15 (1.2)	8 (1.2)	0
Metabolism and nutrition disorders			
Hypercholesterolaemia	12 (1.0)	3 (0.4)	1 (0.5)
Nervous system disorders			
Headache	54 (4.4)	15 (2.2)	5 (2.5)
Dizziness	13 (1.1)	8 (1.2)	3 (1.5)
Vascular disorders			
Hypertension	20 (1.6)	7 (1.0)	0
Gastrointestinal disorders			
Diarrhoea	45 (3.7)	16 (2.3)	2 (1.0)
Nausea	32 (2.6)	18 (2.6)	3 (1.5)
Dyspepsia	19 (1.6)	11 (1.6)	3 (1.5)
Abdominal pain upper	23 (1.9)	5 (0.7)	3 (1.5)
Vomiting	21 (1.7)	10 (1.5)	0
Constipation	16 (1.3)	6 (0.9)	2 (1.0)
Gastritis	12 (1.0)	7 (1.0)	0
Gastroenteritis	12 (1.0)	5 (0.7)	0
Hepatobiliary Disorders			
Alanine aminotransferase increased	14 (1.2)	7 (1.0)	1 (0.5)
Musculoskeletal and connective tissue disorders			
Rheumatoid arthritis	17 (1.4)	17 (2.5)	1 (0.5)
Back pain	18 (1.5)	5 (0.7)	1 (0.5)
Arthralgia	13 (1.1)	16 (2.3)	4 (2.0)
General disorders and administration site conditions			
Oedema peripheral	17 (1.4)	16 (2.3)	3 (1.5)
Pyrexia	13 (1.1)	5 (0.7)	1 (0.5)

Overall Infections

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

The most commonly reported infections were upper respiratory tract infections and nasopharyngitis, and urinary tract infections.

Serious Infections

In the five controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.6 events/100 patient years) who received placebo and 8 patients (2.8 events/100 patient years) who received 5 mg twice daily of XELJANZ.

During the 0 to 12 months exposure, the overall frequencies of serious infections were 2.4% (3.2 events/100 patient years) for the 5 mg twice daily XELJANZ group.

The most common serious infections reported with XELJANZ included pneumonia, urinary tract infection, and herpes zoster (see **WARNINGS AND PRECAUTIONS**).

Tuberculosis

In the five controlled trials, during 0 to 3 months exposure, no cases of tuberculosis were reported in patients who received placebo or 5 mg twice daily of XELJANZ.

During the 0 to 12 months exposure, tuberculosis was reported in 0 patients who received 5 mg twice daily of 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**).

Opportunistic Infections (excluding tuberculosis)
In the five controlled trials, during 0 to 3 months exposure, opportunistic infections were reported in 0 patients who received placebo and 2 (0.2%) patients (0.7 events/100 patient years) who received 5 mg twice daily of XELJANZ.

During the 0 to 12 months exposure, opportunistic infections were reported in 3 (0.3%) patients (0.3 events/100 patient years) who received 5 mg twice daily of XELJANZ.
The median XELJANZ exposure prior to diagnosis of an opportunistic infection was 8 months (range from 41 to 698 days).

Malignancy (excluding nonmelanoma skin cancer)
In the five controlled trials, during the 0 to 3 months exposure, malignancies (excluding nonmelanoma skin cancer) were reported in 0 patients who received placebo and 2 (0.2%) patients (0.7 events/100 patient years) who received 5 mg twice daily of XELJANZ.

During the 0 to 12 months exposure, malignancies (excluding nonmelanoma skin cancer) were reported in 5 (0.4%) patients (0.6 events/100 patient years) who received 5 mg twice daily of XELJANZ.

The most common types of malignancy, (excluding nonmelanoma skin cancer), 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**).

Nonmelanoma skin cancer
In the five controlled trials, during the 0 to 3 months exposure, nonmelanoma skin cancer was reported in 1 (0.2%) patient (0.6 events/100 patient years) who received placebo and 2 (0.2%) patients (0.7 events/100 patient years) who received 5 mg twice daily of XELJANZ.

During the 0 to 12 months exposure, nonmelanoma skin cancer was reported in 3 (0.3%) patients (0.3 events/100 patient years) who received 5 mg twice daily of XELJANZ.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Blood and lymphatic system disorders: Neutropenia

Cardiovascular: congestive heart failure, myocardial infarction

Gastrointestinal disorders: abdominal pain

General disorders and administration site conditions: Influenza

Hepatobiliary Disorders: Hepatic steatosis

Infections and infestations: Sepsis, pneumonia bacterial, pneumonia pneumococcal, pyelonephritis, cellulitis, gastroenteritis viral, viral infection, herpes simplex, herpes zoster. Tuberculosis of central nervous system, encephalitis, necrotising fasciitis, meningitis cryptococcal, disseminated tuberculosis, urosepsis, pneumocystis jiroveci pneumonia, staphylococcal bacteraemia, tuberculosis, arthritis bacterial, atypical mycobacterial infection, mycobacterium avium complex infection, cytomegalovirus infection, bacteraemia, diverticulitis

Injury, Poisoning and Procedural Complications: Muscle strain, fall

Investigations: Transaminases increased, blood creatinine increased, gamma glutamyltransferase increased, liver function test abnormal, Weight increased, Blood creatine phosphokinase increased

Metabolism and nutrition disorders: Dehydration

Musculoskeletal and connective tissue disorders: Tendonitis, joint swelling

Neoplasm benign, malignant and unspecified (Including Cysts and Polyps): Nonmelanoma skin cancers

Nervous system disorders: Paraesthesia

Respiratory, thoracic and mediastinal disorders: Sinus congestion, cough

Skin and subcutaneous tissue disorders: Erythema, pruritus

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory Tests

Creatine Kinase

Treatment with XELJANZ was associated with increases in creatine kinase (CK). Maximum effects were generally observed within 6 months. Rhabdomyolysis was reported in one patient in the XELJANZ rheumatoid arthritis clinical trials. CK levels should be checked in patients with symptoms of muscle weakness and/or muscle pain to evaluate for evidence of rhabdomyolysis (see **WARNINGS and PRECAUTIONS**).

ECG Findings: In placebo-controlled phase 2 clinical trials in patients with rheumatoid arthritis, steady-state treatment with 5-10 mg BID XELJANZ was associated with statistically significant 4-7 bpm decreases in heart rate and 4-10 ms increases in the PR interval compared with placebo (see **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**, **DRUG INTERACTIONS**).

Lipids

Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) generally reached maximal effects at 6 weeks following initiation of XELJANZ in the controlled double-blind clinical trials. Changes in lipid parameters from baseline through the end of the study (6-12 months) in the controlled clinical studies are summarized below:

- Mean LDL cholesterol increased by 14% in the XELJANZ 5 mg BID arm.
- Mean HDL cholesterol increased by 16% in the XELJANZ 5 mg BID arm.
- Mean LDL/HDL ratios were essentially unchanged in XELJANZ -treated patients.

In the five controlled clinical trials, 4.4% of patients treated with 5 mg BID, initiated lipid-lowering medication while on study.

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

Liver Enzyme Tests

Confirmed increases in liver enzymes >3x upper limit of normal (ULN) were uncommonly observed. 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 portion of the phase 3 monotherapy study (0-3 months), ALT elevations >3x ULN were observed in 1.65% and 0.41% of patients receiving placebo and 5 mg respectively. In

this study, AST elevations >3x ULN were observed in 1.65%, and 0.41% of patients receiving placebo and 5 mg BID, respectively.

In the controlled portion of the phase 3 studies on background DMARDs (0-3 months), ALT elevations >3x ULN were observed in 0.9% and 1.24% of patients receiving placebo and 5 mg BID, respectively. In these studies, AST elevations >3x ULN were observed in 0.72% and 0.52% of patients receiving placebo and 5 mg BID, respectively.

Lymphocytes
In the five controlled clinical trials, confirmed decreases in absolute lymphocyte counts below 500 cells/mm^3 occurred in 0.2% of patients for the 5 mg BID XELJANZ group during 12 months of exposure.

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

Neutrophils
In the controlled clinical studies, confirmed decreases in ANC below 1000/mm^3 occurred in 0.08% of patients in the 5 mg BID XELJANZ group during 12 months of exposure. There were no confirmed decreases in ANC below 500/mm^3 observed in any treatment group.

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

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

Serum creatinine
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.

DRUG INTERACTIONS

Overview
The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19.

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 185 times the steady state C_{max} of a 5 mg BID dose.

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 also low.

Tofacitinib exposure is increased when XELJANZ is coadministered with potent CYP3A4 inhibitors (e.g., ketoconazole) or when administration of one or more concomitant medications results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole). Tofacitinib exposure is decreased when XELJANZ is coadministered with potent CYP3A4 inducers (e.g. rifampin). Inhibitors of CYP2C19 or P-glycoprotein are unlikely to alter the PK of tofacitinib.

The 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 rheumatoid patients, the oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalize CYP enzyme activity in RA patients. Therefore, coadministration with XELJANZ/XELJANZ XR is not expected to result in clinically relevant increases in the metabolism of CYP substrates in RA patients.

Drug-Drug Interactions

Table 2 Summary of Drug-Drug Interactions

Drug	Reference	Effect	Clinical comment
Methotrexate	CT	Coadministration with methotrexate (15-25 mg MTX once weekly) had no effect on the PK of tofacitinib and decreased methotrexate AUC and Cmax by 10% and 13% respectively.	No dose adjustment is required for either drug.
Ketoconazole	CT	Coadministration of ketoconazole, a strong CYP3A4 inhibitor, with a single dose of XELJANZ increased the AUC and Cmax of tofacitinib by 103% and 16%, respectively	XELJANZ XR is not recommended in patients coadministered with strong inhibitors of CYP3A4. Maximum recommended dose is XELJANZ 5 mg once daily when coadministered with strong inhibitors of CYP3A4

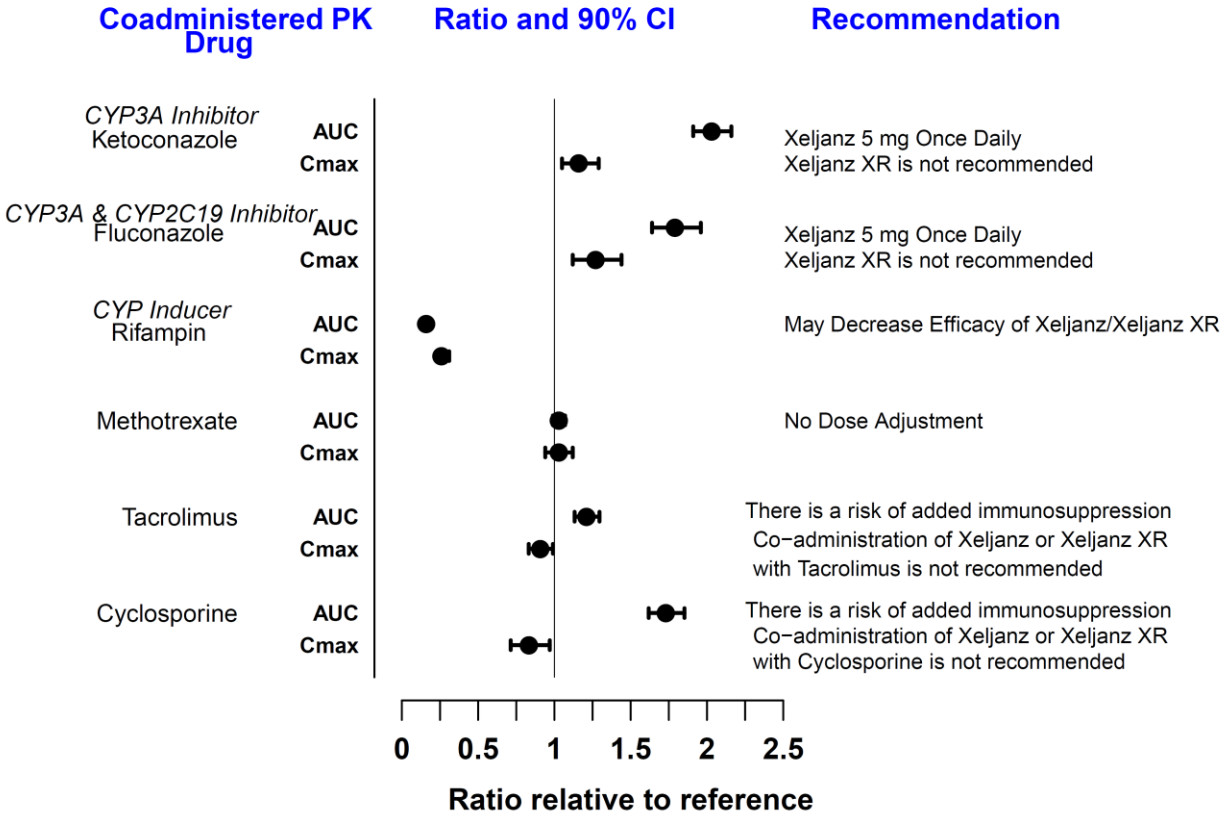
Drug	Reference	Effect	Clinical comment
Fluconazole	CT	Coadministration of fluconazole, a moderate inhibitor of CYP3A4 and a strong inhibitor of CYP2C19, increased the AUC and Cmax of tofacitinib by 79% and 27%, respectively	XELJANZ XR is not recommended in patients coadministered with medications that result in moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Maximum recommended dose is XELJANZ 5 mg once daily when coadministered with one or more medications that result in moderate inhibition of CYP3A4 and potent inhibition of CYP2C19
Tacrolimus and Cyclosporine	CT	Coadministration of tacrolimus, a mild inhibitor of CYP3A4, increased the AUC of tofacitinib by 21% and decreased the Cmax of tofacitinib by 9%. Coadministration of cyclosporine, a moderate inhibitor of CYP3A4, increased the AUC of tofacitinib by 73% and decreased Cmax of tofacitinib by 17%.	There is a risk of added immunosuppression when XELJANZ/XELJANZ XR is co-administered with potent immunosuppressive drugs (e.g: tacrolimus, cyclosporine, azathioprine). The combined use with these potent immunosuppressives has not been studied in rheumatoid arthritis patients and-is not recommended.
Rifampin	CT	Coadministration of rifampin, a strong CYP3A4 inducer, decreased the AUC and Cmax of tofacitinib by 84% and 74%, respectively	Coadministration of XELJANZ/XELJANZ XR with potent inducers of CYP3A4 may result in loss of or reduced clinical response /efficacy.
Midazolam	CT	Coadministration of XELJANZ with midazolam, a highly sensitive CYP3A4 substrate, had no effect on midazolam PK	No dosage adjustment is required for CYP3A4 substrates such as midazolam.
Oral contraceptives (Ethinyl Estradiol and Levonorgestrel)	CT	Coadministration of XELJANZ with oral contraceptives had no effect on the PK of either oral contraceptive in healthy females	No dose adjustment is required for either oral contraceptives ethinyl estradiol and levonorgestrel.

Drug	Reference	Effect	Clinical comment
Metformin	CT	Coadministration of XELJANZ with metformin, a substrate of Organic Cationic Transporter and Multidrug and Toxic Compound Extrusion, had no effect on the PK of metformin	No dosage adjustment is required for metformin.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

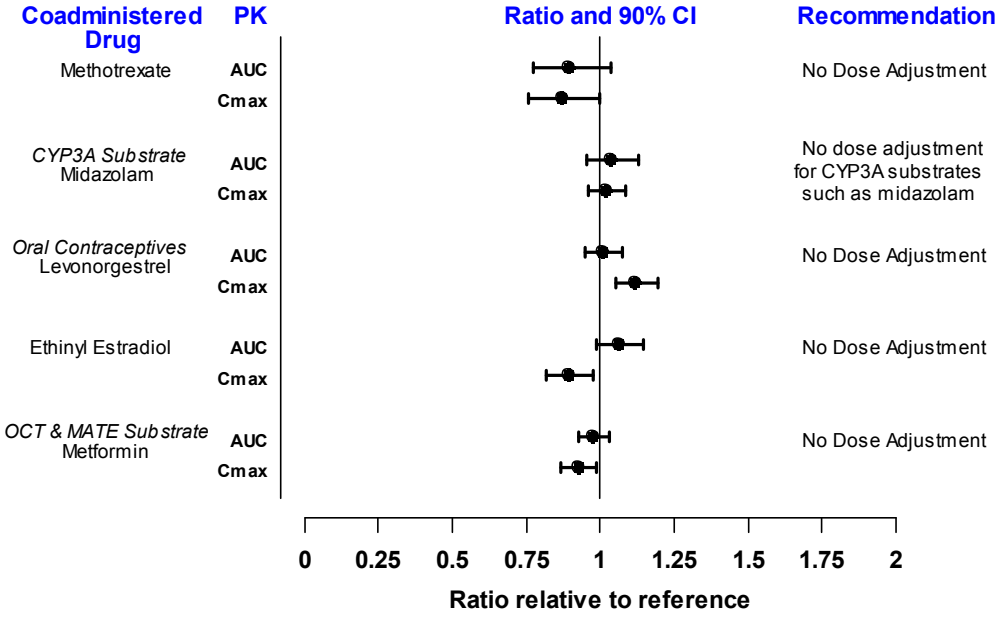
The impact of extrinsic factors on tofacitinib pharmacokinetics is summarized in Figure 1 and 2 with dosage adjustment recommendations.

Figure 1: Impact of Co-administered of drugs on Pharmacokinetics Tofacitinib



Note: Reference group is administration of tofacitinib alone; PK=Pharmacokinetics; CI=Confidence Interval

Figure 2: Impact of Tofacitinib on Pharmacokinetics of Co-administered Drugs



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

Drugs that Decrease Heart Rate and/or Prolong the PR Interval: XELJANZ results in a decrease in heart rate and an increase in the PR interval (See **WARNINGS AND PRECAUTIONS**, **Monitoring and Laboratory Tests**, **ADVERSE REACTIONS**, Electrocardiography). Caution should be observed if XELJANZ/XELJANZ XR is used concomitantly with other drugs that lower heart rate and/or prolong the PR interval, such as antiarrhythmics, beta blockers, alpha2 adrenoceptor agonists, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, and some HIV protease inhibitors.

Combination with Biological DMARDs

XELJANZ/XELJANZ XR has not been studied and is not indicated to be used in combination with biological DMARDs such as TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators.

Drug-Food Interactions

Grapefruit juice affects CYP450 3A-mediated metabolism and concomitant administration with XELJANZ/XELJANZ XR should be avoided.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Herb Interactions

St John's Wort is a CYP3A4 inducer and co-administration with XELJANZ/XELJANZ XR may result in loss of or reduced clinical response.

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

DOSAGE AND ADMINISTRATION

Dosing Considerations
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 XELJANZ/ XELJANZ XR with potent immunosuppressants or biologic DMARDS (tumor necrosis factor (TNF) antagonists, interleukin 1 receptor (IL-1R) antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, and selective co-stimulation modulators) has not been studied in rheumatoid arthritis patients and its use should be avoided.

Recommended Dose and Dosage Adjustment

XELJANZ/ XELJANZ XR Posology

Adults
XELJANZ / XELJANZ XR is to be used in combination with methotrexate.

XELJANZ / XELJANZ XR, monotherapy may be considered in cases of intolerance to methotrexate.

The recommended dose of XELJANZ is 5 mg administered twice daily. 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 between XELJANZ Tablets and XELJANZ XR Tablets
Where appropriate, 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.

Where appropriate, patients treated with XELJANZ XR 11 mg once daily may be switched to XELJANZ 5 mg twice daily 24 hours following the last dose of XELJANZ XR 11 mg.

Patients treated with XELJANZ XR 11 mg once daily who require a dose reduction due to renal or hepatic impairment or drug interactions, (see **WARNINGS AND PRECAUTIONS, Renal; WARNINGS AND PRECAUTIONS, Hepatic** and **DRUG INTERACTIONS**) may be switched to XELJANZ 5 mg once daily, 24 hours following the last dose of XELJANZ XR 11 mg once daily.

Dose Modification due to Serious Infections and Cytopenias (see Tables 3-5 below)

- It is recommended that XELJANZ/XELJANZ XR not be initiated in patients with an absolute neutrophil count (ANC) less than 1000/mm^3, hemoglobin (Hgb) levels < 9 g/d, or with a lymphocyte count less than 500 cells/mm^3(see **WARNINGS and PRECAUTIONS**).
- Dose interruption is recommended for management of lymphopenia, neutropenia and anemia (see **WARNINGS and PRECAUTIONS** and **ADVERSE REACTIONS**).
- Avoid use of XELJANZ/XELJANZ XR if a patient develops a serious infection until the infections is controlled.

Table 3: Dose Adjustments for Neutropenia

Low ANC	
Lab Value (cells/mm^3)	**Recommendation**
ANC >1000	Maintain dose
ANC 500-1000	For persistent decreases in this range, interrupt administration with XELJANZ/XELJANZ XR until ANC is >1000 cells/mm^3 When ANC is >1000 cells/mm^3, resume XELJANZ 5 mg BID When ANC is > 1000 cells/mm^3, resume XELJANZ XR 11 mg once daily.
ANC <500 (Confirmed by repeat testing)	Discontinue treatment with XELJANZ/XELJANZ XR

Table 4: Dose Adjustments for Anemia

Low Hemoglobin Value	
Lab Value (g/dL))	**Recommendation**
< 2 g/dL decrease and ≥ 9.0 g/dL	Maintain dose
≥ 2 g/dL decrease or < 8.0 g/dL (Confirmed by repeat testing)	Interrupt the administration of XELJANZ/XELJANZ XR until hemoglobin values have normalized

Table 5: Dose Adjustments for Lymphopenia Low Lymphocyte Count

Low Lymphocyte Count	
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

Dose Modification in Patients with Renal or Hepatic Impairment

XELJANZ

- XELJANZ should not be used in patients with severe hepatic impairment
- XELJANZ 5 mg once daily is the recommended dose in patients:
    - With moderate (CLcr ≥30 and <60 mL/min) or severe (CLcr ≥15 and <30 mL/min) renal insufficiency, including patients with ESRD undergoing dialysis. Use XELJANZ with Caution in this patient population.
    - With moderate hepatic impairment.

XELJANZ XR

- XELJANZ XR should not be used in patients with moderate to severe hepatic impairment.
- XELJANZ XR is not recommended in patients with moderate (CLcr ≥30 and <60 mL/min), or severe renal insufficiency (CLcr ≥15 and <30 mL/min), including patients with ESRD undergoing dialysis.

In patients with moderate hepatic impairment or moderate to severe renal impairment XELJANZ 5 mg once daily may be considered.

Dose Modification due to Drug Interactions

Coadministration of potent inducers of CYP3A4 (e.g. rifampin) with XELJANZ/XELJANZ XR may result in loss of efficacy or reduced clinical response to XELJANZ/XELJANZ XR. Coadministration of potent inducers of CYP3A4 with XELJANZ/XELJANZ XR is not recommended.

XELJANZ

- XELJANZ 5 mg once daily is the recommended dose in patients:
    - Receiving potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g ketoconazole).
    - Receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g. fluconazole).

XELJANZ XR

- XELJANZ XR is not recommended in patients
    - Receiving potent inhibitors of Cytochrome P450 3A4 (CYP3A4) (e.g ketoconazole).
    - Receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g. fluconazole).

In patients with dose modifications due to drug interactions, XELJANZ 5 mg once daily may be considered.

Special Populations

Geriatrics (>65 years)

No dosage adjustment is required in patients aged 65 years and older (see **WARNINGS and PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY** section).

Pediatrics (<18 years of age)
The safety and efficacy of XELJANZ/XELJANZ XR in children aged from neonates to less than 18 years of age has not yet been established. Therefore XELJANZ/XELJANZ XR should not be used in this patient population (see **WARNINGS AND PRECAUTIONS** and **ACTION AND CLINICAL PHARMACOLOGY** section).

Missed Dose
For a missed dose, resume at the next scheduled dose.

OVERDOSAGE

There is no experience with overdose of XELJANZ/XELJANZ XR (tofacitinib). There is no specific antidote for overdose with XELJANZ/XELJANZ XR. Treatment should be symptomatic and supportive. 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.

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

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain-containing receptors for several cytokines, including IL-2, -4,-7,-9, -15, and -21. These cytokines are integral to lymphocyte activation, proliferation, and function and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and Type I interferons. At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling.

Pharmacodynamics
Treatment with XELJANZ (tofacitinib) was associated with dose-dependent reductions of circulating CD16/56+ natural killer cells, with estimated maximum reductions occurring at approximately 8-10 weeks after initiation of therapy. These changes generally resolved within 2-6 weeks after discontinuation of treatment. Treatment with XELJANZ was associated with dose-dependent increases in B cell counts. Changes in circulating T-lymphocyte counts and T-

lymphocyte subsets were small and inconsistent. The clinical significance of these changes is unknown.
Changes in total serum IgG, M, and A levels over 6-month dosing of patients with rheumatoid arthritis were small, not dose-dependent and similar to those seen on placebo.

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 half-life.

Pharmacokinetics

XELJANZ

Following oral administration of XELJANZ, the PK profile of XELJANZ is characterized by rapid absorption (peak plasma concentrations are reached within 0.5-1 hour), rapid elimination (half-life of ~3 hours) and dose-proportional increases in systemic exposure in the therapeutic dose range. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after BID administration.

XELJANZ XR

Following oral administration of XELJANZ XR, peak plasma tofacitinib concentrations are reached at 4 hours and the half-life is ~6 hours. Steady state concentrations are achieved within 48 hours with negligible accumulation after once daily administration. At steady state, Cmin for XELJANZ XR 11 mg QD is approximately 29% lower and Ctrough is approximately 26% lower compared to XELJANZ 5 mg BID. 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

Tofacitinib is well-absorbed, with an absolute oral bioavailability of 74% following administration of XELJANZ. 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 meal.

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 α1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

Metabolism:

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.

Excretion:
Approximately 94% of a radioactive dose of XELJANZ was recovered from the urine (80%) and feces (14%), with the majority of excreted radioactivity recovered within 24 hours after dosing.

Table 6: Summary of Tofacitinib Pharmacokinetic Parameters after Repeated Oral Administration of XELJANZ 10 mg BID or Single IV Administration in Humans

	Oral Administration			**IV Administration**	
	C_{max} (ng/mL)	**$t_{½}$ (h)**	**$AUC_{0-12hrs}$ (ng·h/mL)**	**Clearance (L/h)**	**Volume of distribution (L)**
Healthy Volunteers	79.4	3.0	311	25	87
Patients	116	3.62	507	N/A (no IV data)	N/A (no IV data)

N/A = Not available; C_{max} = maximum plasma concentration; $t_{½}$ = terminal elimination half-life; AUC_{0-12} = area under the plasma concentration-time curve from time 0 to 12 hours post dose; CL = total systemic clearance; Vss = volume of distribution at steady state

Table 7: Summary of Tofacitinib Pharmacokinetic Parameters after Repeated Oral Administration of XELJANZ XR 11 mg QD in Humans

	C_{max} (ng/mL)	**$t_{½}$ (h)**	**$AUC_{0-24hrs}$ (ng·h/mL)**	**Tmax (h)**
Healthy Volunteers	38.23	5.89	269	4.0

C_{max} = maximum plasma concentration; $t_{½}$ = terminal elimination half-life; AUC_{0-24} = area under the plasma concentration-time curve from time 0 to 24 hours post dose

Special Populations and Conditions

Pediatrics (< 18 years of age):
The pharmacokinetics, safety and effectiveness of XELJANZ/XELJANZ XR in pediatric patients have not been established.

Geriatrics (>65 years of age):
Population PK analysis in rheumatoid arthritis patients indicated that elderly patients 80 years of age were estimated to have <5% higher XELJANZ AUC relative to the mean age of 55 years. Of the 3315 patients who enrolled in studies I to V, a total of 505 (15%) rheumatoid arthritis patients were 65 years of age and older, including 71 (2%) patients 75 years and older. The frequency of serious infection among XELJANZ treated subjects 65 years of age and older was higher than 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 (see **WARNINGS AND PRECAUTIONS**).

Gender
Female patients were estimated to have 7% lower XELJANZ AUC compared to male rheumatoid arthritis patients by population PK analysis.

Race
No major differences (<5%) were observed in XELJANZ AUC between White, Black and Asian patients by population PK analysis. However, there was a higher incidence of adverse events in Asian patients. Therefore, XELJANZ/XELJANZ XR should be used with caution in Asian patients (see **WARNINGS AND PRECAUTIONS**).

Body Weight
Population PK analysis in rheumatoid arthritis patients indicated that systemic exposure (AUC) of XELJANZ in the extremes of body weight (40 kg, 140 kg) were similar to that of a 70 kg patient. 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 XELJANZ is estimated to be approximately 27%.

Hepatic Impairment:
Subjects with mild and moderate hepatic impairment had 3%, and 65% higher XELJANZ AUC, respectively, compared with healthy subjects.

No dose adjustment of XELJANZ/XELJANZ XR is required in patients with mild hepatic impairment. XELJANZ XR has not been studied in patients with moderate and severe hepatic impairment. Therefore, XELJANZ XR should not be used in patients with moderate to severe hepatic impairment.

The recommended dose of XELJANZ is 5 mg once daily in patients with moderate hepatic impairment. XELJANZ/XELJANZ XR has not been studied in patients with severe hepatic impairment or in patients with positive hepatitis B virus or hepatitis C virus serology, and should not be used in these populations.

Renal Impairment:
Subjects with mild, moderate, and severe renal impairment had 37%, 43% and 123% higher XELJANZ AUC, respectively, compared with healthy subjects. In subjects with end-stage renal disease (ESRD) undergoing dialysis, the contribution of dialysis to the total clearance of tofacitinib was relatively small.

No dose adjustment of XELJANZ/XELJANZ XR is required in patients with mild renal impairment. XELJANZ XR has not been studied in patients with moderate and severe renal impairment. Therefore, XELJANZ XR is not recommended in patients with moderate and severe renal impairment, including patients with ESRD undergoing dialysis.

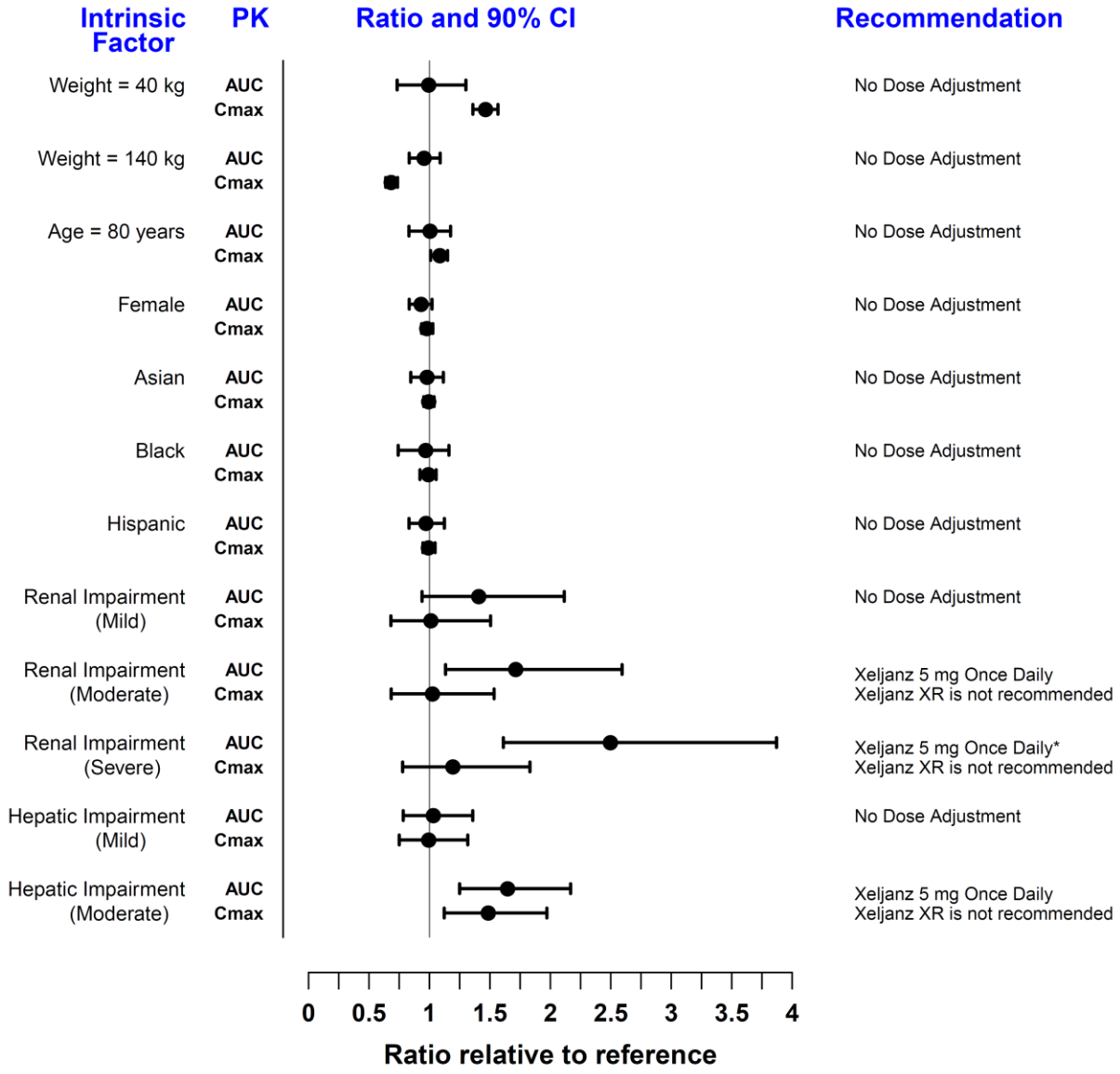
The recommended dose of XELJANZ is 5 mg once daily in patients with moderate and severe renal impairment including patients with ESRD undergoing dialysis.

In clinical trials, XELJANZ/XELJANZ XR was not evaluated in rheumatoid arthritis patients with baseline creatinine clearance values (estimated by the Cockroft-Gault equation) less than 40 mL/min.

Genetic Polymorphism:
Mean C_{max} and $AUC_{(0-\infty)}$ values of tofacitinib following administration of XELJANZ in poor metabolizers of CYP2C19 (carriers of CYP2C19*2/*2, CYP2C19*2/*3 or CYP2C19*3/*3 alleles) were approximately 15% and 17% greater, respectively, than those in normal metabolizers, indicating that CYP2C19 is a minor contributor of XELJANZ clearance.

The impact of intrinsic factors on tofacitinib following administration of XELJANZ pharmacokinetics is summarized in Figure 3 with dosage adjustment recommendations.

Figure 3: Impact of Intrinsic factors on Tofacitinib Pharmacokinetics



* Supplemental doses are not necessary in patients after dialysis
PM=poor metabolizer; PK=Pharmacokinetics; CI=Confidence Interval

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;
Reference group for genetic polymorphism data is extensive metabolizers of CYP2C19.

STORAGE AND STABILITY

Store between 15°C and 30°C.

DOSAGE FORMS, COMPOSITION AND PACKAGING

XELJANZ
Tablet: 5 mg tofacitinib (as tofacitinib citrate) (White to off white round immediate-release film-coated tablets)
HDPE bottles with desiccant and child-resistant caps containing 60 or 180 film-coated tablets.
Foil / foil blisters containing 56 film-coated tablets.

The tablet core contains Croscarmellose Sodium, Lactose Monohydrate, Magnesium Stearate, Microcrystalline Cellulose. The film coat contains HPMC 2910/Hypromellose 6 cP, Lactose Monohydrate, Macrogol/PEG 3350, Titanium dioxide, Triacetin (Glycerol Triacetate)

XELJANZ XR
Tablets: 11 mg tofacitinib (as tofacitinib citrate) (Pink oval extended-release-coated tablets)
HDPE bottles with desiccant and child-resistant caps containing 14 or 30 extended release film-coated tablets.

The tablet core contains: sorbitol, hydroxyethyl cellulose, copovidone, magnesium stearate. The Film Coat contains cellulose acetate, hydroxypropyl cellulose, HPMC 2910/hypromellose, titanium dioxide, triacetin, red iron oxide. The Printing ink contains shellac glaze, ammonium hydroxide, propylene glycol, ferrosoferric oxide/black iron oxide.

PART II: SCIENTIFIC INFORMATION

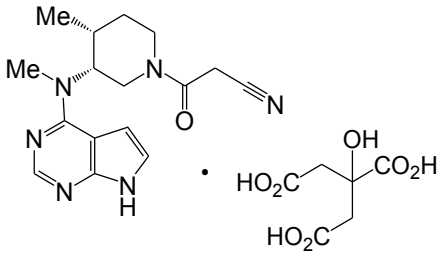
PHARMACEUTICAL INFORMATION

The active ingredient in XELJANZ (tofacitinib, CP-690,550) is the citrate salt and is designated as CP-690,550-10.

CP-690,550-10 powder is a white to off-white powder with the following chemical name: (3R,4R)-4-methyl-3-(methyl-7H-pyrrolo [2,3-d]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate (1:1) .

The solubility of CP-690,550-10 in water (unbuffered; pH 3.54) is 2.9 mg/mL.

CP-690,550-10 has a molecular weight of 504.5 Daltons (or 312.4 Daltons as the CP 690,550 free base) and a molecular formula of $C_{16}H_{20}N_6O \cdot C_6H_8O_7$. The chemical structure of CP-690,550-10 is:



CLINICAL TRIALS

Description of Clinical Studies

The efficacy and safety of XELJANZ were assessed in five randomized, double-blind, multicenter studies in patients ≥18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had ≥6 tender and ≥6 swollen joints at randomization (≥4 swollen and ≥4 tender joints for study II). XELJANZ, 5 or 10 mg BID, was given as monotherapy (study I) and in combination with nonbiologic DMARDs (study II) in patients with an inadequate response to DMARDs (nonbiologic or biologic). XELJANZ, 5 or 10 mg BID was given in combination with methotrexate in patients with either an inadequate response to MTX (studies III and study IV) or inadequate efficacy or lack of tolerance to at least one approved TNF-inhibiting biologic agent (study V).

The primary endpoints for Studies I and V were the proportion of patients who achieved an ACR20 response, mean change from baseline in HAQ-DI and proportion of patients who achieved DAS28-4(ESR) less than 2.6 at Month 3. The primary endpoints for Studies II, III, and IV were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in HAQ-DI at Month 3 and proportion of patients who achieved DAS28-4(ESR) less than 2.6 at Month 6.

Baseline demographics were generally similar among the treatment groups in each study and comparable between the studies. The mean age ranged from 50 to 56 years. Most (80 to 87%) of the patients were female. With the exception of Study A3921044 (46%), the majority (55% to 86%) of the patients in each study were white. The baseline demographics in each study are shown in Table 8.

Study demographics and trial design

Table 8: Summary of patient demographics for clinical trials in RA

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Age (yrs) Mean (Range)	Female (%)	Mean Disease Duration (yrs)
Background DMARD Studies*						
A3921046 Study II Sync	MC, DB, PG, PC, R, Background DMARD 12 Months	XELJANZ: 5 mg BID, 10 mg BID Placebo → 5 mg Placebo → 10 mg NR advance to next period at 3 months, All advance to next period at 6 months	792	52.3 (18-86)	81.4	8.1-10.2
A3921064 Study III Standard	MC, DB, PG, PC, R, Background MTX 12 Months	XELJANZ: 5 mg BID, 10 mg BID Placebo → 5 mg Placebo →10 mg Adalimumab 40 mg sc QOW NR advance to next period at 3 months, All advance to next period at 6 months..	717	52.9 (18-83)	81.7	6.9-9.0
A3921044 (1-Year Analysis) Study IV Scan	MC, DB, PG, PC, R, Background MTX 24 Months	XELJANZ: 5 mg BID, 10 mg BID Placebo → 5 mg Placebo →10 mg NR advance to next period at 3 months, All advance to next period at 6 months	797	[52.0-53.7]**(18-82)	85.2	8.8-9.5
A3921032 Study V Step	MC, DB, PG, PC, R, Background MTX 6 Months	XELJANZ: 5 mg BID, 10 mg BID Placebo → XELJANZ 5 mg BID at 3 months Placebo → XELJANZ 10 mg BID at 3 months	399	55.0 (20-84)	84.0	11.2-13.0

Monotherapy Studies						
A3921045 (Study I) Solo	MC, DB, PG, PC, R 6 Months	XELJANZ 5 mg BID, 10 mg BID Placebo →5 mg XELJANZ at 3 months, Placebo → 10 mg BID XELJANZ at 3 months	610	51.8 (21-81)	86.6	7.3-8.6

*In addition to their randomized treatment, all patients in background DMARD studies also received methotrexate (specified in Studies 1032, 1044, and 1064, permitted in Study 1046) or other DMARDs, mostly methotrexate (Study 1046).
** Range of mean across treatment groups
N = number of patients randomized, MC = multicenter, DB = double blind, PG = parallel group, PC = placebo controlled, R = randomized, NR = nonresponder (patient who failed to improve at Month 3 by at least 20% from baseline in the number of swollen and tender/pain ful joint count), MTX = methotrexate, DMARD = disease modifying antirheumatic drug, sc = subcutaneous, QOW = every other week, LT = long term, OL =op en label

Study Results

Clinical Response

In Studies I and V, patients treated with 5 mg BID XELJANZ had statistically superior ACR20, ACR50, and ACR70 response rates at month 3 vs. placebo-treated patients. In Studies II, III and IV, patients treated with 5 mg BID XELJANZ had statistically superior ACR20, ACR50, and ACR70 response rates at month 3 and 6 vs placebo-treated patients (Table 8). In Studies I, II and V, improvement in ACR20 response rate vs. placebo was observed within 2 weeks. In studies II, III, and IV, ACR response rates were maintained to 12 months in XELJANZ treated patients.

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

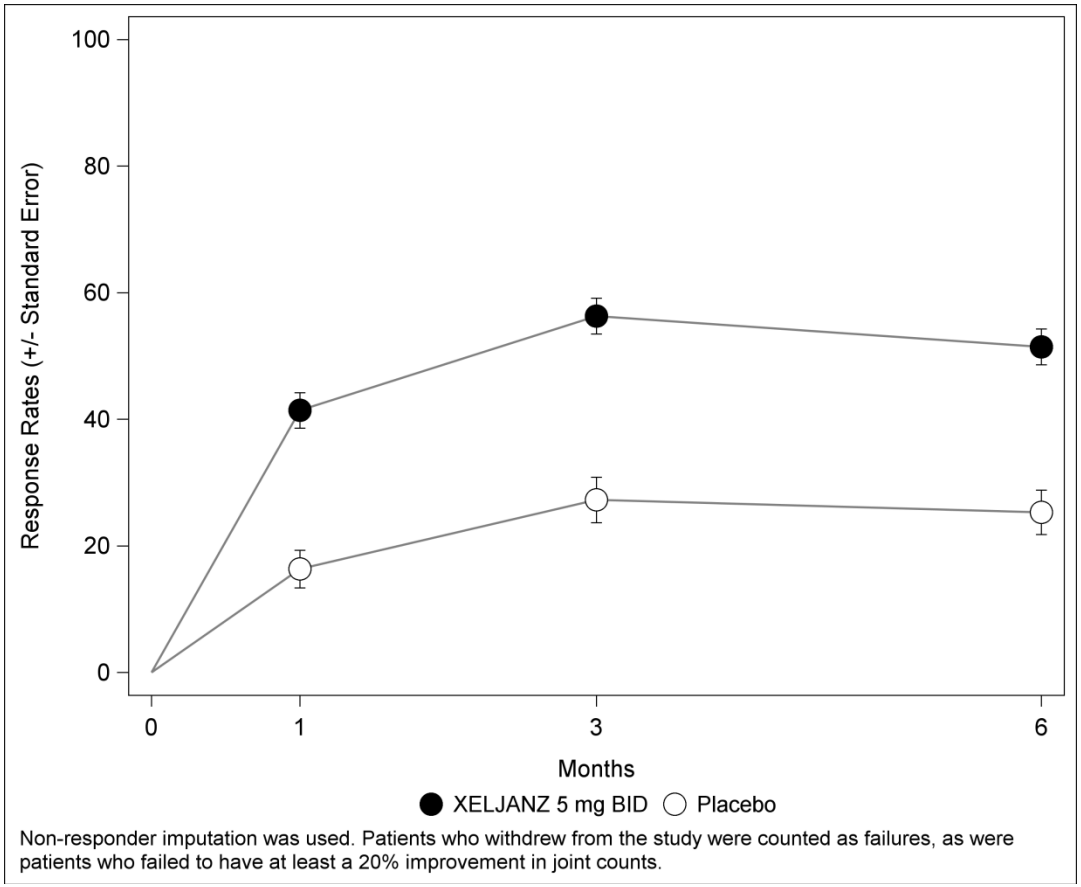
The proportion of patients with DAS28-4(ESR) less than 2.6 for each study is summarized in Table **9**.

Table 9: Proportion of Patients with an ACR Response

	Percent of Patients										
	Monotherapy		**DMARD Inadequate Responders**		**MTX Inadequate Responders**			**MTX Inadequate Responders**		**TNF Inhibitor Inadequate Responders**	
	Study I (SOLO)		**Study II (SYNC)**		**Study III (Standard)**			**Study IV (SCAN)**		**Study V (STEP)**	
Response Rate	PBO N=120	XELJANZ 5 mg BID N=241	PBO + DMARD N=157	XELJANZ 5 mg BID + DMARD N=311	PBO + MTX N=106	XELJANZ 5 mg BID + MTX N=196	ADA 40mg QW + MTX N=199	PBO + MTX N=154	XELJANZ 5 mg BID + MTX N=309	PBO N=131	XELJANZ 5 mg BID + MTX N=132
ACR20[†] Month 3 Month 6	 27% NA	 60%*** 69%	 27% 31%	 56%*** 53%***	 26% 28%	 61%*** 52%***	 56%*** 47%**	 27% 25%	 56%*** 51%***	 24% NA	 42%* 52%
ACR50[††] Month 3 Month 6	 13% NA	 31%*** 42%	 10% 13%	 27%*** 34%***	 7% 12%	 34%*** 37%***	 24%*** 28%**	 8% 8%	 29%*** 32%***	 8% NA	 27%*** 37%
ACR70[††] Month 3 Month 6	 6% NA	 15%* 22%	 2% 3%	 8%** 13%***	 2% 2%	 12%** 20%***	 9%* 9%*	 3% 1%	 11%** 15%***	 2% NA	 14%** 16%

* *p<0.05,* XELJANZ *vs. placebo + MTX/DMARD*
** *p<0.001,* XELJANZ *vs. placebo + MTX/DMARD*
*** *p<0.0001,* XELJANZ *vs. placebo + MTX/DMARD*
† Primary endpoint, Type I error controlled
†† Secondary Endpoint, Type I error not controlled

FIGURE 4: Percentage of ACR20 Responders by Visit for Study IV



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

Table 10: Proportion of Patients with DAS28-4(ESR) Less Than 2.6

DAS28-4 (ESR)Less Than 2.6	Monotherapy		DMARD Inadequate Responders		MTX Inadequate Responders			MTX Inadequate Responders		TNF Inhibitor Inadequate Responders	
	Study I (SOLO)		Study II (SYNC)		Study III (Standard)			Study IV (SCAN)		Study V (STEP)	
	PBO N=122	XELJANZ 5 mg BID N=243	PBO + DMARD N=159	XELJANZ 5 mg BID + DMARD N=315	PBO + MTX N=108	XELJANZ 5 mg BID + MTX N=204	ADA 40mg QW + MTX N=204	PBO + MTX N=160	XELJANZ 5 mg BID + MTX N=321	PBO N=132	XELJANZ 5 mg BID + MTX N=133
Proportion of responders at Month 3 (n)	4% (5)	5% (13)	NA	NA	NA	NA	NA	NA	NA	2% (2)	6% (8)
Proportion of Responders at Month 6 (n)	NA	NA	3% (4)	8%* (24)	1% (1)	5% (11)	6%* (12)	1% (2)	6%[†](19)	NA	NA

*Statistically significant ($p<0.05$)
[†]Statistical significance could not be declared in Study IV due to Step-down procedure
BID = twice daily, DAS = Disease Activity Score, ESR = erythrocyte sedimentation rate, N =number of patients, n = number of patients meeting pre-specified criteria

Physical Function Response

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg BID demonstrated significantly greater improvement from baseline in physical functioning compared to placebo at month 3 (studies I, II, III, and V). XELJANZ 5 mg BID treated patients exhibited significantly greater improved physical functioning compared to placebo as early as week 2 in studies I and II. In Study III, mean HAQ-DI improvements were maintained to 12 months in XELJANZ -treated patients. At month 3, patients in the XELJANZ 5 mg BID had decreases from baseline in HAQ-DI values (Table 11) which were not less than those of adalimumab-treated patients.

Table 11: Mean Change from Baseline in HAQ-DI

	Monotherapy		DMARD Inadequate Responders		MTX Inadequate Responders			MTX Inadequate Responders		TNF Inhibitor Inadequate Responders	
	Study I (SOLO)		Study II (SYNC)		Study III (Standard)			Study IV (SCAN)		Study V (STEP)	
LS Mean Change in HAQ-DI	PBO N=109	XELJANZ 5 mg BID N=237	PBO + DMARD N=147	XELJANZ 5 mg BID + DMARD N=292	PBO + MTX N=98	XELJANZ 5 mg BID + MTX N=188	ADA 40mg QW + MTX N=190	PBO + MTX N=146	XELJANZ 5 mg BID + MTX N=294	PBO N=118	XELJANZ 5 mg BID + MTX N=117
Month 3*	-0.22	-0.51***	-0.21	-0.47***	-0.25	-0.56***	-0.51***	-0.15	-0.4†	-0.18	-0.43**

* Primary efficacy time point
** *p<0.001,* XELJANZ *vs. placebo + MTX/DMARD*
*** *p<0.0001,*-XELJANZ *vs. placebo + MTX/DMARD*
† Statistical significance could not be declared in Study IV due to Step-down procedure
BID = twice daily, CI = confidence interval, FAS = full analysis set, LS = least squares, N = number of patients.
Results are obtained from a longitudinal linear model with change from baseline as a dependent variable and treatment, baseline, visit, region as fixed effects and patient as random effect.

DETAILED PHARMACOLOGY

Mechanism of Action

Tofacitinib is a potent, selective inhibitor of the JAK family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib, inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In cellular settings where JAK kinases signal in pairs, tofacitinib preferentially inhibits signaling by heterodimeric receptors associated with JAK3 and/or JAK1 with functional selectivity over receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib blocks signaling through the common gamma chain-containing receptors for several cytokines, including IL-2, -4,-7,-9, -15, and -21. These cytokines are integral to lymphocyte activation, proliferation, and function and inhibition of their signaling may thus result in modulation of multiple aspects of the immune response. In addition, inhibition of JAK1 will result in attenuation of signaling by additional pro-inflammatory cytokines, such as IL-6 and Type I interferons. At higher exposures, inhibition of erythropoietin signaling could occur via inhibition of JAK2 signaling.

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 were small and inconsistent. The clinical significance of these changes is unknown.

Changes in total serum IgG, M, and A levels over 6-month dosing of patients with rheumatoid arthritis were small, not dose-dependent and similar to those seen on placebo.

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 half-life.

Pharmacokinetics

XELJANZ

Following oral administration of XELJANZ, the PK profile of tofacitinib is characterized by rapid absorption (peak plasma concentrations are reached within 0.5-1 hour), rapid elimination (half-life of ~3 hours) and dose-proportional increases in systemic exposure in the therapeutic range. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after BID administration.

A geometric mean accumulation ratio (Rac) of 1.12 following BID dosing indicates little difference between single dose and steady state concentrations as well as the predictability of steady state PK from single dose data. The dose-AUC relationship was adequately described by a linear model fit to log-both sides transformed data while the dose-C_{max} relationship were best

described by a nonlinear sigmoidal, hyperbolic model fit to log-transformed C_{max} data. Although the nonlinear model provided better description of the dose-C_{max} relationship relative to a linear model, when compared to 5 mg, the mean model predicted relative changes in dose-normalized C_{max} were approximately +7% for 10 mg, +2% for 30 mg, and -10% for 50 mg doses. These small changes from linearity support the conclusion that XELJANZ C_{max} is approximately dose proportional at least up to 5 times the 10 mg dose.

XELJANZ XR

Following oral administration of XELJANZ XR, peak plasma concentrations of tofacitinib are reached at 4 hours and the half-life is ~6 hours. Steady state concentrations are achieved within 48 hours with negligible accumulation (accumulation ratio: 1.12) 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.

TOXICOLOGY

Single and Repeat-Dose Toxicity

Tofacitinib caused death in rats at single oral doses of ≥ 500 mg/kg. Single intravenous doses up to 3 mg/kg did not induce local or systemic toxicity in rats. In cynomolgus monkeys emesis and decreased activity were observed at single oral doses of ≥ 200 mg/kg (divided 3 times daily [TID], ~ 7 hours apart).

Immune and hematopoietic organ systems were identified as main targets in repeat-dose toxicity studies. Effects on the immune system (including decreased circulating lymphocytes, lymphoid depletion of lymph nodes, spleen, thymus and bone marrow, and bacterial and viral infections) were consistent with inhibition of JAK1/3. Decreases in hemoglobin, hematocrit, erythrocyte numbers and reticulocytes were attributed to JAK2 inhibition. These effects were generally reversible during a 4-week recovery phase in the 4- and 6-week monkey and rat studies, respectively. Repeated oral doses up to 10 mg/kg once daily in rats (up to approximately 15 times human clinical exposure at 5 mg BID) and 1 mg/kg twice daily in adult cynomolgus monkeys (approximately 1 times human exposure at 5 mg BID) were tolerated in studies up to 6 months and 39 weeks duration, respectively. In the 39-week juvenile monkey study, the T-dependent antibody response to antigen immunization was decreased at the high dose of 5 mg/kg twice daily, approximately 5 times human exposure at 5 mg BID.

Mutagenesis

Tofacitinib was not mutagenic in the bacterial reverse mutation assay. Reproducible increases in chromosomal abnormalities were observed in a human lymphocyte *in vitro* cytogenetic assay, at high cytotoxic concentrations with metabolic activation, but no effects were observed without metabolic activation. In follow up studies, XELJANZ was not mutagenic in mammalian cells (*in vitro* CHO/HGPRT assay) and did not induce primary DNA damage in an *in vivo/in vitro* rat hepatocyte unscheduled DNA synthesis assay. XELJANZ was also negative in the *in vivo* rat micronucleus test.

Carcinogenesis

In the 39-week repeat-dose toxicity study in adult monkeys, lymphomas were observed at the high dose of 5 mg/kg twice daily (approximately 6 times human exposure at 5 mg BID), but not at the lower dose of 1 mg/kg twice daily (approximately 1 times human exposure at 5 mg BID).

No treatment-related tumors were observed in a 6-month rasH2 transgenic mouse study up to the high dose of 200 mg/kg/day, approximately 38 times human exposure at 5 mg BID.

In a 2-year rat carcinogenicity study, tofacitinib induced benign Leydig cell tumors and malignant hibernomas (tumors of brown adipose tissue) at oral doses of ≥ 30 mg/kg/day (≥ 35 times human exposure at 5 mg BID) and benign thymomas at 100/75 mg/kg/day (approximately 187 times human exposure at 5 mg BID). No treatment-related tumors were found in rats at 10 mg/kg/day (approximately 16 times human exposure at 5 mg BID). The relevance of benign Leydig cell tumors to human risk is unknown.

Developmental and Reproductive Toxicity

Tofacitinib had no effect on fertility of male rats; however, in treated female rats XELJANZ decreased pregnancy rate, numbers of corpora lutea, implantation sites, and viable fetuses, with an increase in early resorptions at oral doses of ≥ 10 mg/kg/day (≥ 17 times human exposure at 5 mg BID). The non-observed-adverse-effect-level (NOAEL) for female fertility and early embryonic development was 1 mg/kg/day (approximately 1 times human exposure at 5 mg BID).

Tofacitinib was teratogenic (external, visceral and skeletal abnormalities) in rabbits and rats at oral doses of 30 and 100 mg/kg/day (approximately 13 and 146 times human exposure at 5 mg BID), respectively. In rabbits, teratogenic effects occurred in the absence of maternal toxicity, consisted of thoracogastroschisis, omphalocele, craniofacial malformations (microstomia, microphthalmia, and cleft lip and palate), membranous ventricular septal defects, gallbladder agenesis, short or absent tail, and skeletal malformations (fused sternebrae and vertebral and/or rib anomalies). In addition, there was an increase in postimplantation loss (early and late resorptions) and consequently, reduced number of viable fetuses. The developmental NOAEL in rabbits was 10 mg/kg/day (approximately 3 times human exposure at 5 mg BID). In rats, XELJANZ increased postimplantation loss (early and late resorptions), reduced fetal body weights, and increased incidences of fetal malformations at doses that induced maternal toxicity. Malformations suggestive of teratogenicity included anasarca, membranous ventricular septal defects, and skeletal abnormalities (absent cervical arch, bent limb bones, hemicentric thoracic centrum, and rib and sternal anomalies). The developmental NOAEL in rats was 30 mg/kg/day (approximately 58 times human exposure at 5 mg BID).

In the peri/postnatal development study in rats, tofacitinib decreased the number of delivered and live born pups, and reduced pup survival at oral doses of 50 mg/kg/day (approximately 73 times human exposure at 5 mg BID). There was no effect on sexual maturation, or the ability of these F1 generation rats to learn, mate and produce viable F2 generation fetuses of treatment of the dams at oral doses up to 10 mg/kg/day (up to 17 times human exposure at 5 mg BID).

Table 12: Summary of Toxicology Studies

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
Single-Dose Toxicity					
Single-Dose Oral Toxicity Study in Sprague-Dawley Rats (01-2063-07)	Single Dose	Rat/ Sprague-Dawley	3M, 3F	0, 500, 1000, 2000 (Oral gavage, 20 mL/kg, 0.5% Methylcellulose/ Suspension)	**500 mg/kg:** 1 female died on Day 1; red-stained fur (nose/muzzle); ↓ eosinophils, ↓ fibrinogen, ↑ ALT, ↑ AST, ↑ glucose, ↑ BUN. **≥500 mg/kg:** ↓ activity, lethargy, partially closed eyes, labored respiration, salivation; lympho-cytolysis in mesenteric lymph node and decreased numbers of lymphocytes within the minimal zone of the splenic white pulp. **1000 mg/kg:** 6/6 animals died by Day 2; necrosis of centrilobular hepatocytes. **≥1000 mg/kg:** lacrimation and cold to touch; stomach distension; necrosis of individual hepatocytes; lymphocytolysis within the splenic white pulp. **2000 mg/kg:** 6/6 animals died by Day 2; slow respiration and eye staining/nasal discharge.
Single-Dose IV Toxicity Study in Rats with a 14-Day Recovery (09GR453)	Single Dose	Rat/Sprague-Dawley	10M, 10F[b]	0, 0.5, 1, 3 (IV, 0.5-3 mL/kg, 10mM Lactic acid in normal saline)	**≤3 mg/kg:** None
Single-Day Oral Toxicity Study in Cynomolgus Monkeys (00-2063-04)	1 Day	Monkey/ Cynomolgus	2M, 2F	40, 200, 1000[c] (Oral gavage, 7 mL/kg, 0.5% Methylcellulose/Suspension	**≥200 mg/kg:** Emesis, ↓ activity
Repeat-Dose Toxicity					
Pivotal Studies					
6-Week Oral Toxicity Study with 1-Month Recovery in Sprague-Dawley Rats (01-2063-06)	6 Weeks	Rat/Sprague-Dawley	10-15/sex/dose	1, 10, 100 Oral gavage, QD, 10 mL/kg (0.5% Methylcellulose/ Suspension	**1 mg/kg/day (LOEL):** ↓ WBC count, ↓ lymphocytes, ↓ eosinophils, ↓ basophils, ↓ RBC count, ↓ HCT, ↓ HGB, lymphoid depletion in bone marrow. **10 mg/kg/day**: Same as above, + ↓ reticulocytes, lymphoid depletion in spleen, thymus, and mesenteric lymph node.

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
					100 mg/kg/day: Same as above, + ↑ neutrophils, ↑ AST. **100 mg/kg/day (Recovery)**: Recovery of reticulocytes and AST, no microscopic findings in lymphoid tissues, partial recovery of WBC count, lymphocytes, RBC parameters, and lymphoid cells in bone marrow.
6-Month Oral Toxicity Study in Rats (77435)	6 Months	Rat/Sprague-Dawley	15/sex/dose	1, 10, 100 (Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose/ Suspension)	**1 mg/kg/day (LOEL):** ↓ WBC, ↓ lymphocytes, ↓ eosinophils, ↓ basophils, ↓ large unstained cells, ↓ RBC count, ↓ HCT, ↓ HGB, ↑ neutrophils (F), ↓ spleen weight, ↓ T lymphocytes, T-cells (CD3+), T-cell subtypes (CD4+, CD8+), B cells (CD45RA+), NK cells (CD161+). **10 mg/kg/day:** Same as above, + ↓ reticulocytes; neutrophils, ↑ glucose, ↑ alkaline phosphatase; ↓ triglycerides (F), ↓ spleen weight, lymphoid atrophy (lymph nodes, spleen, thymus) (F), alveolar histiocytosis. **100 mg/kg/day:** Same as above, + ↑ neutrophils, ↑ reticulocytes, ↑ globulin; ↓ triglycerides, ↑ liver weight; ↓ thymus weight, lymphoid atrophy (GALT), hepatocellular hypertrophy.
1-Month Oral Toxicity Study with 1-Month Recovery in Cynomolgus Monkeys (01-2063-09)	4 Weeks	Monkey/ Cynomolgus	3/sex/dose	10, 50, 100 Oral gavage, TID[d], 5 mL/kg, 0.5% Methylcellulose/ Suspension	**10 mg/kg/day:** ↓ lymphocytes, ↓ lymphocyte subsets (helper T cells, cytotoxic/suppressor T cells, and NK cells, ↓ HGB. **50 mg/kg/day:** Same as above, + death, body weight loss, decreased activity, ↑ WBC, ↓ RBC count, ↓ HCT, ↓ reticulocytes, ↑ AST, ↑ ALT, ↓ Ca, ↓ neutrophil pool, slight granulocytic depletion in bone marrow, lymphoid depletion in spleen, bacterial and viral infection secondary to immunosuppression in heart, kidney, gastrointestinal tract, buccal cavity, and skin. **100 mg/kg/day:** Same as above (except no ↑ WBC count), + RBC depletion in bone marrow, and ↑ immature myeloid cells in bone marrow, lymphoid depletion in mesenteric lymph node. **50 mg/kg/day (Recovery:** Complete recovery with

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
					the exceptions of partial recovery of ↑ neutrophils, ↑ ALT and ↑ AST, ↓ (CD16+, CD3-), ↓ RBC count; rebound effect in lymphocytes, (CD4+, CD3+), and (CD8+, CD3+), lymphocytes, and reticulocytes.
39-Week Oral Toxicity Study in Monkeys (2003-0301)	39 weeks	Monkey/ Cynomolgus	4/sex/dose	0.5, 2, 10[e] Oral gavage, BID, 10 mL/kg, 0.5% Methylcellulose/ Suspension	**0.5 mg/kg/day (LOEL):** ↓ total lymphocytes, ↓ lymphocyte subsets (T-helper, -cytotoxic/suppressor and NK cells); lymphoid hyperplasia (2/4 M). **2 mg/kg/day:** Same as above +, ↓ RBC count, ↓ HCT, ↓ HGB, lymphoid hyperplasia (4/4 M) **10 mg/kg/day:** Same as above, + death, ↑ reticulocytes; RBC hyperplasia in bone marrow; lymphoid hyperplasia (3/4 M, 1/4 F); lymphoma (1/4 M, 2/4 F; 2 confirmed B-cell origin), mononuclear cell infiltrates in the heart (F).
Genotoxicity					
In Vitro Studies					
Microbial Reverse Bacterial Mutation Assay (AMES) (01-2063-11)	In Vitro	*Salmonella typhimurium, Escherichia coli*	NA	0.010-5 mg/plate Plate Incorporation for ~ 48 to 72 hours at 37°C	No genotoxic effect. No cytotoxic effect.
Mammalian Cell Mutation Assays (01-2063-16)	In Vitro	Chinese Hamster ovary (CHO)-K1-BH4 cells,	NA	16-5000 µg/mL 5-hour treatment, 6-8 day incubation	- No Genotoxic effects - Substantial cytotoxicity at 950, 1000, and 1100 µg/mL with average Day 3 relative cell survivals of 43%, 29%, and 17%, respectively.
In Vitro Cytogenetics Assay (01-2063-10)	In Vitro	Human Peripheral Lymphocytes	NA	41.8-2400 µg/mL 3 hours with activation, 3 and 24 hours without activation	**Cytotoxic Effects:** ~ 50% Mitotic suppression achieved in all treatments. **Genotoxic Effects:** XELJANZ did not significantly increase structural chromosome aberrations at 3- and 24-hour treatments without metabolic activation. At 3 hours with metabolic activation, XELJANZ increased structural chromosome aberrations at relatively cytotoxic concentrations.

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
In Vivo Studies					
In Vivo/In Vitro Rat Hepatocyte Unscheduled DNA Synthesis Study (01-2063-17)	Single Dose Hepatocytes, 2-4 and 14-16 HPD	Rat/Sprague-Dawley	M	125, 250, 250 Oral gavage, 10 mL/kg, 0.5% Methylcellulose	**Toxic/Cytotoxic Effects:** Hypoactivity, labored breathing and/or squinted eyes in the 500 mg/kg group **Genotoxic Effects:** None
In Vivo Cytogenetics (Rat Micronucleus) (01-2063-12)	Once daily for 3 days	Rat/Sprague-Dawley	6M, 6F	62.5, 125, 250 Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose	**Toxic/Cytotoxic Effects:** No mortality or adverse clinical signs attributed to drug treatment was observed. A statistically significant decrease in mean percent body weight gain was evident in the male rats. The males also showed statistically significant treatment-related reduction in mean %PCE, suggestive of bone marrow toxicity. **Genotoxic Effects**: None.
Carcinogenicity					
6-Month Oral Gavage Study in Mice (8200-368)	6 Months	Mouse/Model 001178-T (hemizygous), CB6F1/Jic-TgrasH2@Tac Mouse/Model 001178-W (homozygous wild-type), CB6F1/Jic-TgrasH2@Tac	25/sex/dose	25, 75, 200 Oral gavage, QD, 10 mL/kg, 0.5% (w/v) Methylcellulose/ Solution	**≥25 mg/kg/day:** No evidence of treatment-related carcinogenicity.
2-Year Oral Gavage in Rats (6348-463)	103 Weeks[f]	Rat/Sprague-Dawley	60-70/ sex/dose	10/10, 30/30, 75/100[g] Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose/ Solution	**10 mg/kg/day:** Benign angiomas of mesenteric lymph nodes (M). **30 mg/kg/day:** Hyperplasia and benign tumors of interstitial cells of testes (M), malignant hibernomas of multiple organs (F). **75 mg/kg/day:** Same as above (M). **100/75 mg/kg/day**: Benign thymoma in thymus (F).
Investigative					
14-Day Oral Investigative Study in Rats (10GR431)	14 Days	Rat/Sprague-Dawley	8F with BrdU pumps 5F without BrdU pumps	Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose/ Solution	XELJANZ inhibited JAK/STAT signaling in BAT as evidenced by decreased tissue levels of phosphorylated STAT3 (pSTAT3) and pSTAT5 at doses ≥10 mg/kg/day.

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
Investigative Study with Rat Brown Adipocytes (11GR016)	1 hour pre-incubation with XELJANZ then 20 minutes with oPRL and XELJANZ	Rat/Sprague-Dawley/Primary Leydig cells	In vitro	150 mM NaCl, 0.03 mM $NaHCO_3$ /Solution (oPRL), 0.1% dimethyl sulphoxide/Solution (XELJANZ)	XELJANZ inhibited the prolactin-induced increase in STAT5A/B phosphorylation.
Investigative Study with Rat Primary Leydig Cells (11GR015)	1 hour pre-incubation with XELJANZ then 15 minutes with oPRL and XELJANZ	Rat/Sprague-Dawley/ Differentiated primary brown adipocytes/ pSTAT5A/B protein	In vitro	150 mM NaCl, 0.03 mM $NaHCO_3$ /Solution (oPRL), 0.1% dimethyl sulphoxide/Solution (XELJANZ)	XELJANZ inhibited the prolactin-induced increase in STAT5A/B phosphorylation.
Reproductive and Developmental Toxicity					
Oral Fertility and Embryonic Development Study in Male and Female Rats (05GR051)	**(F) Phase 1**: 14 Days premating, throughout cohabitation and through GD 7. **(M) Phase 2**: Minimum of 63 days (beginning 28 days premating)	Rat/Sprague Dawley	20/sex/dose	1, 10, 100 Oral Gavage, QD, 10 mL/kg	**1 mg/kg/day**: No effect. **10 mg/kg/day**: ↑ Postimplantation loss. **100 mg/kg/day**: Same as above, + ↓ pregnancy rate, ↓ corpora lutea, ↓ implantation sites, ↓ viable fetuses, ↑ early resorptions, ↑ pre-implantation loss.
Oral Embryo-Fetal Development Study in Rats (04-2063-24)	GD 6-17	Rat/Sprague Dawley	20F/dose	1, 10, 30 Oral gavage, QD, 10 mL/kg	**≥1 mg/kg/day:** No effect.
Oral Embryo-Fetal Development Study in Rats (09GR353)	GD 6-17	Rat/Sprague Dawley	20F/dose	30, 100, 300 Oral gavage, QD, 10 mL/kg	**30 mg/kg/day:** No effect. **100 mg/kg/day:** ↓ Viable fetuses, ↓ uterine weight, external, visceral and skeletal malformations. **300 mg/kg/day:** ↓ Maternal body weight and food consumption, clinical signs of poor toleration, no viable fetuses to examine.

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
Oral Embryo-Fetal Development Study in Rabbits (05-2063-25)	GD 7-19	Rabbit/New Zealand White	20F/dose	10, 30, 100 Oral gavage, QD, 2 mL/kg	**10 mg/kg/day:** No effect. **30 mg/kg/day:** ↓ Viable fetuses, ↓ uterine weight, external, visceral, and skeletal malformations. **100 mg/kg/day:** Same as above, + ↓ fetal body weights, ↑ visceral variations.
Oral Developmental Peri/Postnatal Reproduction including Postnatal Behavioral/Functional Evaluation in Rats (LIA00468)	GD 6 - DL 21 (or GD 24 for rats not delivering a litter)	Rat/Sprague-Dawley	25F/dose	Oral gavage, QD during dosage period; 10 mL/kg	**10 mg/kg/day**: No effect **50 mg/kg/day**: ↓ Delivered pups, ↓ liveborn pups, ↓ pup survival, ↓ pup body weight.
Developmental and Reproductive - Juvenile					
Oral Fertility Study in Juvenile Rats (10GR250)	PND 21-70 (M) PND 21-55 (F)	Rat/Sprague-Dawley	20/sex/dose	1, 10, 100 Oral gavage, QD, 10 mL/kg 0.5% (w/v) Methylcellulose/ Suspension	**1 mg/kg/day:** No effect. **10 mg/kg/day:** ↓ BW (M), ↓ BW gain (M). **100 mg/kg/day:** Same as above (M&F).
Oral Toxicity Study in Juvenile Rats with a 2-Month Recovery (10GR307)	PND 21-49	Rat/Sprague Dawley	16/sex/dose	1, 10, 100 Oral gavage, QD, 10 mL/kg 0.5% (w/v) Methylcellulose/ Suspension	**1 mg/kg/day:** Females: ↓WBC, ↓ lymphocytes, eosinophils, basophils Males only: ↑ vacuolation in brown adipose tissue, ↓ T cells, ↓ helper T cells, ↓ cytotoxic T cells, ↓ B cells, ↓ NK cells. **10 mg/kg/day:** Same as above, ↓ T cells, ↓ helper T cells, ↓cytotoxic T cells, ↓B cells, ↓ NK cells. Males: ↓ WBC, ↓ lymphocytes, eosinophils, basophils. Females: ↓ body weight and body weight gain, ↓ reticulocytes, ↓ cellularity (thymus) - females, ↓ cellularity (spleen), ↓ lymphoid cellularity-mesenteric lymph node. **100 mg/kg/day:** Same as above, ↓ body weight and body weight gain (M), ↓ RBC, ↓ cellularity: inguino-femoral lymph node, mandibular lymph node.

Study Type	Treatment Duration	Species/ Test system	Animals/ Group	Dose (mg/kg/day)[a]	Results
39-Week Oral Toxicity in Juvenile Monkeys with a 26-Week Recovery (Interim Report) (2501-010)	39 Weeks	Monkey/ Cynomolgus	4/sex/dose	0.5, 2, 10 Oral gavage, BID, 5 mL/kg 0.5% (w/v) Methylcellulose/ Suspension	**0.5 mg/kg/day:** No effect. **2 mg/kg/day:** ↓ total lymphocytes (M), ↓ lymphocyte subsets (NK cells, effector CD8+ T cells, CD8+ T cells (M), ↓ thymus weight (M), ↓ spleen weight (F). **10 mg/kg/day:** ↓ total lymphocytes (M + F), ↓ RBC count, ↓ HCT, ↓ HGB, ↓ lymphocyte subsets (NK cells, CD4+ and CD8+ T cells, naïve CD4+ and CD8+ T cells, central and effector memory CD8+ cells), ↓ spleen and thymus weight.

[a] Doses are expressed as mg active moiety/kg/day unless otherwise noted.
[b] Five/sex were necropsied on Day 2 and 5/sex were retained for a 14-day recovery period and necropsied on Day 15.
[c] 13, 67, 333 mg/kg TID; 7 hours apart.
[d] 3.33, 16.7, 33.3mg/kg TID; 7 hours apart.
[e] 0.25, 1, 5, mg/kg BID; 12 hours apart.
[f] All surviving males in Group 4 were sacrificed on Day 654 (Week 94) of the dosing phase. All surviving males in Group 1 through Group 3 were sacrificed on Day 686 (Week 98) of the dosing phase. All surviving females were sacrificed on Day 715 (Week 103) of the dosing phase.
[g] Dose was lowered from 100 to 75 mg/kg/day starting on Day 133.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; BAT = Brown adipose tissue; BID = Twice daily; BrdU = 5-bromo-2'deoxyuridine; BUN = Blood urea nitrogen; Ca = Calcium; CHO = Chinese hamster ovary; CD = Cluster of differentiation; DL = Day of lactation; F = Female; GALT = Gut associated lymphoid tissue; GGT = Gamma glutamyl transferase; GD = Gestation Day; HGB = Hemoglobin; HCT = Hematocrit; HPD = Hours postdose; IV = Intravenous; JAK = Janus kinase; LOEL = Lowest observed effect level; M = Male; NA = Not applicable; NaCl = Sodium chloride; $NaHCO_3$ = Sodium bicarbonate; NK = Natural killer; oPRL = Ovine prolactin; PND = Postnatal day; PCE = Polychromatic erythrocytes; pSTAT = Phosphorylated signal transducer and activator of transcription; QD = Once daily; RBC = Red blood cells; STAT = Signal transducer and activator of transcription; TID = Three times daily; WBC = White blood cells.

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PART III: CONSUMER INFORMATION

Pr XELJANZ®
Tofacitinib tablets

XELJANZ® XR
Tofacitinib extended-release tablets

This leaflet is part III of a three-part "Product Monograph" published when XELJANZ/ XELJANZ XR was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about XELJANZ/ XELJANZ XR. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
XELJANZ/XELJANZ XR (tofacitinib) in combination with methotrexate (MTX) is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA), in adult patients with moderately to severely active RA who have had an inadequate response to MTX.

What it does:
XELJANZ/XELJANZ XR is believed to interfere with the activity of an enzyme called Janus kinase (JAK), which activates other cellular components which normally start the immune response in your body. By reducing the immune response XELJANZ/XELJANZ XR reduces the signs and symptoms of rheumatoid arthritis.

When it should not be used:
If you are allergic to tofacitinib or any other non-medicinal ingredients in XELJANZ/XELJANZ XR, you should not take XELJANZ/XELJANZ XR (See **What the nonmedicinal ingredients are**).

What the medicinal ingredient is:
The active ingredient of XELJANZ/XELJANZ XR is called tofacitinib citrate

What the nonmedicinal ingredients are:
XELJANZ: Croscarmellose sodium, HPMC 2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, magnesium stearate, microcrystalline cellulose, titanium dioxide, triacetin

XELJANZ XR: ammonium hydroxide, cellulose acetate, copovidone, ferrosoferric oxide/black iron oxide, hydroxyethyl cellulose, hydroxypropyl cellulose, HPMC 2910/hypromellose, magnesium stearate, propylene glycol, red iron oxide, shellac glaze, sorbitol, titanium dioxide, triacetin.

What dosage forms it comes in:
XELJANZ is supplied as 5 mg tablets and is available in bottles or foil blisters.
XELJANZ XR is supplied as 11 mg tablets and is available in bottles.

WARNINGS AND PRECAUTIONS

Serious Warning and Precautions:

- XELJANZ/XELJANZ XR is a medicine that affects your immune system and can lower the ability of your body to fight infections such as tuberculosis, and infections caused by other bacteria, fungi, or viruses that can spread throughout the body. These infections may lead to hospitalization or death. Most patients who developed these infections were taking other medicines that make it harder to fight infections at the same time such as methotrexate or corticosteroids. You should not be using XELJANZ/ XELJANZ XR if you have any kind of infection.
- If a serious infection develops, stop XELJANZ/XELJANZ XR and contact your doctor.
- Your doctor will closely monitor you for the signs and symptoms of infection during and after the treatment with XELJANZ/ XELJANZ XR.
- Lymphoma, other cancers and other serious conditions have been reported in patients treated with XELJANZ

Before taking 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
  - muscle aches
  - cough
  - shortness of breath
  - blood in spit
  - weight loss
  - warm, red, or painful skin or sores on your body
  - diarrhea or stomach pain
  - burning when you urinate or urinating more often than normal
  - feeling very tired
- are being treated for an infection, get a lot of infections or have infections that keep coming back
- have diabetes, HIV/AIDS, or a weak immune system. People with these conditions have a higher chance for infections.
- have tuberculosis, or a history of tuberculosis or have been in close contact with someone with tuberculosis
- have or have had hepatitis B or C
- have gastrointestinal perforations (tear in the stomach or intestines).
- have diverticulitis (inflammation in parts of the large intestine)
- have ulcers in your stomach or intestines
- have low blood counts: treatment with XELJANZ can be associated with low red blood cell counts (anemia), with low white blood cell counts (neutrophils or lymphocytes). Your health care provider will monitor your blood counts frequently after you start XELJANZ/XELJANZ XR, and may adjust your dose of XELJANZ/XELJANZ XR or

withhold the drug temporarily in the event your blood counts drops too low, or administer additional supportive medicines to help your body regain normal blood cell levels.
- have high cholesterol. Your health care provider should monitor your liver tests routinely and blood cholesterol level 4-8 weeks after your start receiving XELJANZ/XELJANZ XR.
- are pregnant or planning to become pregnant
- are breastfeeding or planning to breastfeed. Women should not breastfeed while being treated with XELJANZ/XELJANZ XR
- have or had any type of cancer
- have liver or kidney problems
- have a history of interstitial lung disease
- have muscle pain or muscle weakness
- develop new skin lesions during or after therapy or if existing lesions change appearance.
- are planning to get vaccinated. Certain types of vaccines (shots) should not be given when taking XELJANZ/XELJANZ XR. Before you start XELJANZ/XELJANZ XR, you should be up to date with all recommended vaccinations
- have chest pain or any heart problems.

Before taking XELJANZ XR, tell your doctor if you have known narrowing or blockage of your digestive tract (intestines or another part of your bowel are not as wide as normal)

If you are of child-bearing age, you should use an effective method of contraception while taking XELJANZ/XELJANZ XR and for 4 to 6 weeks after you stop taking XELJANZ/XELJANZ XR.

INTERACTIONS WITH THIS MEDICATION

It is important that your healthcare provider be aware of all medications you are taking prior to starting XELJANZ/XELJANZ XR including the Disease Modifying Anti-Rheumatic Drugs (DMARDs) such as Cimzia™. Enbrel®,Humira®, Kineret®, Orencia®, Remicade®, Rituxan® and Simponi™.

- Tell your doctor if you are taking immunosuppressants (e.g. tacrolimus, sirolimus, cyclosporine), antiarrythmics, beta-blockers, calcium channel blockers, cholinesterase inhibitors, HIV protease inhibitors, rifampin, ketoconazole, fluconazole.
- Tell your doctor if you have received any vaccines (shots) within 1 month prior to starting XELJANZ.
- Avoid grapefruit juice
- St. John's Wort (an herbal medicine also known as hypericum perforatum) may reduce the response to XELJANZ/XELJANZ XR.

PROPER USE OF THIS MEDICATION

Usual adult dose:

The recommended dose of XELJANZ is 5 mg taken by mouth twice daily.

The recommended dose of XELJANZ XR is 11 mg taken by mouth once daily. Swallow XELJANZ XR tablets whole. Do not crush, split or chew the tablets.

Patients taking XELJANZ/XELJANZ XR are usually also prescribed methotrexate.

XELJANZ/XELJANZ XR can be taken with or without food.

Your doctor may reduce the dose if you have liver or kidney problems. You should not increase the dose.

XELJANZ/XELJANZ XR treatment should not be used if you have or develop a serious infection until the infection is controlled.

Overdose

In case of a drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you have missed your dose of XELJANZ/XELJANZ XR, take the next dose as planned at the next scheduled time. Do not take a double dose to make up for a forgotten dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

These are not all the possible side effects you may feel when taking XELJANZ/XELJANZ XR. If you experience any side effects not listed here, contact your healthcare professional.

The side effects of XELJANZ include:

- Upper respiratory tract infection (such as a cold)
- Nasopharyngitis (nose or throat infection runny or stuffy nose)
- Headaches
- High blood pressure
- Diarrhea
- Nausea(feeling queasy)
- Indigestion (heartburn or upset stomach)
- Cough
- Influenza (flu)
- Dizziness
- Vomiting
- Back pain

If any of the above affects you severely, tell your doctor or pharmacist.

XELJANZ/XELJANZ XR may cause abnormal blood test results. Your doctor will decide when to perform blood tests and will interpret the results

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your healthcare professional**		**Stop taking drug and get immediate medical help**
		Only if severe	**In all cases**	
Common	Pneumonia (infection with coughing, fever, fatigue)		✓	
	Urinary tract infections (difficulty or increased need to urinate, pain or burning sensation when passing urine, pain in the pelvis or mid-back, urine that appears cloudy)		✓	
	High blood pressure		✓	
	Gastritis, (abdominal pain, loss of appetite)		✓	
	Shingles/ Herpes Zoster (painful skin rash with blisters)		✓	
	Cellulitis (skin infection with redness, swelling and painful skin)		✓	
Uncommon	Bronchitis (cough, fatigue, shortness of breath)		✓	
	Flu (cough, sore throat, feverish chills)		✓	
	Skin lesions during or after therapy or if existing lesions change appearance		✓	
	Anemia (fatigue, loss of energy, weakness, shortness of breath)		✓	
	Swelling of legs and ankles or the arms and hands (Peripheral edema)		✓	
	Congestive heart failure (shortness of breath when you exert yourself or lie down, swelling in your legs, ankles and feet, irregular heartbeat, persistent cough)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

HOW TO STORE IT

Store between 15°C and 30°C.
Keep out of sight and reach of children.

REPORTING SIDE EFFECTS

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about XELJANZ/ XELJANZ XR:

• Talk to your healthcare professional;

• Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Website (https://www.canada.ca/en/health-canada.html), the manufacturer's website (http://www.Pfizer.ca) or by calling the sponsor, Pfizer Canada Inc., at 1-800-463-6001.

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