PRODUCT MONOGRAPH

P*XELJANZ™
Tofacitinib tablets
5 mg tofacitinib (as tofacitinib citrate)
Tablets for oral administration
Anti-rheumatic, immunomodulator agent

Date of Preparation:
15 September 2015

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Kirkland, Quebec H9J 2M5

TM PF PRISM C.V.
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Clinically Relevant Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Tofacitinib tablets 5 mg (as tofacitinib citrate)</td>
<td>For a complete listing see Dosage Forms, Composition and Packaging section.</td>
</tr>
</tbody>
</table>

INDICATIONS AND CLINICAL USE

XELJANZ (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 (tofacitinib) as monotherapy.

Limitations of use: Use of XELJANZ 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 in pediatric patients have not been established. Therefore XELJANZ 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 (see WARNINGS and PRECAUTIONS, DOSAGE AND ADMINISTRATION and ACTION AND CLINICAL PHARMACOLOGY section).

CONTRAINDICATIONS
WARNINGS AND PRECAUTIONS

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with XELJANZ (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 until the infection is controlled.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ use.
- Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized disease.
- Bacterial, viral, and other infections due to opportunistic pathogens.

Treatment with XELJANZ 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, 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).

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 (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 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 on chronic viral hepatitis reactivation is unknown. XELJANZ 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 has not been studied in patients with severe hepatic impairment, and should not be used in these patients. Dose adjustment is recommended for patients with moderate hepatic impairment (see DOSAGE and ADMINISTRATION).

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, and urinary tract infection. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcus, esophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus, and BK virus 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., histoplasmosis, coccidioidomycosis, and listeriosis).
XELJANZ 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 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 should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes.

Treatment with XELJANZ was associated with increased rates of infections in Asian patients compared to other races (see Special Populations and ADVERSE EVENTS). XELJANZ 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.

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 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.

**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 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.
**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 should be used with caution in patients with a risk or history of ILD.

**Immunologic**

XELJANZ can increase the risk of infections and immunosuppression when co-administered with potent immunosuppressants such as cyclosporine, azathioprine and tacrolimus. Combined use of XELJANZ 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 response to vaccination or on the secondary transmission of infection by live vaccines to patients receiving XELJANZ. It is recommended that live vaccines not be given concurrently with XELJANZ.

It is recommended that all patients be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating XELJANZ therapy. 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 (excluding nonmelanoma skin cancer [NMSC])**

The possibility exists for XELJANZ to affect host defenses against malignancies. The impact of treatment with XELJANZ on the development and course of malignancies is not known, but malignancies were observed in clinical studies.
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. While patients with rheumatoid arthritis, particularly those with highly active disease, may be at a higher risk (up to several fold) for the development of lymphoma, the role of Janus-associated kinase (JAK) inhibition in the development of lymphoma is not known.

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**
Dosage adjustment 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**
There are no adequate and well-controlled studies on the use of XELJANZ 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. XELJANZ should not be used during pregnancy (see TOXICOLOGY section).

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

**Pediatrics (<18 years of age)**
The safety and effectiveness of XELJANZ in pediatric patients have not been established (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 (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 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/mm³ were associated with an increased incidence of treated and serious infections.

Avoid initiation of XELJANZ treatment in patients with a low lymphocyte count (i.e., less than 500 cells/mm³). In patients who develop a confirmed absolute lymphocyte count less than 500 cells/mm³, XELJANZ 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/mm³) compared to placebo.

Avoid initiation of XELJANZ treatment in patients with a low neutrophil count (i.e., ANC<1000/mm³). For patients who develop a persistent ANC of 500-1000/mm³, interrupt dosing until ANC is >1000 cells/mm³. In patients who develop an absolute neutrophil count <500 cells/mm³, 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 treatment in patients with low hemoglobin values (i.e., <9 g/dL). Treatment with XELJANZ should be interrupted in patients who develop hemoglobin levels <8 g/dL or whose hemoglobin level drops >2 g/dL on treatment.

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 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 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 and every 6 months thereafter.

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

Lymphocytes, neutrophils and hemoglobin tests should be performed at baseline, approximately 4-8 weeks after initiation with XELJANZ 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 (see WARNINGS AND PRECAUTIONS, Cardiovascular; ADVERSE REACTIONS, ECG Findings; DRUG INTERACTIONS).
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 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)

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

**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, tuberculosiis, 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/mm³ 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/mm³ 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/mm³ 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/mm³ observed in any treatment group.

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

In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical 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 XELJANZ is primarily mediated by CYP3A4 with minor contribution from CYP2C19.

In vitro studies indicate that XELJANZ 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\text{max} of a 5 mg BID dose.

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

XELJANZ exposure is increased when 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). XELJANZ exposure is decreased when coadministered with potent CYP3A4 inducers (e.g. rifampin). Inhibitors of CYP2C19 or P-glycoprotein are unlikely to alter the PK of XELJANZ.

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 XELJANZ does not vary with time, indicating that XELJANZ does not normalize CYP enzyme activity in RA patients. Therefore, coadministration
with XELJANZ 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**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Effect</th>
<th>Clinical comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>CT</td>
<td>Coadministration with methotrexate (15-25 mg MTX once weekly) had no effect on the PK of XELJANZ and decreased methotrexate AUC and Cmax by 10% and 13% respectively.</td>
<td>No dose adjustment is required for either drug.</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>CT</td>
<td>Coadministration of ketoconazole, a strong CYP3A4 inhibitor, with a single dose of XELJANZ increased the AUC and Cmax of XELJANZ by 103% and 16%, respectively.</td>
<td>Maximum recommended dose of XELJANZ is 5 mg once daily when coadministered with strong inhibitors of CYP3A4</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>CT</td>
<td>Coadministration of fluconazole, a moderate inhibitor of CYP3A4 and a strong inhibitor of CYP2C19, increased the AUC and Cmax of XELJANZ by 79% and 27%, respectively.</td>
<td>Maximum recommended dose of XELJANZ is 5 mg once daily when coadministered with one or more medications that result in moderate inhibition of CYP3A4 and potent inhibition of CYP2C19</td>
</tr>
<tr>
<td>Tacrolimus and Cyclosporine</td>
<td>CT</td>
<td>Coadministration of tacrolimus, a mild inhibitor of CYP3A4, increased the AUC of XELJANZ by 21% and decreased the Cmax of XELJANZ by 9%. Coadministration of cyclosporine, a moderate inhibitor of CYP3A4, increased the AUC of XELJANZ by 73% and decreased Cmax of XELJANZ by 17%.</td>
<td>There is a risk of added immunosuppression when XELJANZ 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.</td>
</tr>
<tr>
<td>Rifampin</td>
<td>CT</td>
<td>Coadministration of rifampin, a strong CYP3A4 inducer, decreased the AUC and Cmax of XELJANZ by 84% and 74%, respectively.</td>
<td>Coadministration of XELJANZ with potent inducers of CYP3A4 may result in loss of or reduced clinical response /efficacy.</td>
</tr>
<tr>
<td>Drug</td>
<td>Reference</td>
<td>Effect</td>
<td>Clinical comment</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-----------</td>
<td>------------------------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Midazolam</td>
<td>CT</td>
<td>Coadministration of XELJANZ with midazolam, a highly sensitive CYP3A4 substrate, had no effect on midazolam PK</td>
<td>No dosage adjustment is required for CYP3A4 substrates such as midazolam.</td>
</tr>
<tr>
<td>Oral contraceptives (Ethinyl Estradiol and Levonorgestrel)</td>
<td>CT</td>
<td>Coadministration of XELJANZ with oral contraceptives had no effect on the PK of either oral contraceptive in healthy females</td>
<td>No dose adjustment is required for either oral contraceptives ethinyl estradiol and levonorgestrel.</td>
</tr>
<tr>
<td>metformin</td>
<td>CT</td>
<td>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</td>
<td>No dosage adjustment is required for metformin.</td>
</tr>
</tbody>
</table>

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 drugs on Pharmacokinetics of XELJANZ**

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>PK Ratio and 90% CI</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A Inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A &amp; CYP2C19 Inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP Inducer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclosporine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Reference group is administration of tofacitinib alone; 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 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 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 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 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 (tofacitinib) is coadministered with potent immunosuppressive drugs (e.g. azathioprine, tacrolimus, cyclosporine). Combined use of XELJANZ 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**

**Posology**

**Adults**
The recommended posology is 5 mg administered twice daily in combination with methotrexate.

Monotherapy may be considered in cases of intolerance to methotrexate.

XELJANZ is given orally with or without food.

**Dose Modification due to Serious Infections and Cytopenias** (see Tables 3-5 below)
- It is recommended that XELJANZ not be initiated in patients with an absolute neutrophil count (ANC) less than 1000/mm³, hemoglobin (Hgb) levels < 9 g/d, or with a lymphocyte count less than 500 cells/mm³ (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 if a patient develops a serious infection until the infections is controlled.

**Dose Modification in Patients with Renal or Hepatic Impairment**
- XELJANZ dosage should be reduced to 5 mg once daily in patients:
  - With moderate (\(\text{CLcr} \geq 30\) and < 60 mL/min) or severe (\(\text{CLcr} \geq 15\) and < 30 mL/min) renal insufficiency
  - With moderate hepatic impairment
- XELJANZ should not be used in patients with severe hepatic impairment.

**Dose Modification due to Drug Interactions**
- XELJANZ should be reduced to 5mg once daily 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).
Coadministration of potent inducers of CYP3A4 (e.g. rifampin) with XELJANZ may result in loss of or reduced clinical response to XELJANZ. Coadministration of potent inducers of CYP3A4 with XELJANZ is not recommended.

**Table 3: Dose Adjustments for Neutropenia**

<table>
<thead>
<tr>
<th>Low ANC</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC &gt;1000</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>ANC 500-1000</td>
<td>For persistent decreases in this range, interrupt administration with XELJANZ until ANC is &gt;1000 cells/mm³</td>
</tr>
<tr>
<td>ANC &lt;500 (Confirmed by repeat testing)</td>
<td>Discontinue treatment with XELJANZ</td>
</tr>
</tbody>
</table>

**Table 4: Dose Adjustments for Anemia**

<table>
<thead>
<tr>
<th>Low Hemoglobin Value</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2 g/dL decrease and ≥ 9.0 g/dL</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>≥ 2 g/dL decrease or &lt; 8.0 g/dL (Confirmed by repeat testing)</td>
<td>Interrupt the administration of XELJANZ until hemoglobin values have normalized</td>
</tr>
</tbody>
</table>

**Table 5: Dose Adjustments for Lymphopenia Low Lymphocyte Count**

<table>
<thead>
<tr>
<th>Low Lymphocyte Count</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocyte count greater than or equal to 500</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>Lymphocyte count less than 500 (Confirmed by repeat testing)</td>
<td>Discontinue XELJANZ</td>
</tr>
</tbody>
</table>

**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 in children aged from neonates to less than 18 years of age has not yet been established (see **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 (tofacitinib). There is no specific antidote for overdose with XELJANZ. 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**
XELJANZ 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, XELJANZ, inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In cellular settings where JAK kinases signal in pairs, XELJANZ 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 XELJANZ 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**

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.

**Absorption:**
XELJANZ is well-absorbed, with an absolute oral bioavailability of 74%. Coadministration of XELJANZ with a high-fat meal resulted in no changes in AUC while C\text{max} was reduced by 32%. In clinical trials, XELJANZ was administered without regard to meal.

**Distribution:**
After intravenous administration, the volume of distribution is 87 L. The protein binding of XELJANZ is ~40%. XELJANZ binds predominantly to albumin and does not appear to bind to \(\alpha\)1-acid glycoprotein. XELJANZ distributes equally between red blood cells and plasma.

**Metabolism**
Clearance mechanisms for XELJANZ are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of XELJANZ 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 XELJANZ, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. The pharmacologic activity of XELJANZ 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 XELJANZ Pharmacokinetic Parameters after Repeated Oral Administration of 10 mg BID or Single IV Administration in Humans**

<table>
<thead>
<tr>
<th>Oral Administration</th>
<th>IV Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C_{\text{max}}) (ng/mL)</td>
<td>(t_{1/2}) (h)</td>
</tr>
<tr>
<td>Healthy Volunteers</td>
<td>79.4</td>
</tr>
<tr>
<td>Patients</td>
<td>116</td>
</tr>
</tbody>
</table>
N/A = Not available; $C_{\text{max}}$ = maximum plasma concentration; $t^{1/2}$ = 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

**Special Populations and Conditions**

**Pediatrics (< 18 years of age):**
The pharmacokinetics, safety and effectiveness of XELJANZ 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 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 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 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 ($C_{\text{max}}$) and lower trough ($C_{\text{min}}$) 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 AUC, respectively, compared with healthy subjects.

No dose adjustment is required in patients with mild hepatic impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment. XELJANZ 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 AUC, respectively, compared with healthy subjects. In subjects with end-stage renal disease (ESRD), the contribution of dialysis to the total clearance of XELJANZ was relatively small.

No dose adjustment is required in patients with mild renal impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with moderate and severe renal impairment, including patients with ESRD.

In clinical trials, XELJANZ 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 $C_{\text{max}}$ and $AUC_{(0-\infty)}$ values 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 XELJANZ pharmacokinetics is summarized in Figure 3 with dosage adjustment recommendations.
Figure 3: Impact of Intrinsic factors on XELJANZ-Pharmacokinetics

<table>
<thead>
<tr>
<th>Intrinsic Factor</th>
<th>PK</th>
<th>Ratio and 90% CI</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight = 40 kg</td>
<td>AUC</td>
<td></td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight = 140 kg</td>
<td>AUC</td>
<td></td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age = 80 years</td>
<td>AUC</td>
<td></td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>AUC</td>
<td></td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>AUC</td>
<td></td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>AUC</td>
<td></td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>AUC</td>
<td></td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Impairment (Mild)</td>
<td>AUC</td>
<td></td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Impairment (Moderate)</td>
<td>AUC</td>
<td></td>
<td>Reduce Dose to 5 mg Once Daily</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Impairment (Severe)</td>
<td>AUC</td>
<td></td>
<td>Reduce Dose to 5 mg Once Daily*</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment (Mild)</td>
<td>AUC</td>
<td></td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic Impairment (Moderate)</td>
<td>AUC</td>
<td></td>
<td>Reduce Dose to 5 mg Once Daily</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genetic Polymorphism (CYP2C19 PMs)</td>
<td>AUC</td>
<td></td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td></td>
<td>Cmax</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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

Tablet: 5 mg (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)
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_{6}O•C_{6}H_{8}O_{7}. The chemical structure of CP-690,550-10 is:

XELJANZ is supplied for oral administration as a 5 mg white round immediate-release film-coated tablet. Each tablet of XELJANZ contains the appropriate amount of XELJANZ as a citrate salt and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, magnesium stearate, HPMC 2910/Hypromellose 6cP, titanium dioxide, macrogol/PEG3350, triacetin.
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 7.
## Study demographics and trial design

### Table 7: Summary of patient demographics for clinical trials in RA

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Treatment</th>
<th>N</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A3921045</td>
<td>Solo MC, DB, PG, R 6 Months</td>
<td>XELJANZ 5 mg BID, 10 mg BID Placebo → 5 mg XELJANZ at 3 months, Placebo → 10 mg BID XELJANZ at 3 months</td>
<td>610</td>
<td>51.8 (21-81)</td>
</tr>
</tbody>
</table>

*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/painful joint count), MTX = methotrexate, DMARD = disease modifying antirheumatic drug, sc = subcutaneous, QOW = every other week, LT = long term, OL = open 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 8: Proportion of Patients with an ACR Response

<table>
<thead>
<tr>
<th>Percent of Patients</th>
<th>Monotherapy</th>
<th>DMARD Inadequate Responders</th>
<th>MTX Inadequate Responders</th>
<th>MTX Inadequate Responders</th>
<th>TNF Inhibitor Inadequate Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study I (SOLO)</td>
<td>Study II (SYNC)</td>
<td>Study III (Standard)</td>
<td>Study IV (SCAN)</td>
<td>Study V (STEP)</td>
</tr>
<tr>
<td>Response Rate</td>
<td>PBO</td>
<td>XELJANZ 5 mg BID</td>
<td>XELJANZ 5 mg BID + DMARD</td>
<td>ADA 40mg QW + MTX</td>
<td>PBO</td>
</tr>
<tr>
<td>N=120</td>
<td>N=241</td>
<td>N=157 (311)</td>
<td>N=196 (311)</td>
<td>N=199 (309)</td>
<td>N=131</td>
</tr>
<tr>
<td>ACR20† Month 3</td>
<td>27%</td>
<td>60%***</td>
<td>27%</td>
<td>26%</td>
<td>27%</td>
</tr>
<tr>
<td>Month 6</td>
<td>69%</td>
<td>56%***</td>
<td>56%***</td>
<td>56%***</td>
<td>56%***</td>
</tr>
<tr>
<td></td>
<td>31%</td>
<td>53%***</td>
<td>52%***</td>
<td>47%**</td>
<td>51%***</td>
</tr>
<tr>
<td>ACR50‡‡ Month 3</td>
<td>13%</td>
<td>31%***</td>
<td>10%</td>
<td>7%</td>
<td>24%***</td>
</tr>
<tr>
<td>Month 6</td>
<td>42%</td>
<td>27%***</td>
<td>34%***</td>
<td>24%***</td>
<td>29%***</td>
</tr>
<tr>
<td></td>
<td>13%</td>
<td>34%***</td>
<td>37%***</td>
<td>32%***</td>
<td>32%***</td>
</tr>
<tr>
<td>ACR70‡‡ Month 3</td>
<td>6%</td>
<td>15%*</td>
<td>2%</td>
<td>2%</td>
<td>11%**</td>
</tr>
<tr>
<td>Month 6</td>
<td>22%</td>
<td>8%**</td>
<td>2%</td>
<td>9%*</td>
<td>15%***</td>
</tr>
<tr>
<td></td>
<td>3%</td>
<td>13%***</td>
<td>2%</td>
<td>9%*</td>
<td>1%</td>
</tr>
</tbody>
</table>

* 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 9: Proportion of Patients with DAS28-4(ESR) Less Than 2.6

<table>
<thead>
<tr>
<th>DAS28-4 (ESR) Less Than 2.6</th>
<th>Monotherapy</th>
<th>DMARD Inadequate Responders</th>
<th>MTX Inadequate Responders</th>
<th>MTX Inadequate Responders</th>
<th>TNF Inhibitor Inadequate Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study I (SOLO)</td>
<td>Study II (SYNC)</td>
<td>Study III (Standard)</td>
<td>Study IV (SCAN)</td>
<td>Study V (STEP)</td>
</tr>
<tr>
<td></td>
<td>PBO N=122</td>
<td>XELJANZ 5 mg BID N=243</td>
<td>PBO + DMARD N=159</td>
<td>XELJANZ 5 mg BID + DMARD N=315</td>
<td>PBO N=108</td>
</tr>
<tr>
<td>Proportion of responders at Month 3 (n)</td>
<td>4% (5)</td>
<td>5% (13)</td>
<td>NA</td>
<td>NA</td>
<td>3% (4)</td>
</tr>
<tr>
<td>Proportion of Responders at Month 6 (n)</td>
<td>NA</td>
<td>NA</td>
<td>3% (4)</td>
<td>8%* (24)</td>
<td>1% (1)</td>
</tr>
</tbody>
</table>

*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 10) which were not less than those of adalimumab-treated patients.
Table 10: Mean Change from Baseline in HAQ-DI

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Study I (SOLO)</th>
<th>Study II (SYNC)</th>
<th>Study III (Standard)</th>
<th>Study IV (SCAN)</th>
<th>Study V (STEP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMARD Inadequate Responders</td>
<td>PBO</td>
<td>XELJANZ 5 mg BID</td>
<td>PBO + DMARD</td>
<td>XELJANZ 5 mg BID + DMARD</td>
<td>PBO + MTX</td>
</tr>
<tr>
<td>MTX Inadequate Responders</td>
<td>N=109</td>
<td>N=237</td>
<td>N=147</td>
<td>N=292</td>
<td>N=98</td>
</tr>
<tr>
<td>LS Mean Change in HAQ-DI</td>
<td>-0.22</td>
<td>-0.51**</td>
<td>-0.21</td>
<td>-0.47***</td>
<td>-0.25</td>
</tr>
</tbody>
</table>

* 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

XELJANZ 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, XELJANZ, inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In cellular settings where JAK kinases signal in pairs, XELJANZ 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 XELJANZ 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

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 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-Cmax relationship were best described by a nonlinear sigmoidal, hyperbolic model fit to log-transformed Cmax data. Although the nonlinear model provided better description of the dose-Cmax relationship relative to a linear
model, when compared to 5 mg, the mean model predicted relative changes in dose-normalized C\textsubscript{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\textsubscript{max} is approximately dose proportional at least up to 5 times the 10 mg dose.

**TOXICOLOGY**

**Single and Repeat-Dose Toxicity**

XELJANZ 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**

XELJANZ 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, XELJANZ induced benign Leydig cell tumors and malignant hibernomas (tumors of brown adipose tissue) at oral doses of $\geq 30$ mg/kg/day ($\geq 35$ 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**

XELJANZ 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 $\geq 10$ mg/kg/day ($\geq 17$ 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).

XELJANZ 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, XELJANZ 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 11: Summary of Toxicology Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Treatment Duration</th>
<th>Species/Test system</th>
<th>Animals/Group</th>
<th>Dose (mg/kg/day)a</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-Dose Toxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-Dose Oral Toxicity Study in</td>
<td>Single Dose</td>
<td>Rat/Sprague-Dawley</td>
<td>3M, 3F</td>
<td>0, 500, 1000, 2000</td>
<td>500 mg/kg: 1 female died on Day 1; red-stained fur (nose/muzzle); ↓ eosinophils, ↓ fibrinogen, ↑ ALT, ↑ AST, ↑ glucose, ↑ BUN.</td>
</tr>
<tr>
<td>Sprague-Dawley Rats (01-2063-07)</td>
<td></td>
<td></td>
<td></td>
<td>(Oral gavage, 20 mL/kg, 0.5% Methylcellulose/Suspension)</td>
<td>2000 mg/kg: 6/6 animals died by Day 2; necrosis of centrilobular hepatocytes.</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>≥500 mg/kg: ↓ activity, lethargy, partially closed eyes, labored respiration, salivation; lymphocytolysis in mesenteric lymph node and decreased numbers of lymphocytes within the minimal zone of the splenic white pulp.</td>
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<td>1000 mg/kg: 6/6 animals died by Day 2; necrosis of individual hepatocytes; lymphocytolysis within the splenic white pulp.</td>
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<td>≥1000 mg/kg: lacrimation and cold to touch; stomach distension; necrosis of individual hepatocytes; lymphocytolysis within the splenic white pulp.</td>
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<td>2000 mg/kg: 6/6 animals died by Day 2; slow respiration and eye staining/nasal discharge.</td>
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<td>≤3 mg/kg: None</td>
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<tr>
<td>Single-Dose IV Toxicity Study in</td>
<td>Single Dose</td>
<td>Rat/Sprague-Dawley</td>
<td>10M, 10Fb</td>
<td>0, 0.5, 1, 3</td>
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<tr>
<td>Rats with a 14-Day Recovery (09GR453)</td>
<td></td>
<td></td>
<td></td>
<td>(IV, 0.5-3 mL/kg, 10mM Lactic acid in normal saline)</td>
<td>≥200 mg/kg: Emesis, ↓ activity</td>
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<tr>
<td>Single-Day Oral Toxicity Study in</td>
<td>1 Day</td>
<td>Monkey/Cynomolgus</td>
<td>2M, 2F</td>
<td>40, 200, 1000′</td>
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<tr>
<td>Cynomolgus Monkeys (00-2063-04)</td>
<td></td>
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<td>(Oral gavage, 7 mL/kg, 0.5% Methylcellulose/Suspension)</td>
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<td><strong>Repeat-Dose Toxicity</strong></td>
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<td><strong>Pivotal Studies</strong></td>
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<tr>
<td>6-Week Oral Toxicity Study with</td>
<td>6 Weeks</td>
<td>Rat/Sprague-Dawley</td>
<td>10-15/sex/dose</td>
<td>1, 10, 100</td>
<td></td>
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<tr>
<td>1-Month Recovery in Sprague-Dawley</td>
<td></td>
<td></td>
<td></td>
<td>Oral gavage, QD, 10 mL/kg</td>
<td>1 mg/kg/day (LOEL): ↓ WBC count, ↓ lymphocytes, ↓ eosinophils, ↓ basophils, ↓ RBC count, ↓ HCT, ↓ HGB, lymphoid depletion in bone marrow.</td>
</tr>
<tr>
<td>Rats (01-2063-06)</td>
<td></td>
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<td></td>
<td>0.5% Methylcellulose/Suspension</td>
<td>10 mg/kg/day: Same as above, + ↓ reticulocytes, lymphoid depletion in spleen, thymus, and mesenteric lymph node.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Treatment Duration</td>
<td>Species/Test system</td>
<td>Animals/Group</td>
<td>Dose (mg/kg/day)*</td>
<td>Results</td>
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<tr>
<td>6-Month Oral Toxicity Study in Rats (77435)</td>
<td>6 Months</td>
<td>Rat/Sprague-Dawley</td>
<td>15/sex/dose</td>
<td>1, 10, 100 (Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose/Suspension)</td>
<td><strong>100 mg/kg/day</strong>: Same as above, + ↑ neutrophils, ↑ AST.  <strong>100 mg/kg/day (Recovery)</strong>: 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.</td>
</tr>
<tr>
<td>1-Month Oral Toxicity Study with 1-Month Recovery in Cynomolgus Monkeys (01-2063-09)</td>
<td>4 Weeks</td>
<td>Monkey/Cynomolgus</td>
<td>3/sex/dose</td>
<td>10, 50, 100 Oral gavage, TID³, 5 mL/kg, 0.5% Methylcellulose/Suspension</td>
<td><strong>10 mg/kg/day</strong>: Same as above, + ↓ lymphocytes; neutrophils, ↑ glucose, ↑ alkaline phosphatase; ↓ triglycerides (F), ↓ spleen weight, ↓ T lymphocytes, T-cells (CD3+), T-cell subtypes (CD4+, CD8+), B cells (CD45RA+), NK cells (CD161+).  <strong>50 mg/kg/day</strong>: 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.  <strong>100 mg/kg/day</strong>: 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.  <strong>50 mg/kg/day (Recovery)</strong>: Complete recovery with</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Treatment Duration</th>
<th>Species/Test system</th>
<th>Animals/Group</th>
<th>Dose (mg/kg/day)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>39-Week Oral Toxicity Study in Monkeys (2003-0301)</td>
<td>39 weeks</td>
<td>Monkey/Cynomolgus</td>
<td>4/sex/dose</td>
<td>0.5, 2, 10³</td>
<td>Oral gavage, BID, 10 mL/kg, 0.5% Methylcellulose/Suspension</td>
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<td>0.5 mg/kg/day (LOEL): ↓ total lymphocytes, ↓ lymphocyte subsets (T-helper, -cytotoxic/suppressor and NK cells); lymphoid hyperplasia (2/4 M).</td>
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<td></td>
<td>2 mg/kg/day: Same as above, ↓ RBC count, ↓ HCT, ↓ HGB, lymphoid hyperplasia (4/4 M)</td>
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<td>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).</td>
</tr>
</tbody>
</table>

Genotoxicity

In Vitro Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Treatment Duration</th>
<th>Species/Test system</th>
<th>Animals/Group</th>
<th>Dose (µg/mL)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbial Reverse Bacterial Mutation Assay (AMES) (01-2063-11)</td>
<td>In Vitro</td>
<td>Salmonella typhimurium, Escherichia coli</td>
<td>NA</td>
<td>0.010-5 mg/plate Plate Incorporation for ~ 48 to 72 hours at 37°C</td>
<td>No genotoxic effect. No cytotoxic effect.</td>
</tr>
<tr>
<td>Mammalian Cell Mutation Assays (01-2063-16)</td>
<td>In Vitro</td>
<td>Chinese Hamster ovary (CHO)-K1-BH4 cells,</td>
<td>NA</td>
<td>16-5000 µg/mL 5-hour treatment, 6-8 day incubation</td>
<td>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.</td>
</tr>
<tr>
<td>In Vitro Cytogenetics Assay (01-2063-10)</td>
<td>In Vitro</td>
<td>Human Peripheral Lymphocytes</td>
<td>NA</td>
<td>41.8-2400 µg/mL 3 hours with activation, 3 and 24 hours without activation</td>
<td>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.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Treatment Duration</td>
<td>Species/Test system</td>
<td>Animals/Group</td>
<td>Dose (mg/kg/day)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Results</td>
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<tr>
<td><strong>In Vivo Studies</strong></td>
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<tr>
<td>In Vivo/In Vitro Rat Hepatocyte Unscheduled</td>
<td>Single Dose</td>
<td>Rat/Sprague-Dawley</td>
<td>M</td>
<td>125, 250, 250 Oral gavage, 10 mL/kg, 0.5% Methylcellulose</td>
<td>Toxic/Cytotoxic Effects: Hypoactivity, labored breathing and/or squinted eyes in the 500 mg/kg group. Genotoxic Effects: None.</td>
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<tr>
<td>DNA Synthesis Study (01-2063-17)</td>
<td>Hepatocytes,</td>
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<tr>
<td></td>
<td>2-4 and 14-16 HPD</td>
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<tr>
<td>In Vivo Cytogenetics (Rat Micronucleus)</td>
<td>Once daily for 3</td>
<td>Rat/Sprague-Dawley</td>
<td>6M, 6F</td>
<td>62.5, 125, 250 Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose</td>
<td>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.</td>
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<tr>
<td>(01-2063-12)</td>
<td>days</td>
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<td><strong>Carcinogenicity</strong></td>
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<tr>
<td>6-Month Oral Gavage Study in Mice (8200-368)</td>
<td>6 Months</td>
<td>Mouse/Model 001178-T (hemizygous), CB6F1/Jic-TgrasH2@Tac Mouse/Model 001178-W (homozygous wild-type), CB6F1/Jic-TgrasH2@Tac</td>
<td>25/sex/dose</td>
<td>25, 75, 200 Oral gavage, QD, 10 mL/kg, 0.5% (w/v) Methylcellulose/Solution</td>
<td>≥25 mg/kg/day: No evidence of treatment-related carcinogenicity.</td>
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<td>Mouse/Model 001178-T (hemizygous), CB6F1/Jic-TgrasH2@Tac Mouse/Model 001178-W (homozygous wild-type), CB6F1/Jic-TgrasH2@Tac</td>
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<tr>
<td>2-Year Oral Gavage in Rats (6348-463)</td>
<td>103 Weeks&lt;sup&gt;f&lt;/sup&gt;</td>
<td>Rat/Sprague-Dawley</td>
<td>60-70/sex/dose</td>
<td>10/10, 30/30, 75/100&lt;sup&gt;f&lt;/sup&gt; Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose/Solution</td>
<td>10 mg/kg/day: Benign angiomomas 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).</td>
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<tr>
<td><strong>Investigative</strong></td>
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<tr>
<td>14-Day Oral Investigative Study in Rats</td>
<td>14 Days</td>
<td>Rat/Sprague-Dawley</td>
<td>8F with BrdU pumps 5F without BrdU pumps</td>
<td>Oral gavage, QD, 10 mL/kg, 0.5% Methylcellulose/Solution</td>
<td>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.</td>
</tr>
<tr>
<td>(10GR431)</td>
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<tr>
<td>Study Type</td>
<td>Treatment Duration</td>
<td>Species/Test system</td>
<td>Animals/Group</td>
<td>Dose (mg/kg/day)*</td>
<td>Results</td>
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<tr>
<td>Investigative Study with Rat Brown Adipocytes (11GR016)</td>
<td>1 hour pre-incubation with XELJANZ then 20 minutes with oPRL and XELJANZ</td>
<td>Rat/Sprague-Dawley/Primary Leydig cells</td>
<td>In vitro</td>
<td>150 mM NaCl, 0.03 mM NaHCO3/Solution (oPRL), 0.1% dimethyl sulphoxide/Solution (XELJANZ)</td>
<td>XELJANZ inhibited the prolactin-induced increase in STAT5A/B phosphorylation.</td>
</tr>
<tr>
<td>Investigative Study with Rat Primary Leydig Cells (11GR015)</td>
<td>1 hour pre-incubation with XELJANZ then 15 minutes with oPRL and XELJANZ</td>
<td>Rat/Sprague-Dawley/Differentiated primary brown adipocytes/pSTAT5A/B protein</td>
<td>In vitro</td>
<td>150 mM NaCl, 0.03 mM NaHCO3/Solution (oPRL), 0.1% dimethyl sulphoxide/Solution (XELJANZ)</td>
<td>XELJANZ inhibited the prolactin-induced increase in STAT5A/B phosphorylation.</td>
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<tr>
<td><strong>Reproductive and Developmental Toxicity</strong></td>
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<tr>
<td>Oral Fertility and Embryonic Development Study in Male and Female Rats (05GR051)</td>
<td>(F) Phase 1: 14 Days pre-mating, throughout cohabitation and through GD 7. (M) Phase 2: Minimum of 63 days (beginning 28 days pre-mating)</td>
<td>Rat/Sprague Dawley</td>
<td>20/sex/dose</td>
<td>1, 10, 100 Oral Gavage, QD, 10 mL/kg</td>
<td>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.</td>
</tr>
<tr>
<td>Oral Embryo-Fetal Development Study in Rats (04-2063-24)</td>
<td>GD 6-17</td>
<td>Rat/Sprague Dawley</td>
<td>20F/dose</td>
<td>1, 10, 30 Oral gavage, QD, 10 mL/kg</td>
<td>≥1 mg/kg/day: No effect.</td>
</tr>
<tr>
<td>Oral Embryo-Fetal Development Study in Rats (09GR353)</td>
<td>GD 6-17</td>
<td>Rat/Sprague Dawley</td>
<td>20F/dose</td>
<td>30, 100, 300 Oral gavage, QD, 10 mL/kg</td>
<td>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.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Treatment Duration</td>
<td>Species/Test system</td>
<td>Animals/Group</td>
<td>Dose (mg/kg/day)a</td>
<td>Results</td>
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<tr>
<td>Oral Embryo-Fetal Development Study in Rabbits (05-2063-25)</td>
<td>GD 7-19</td>
<td>Rabbit/New Zealand White</td>
<td>20F/dose</td>
<td>10, 30, 100</td>
<td>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.</td>
</tr>
<tr>
<td>Oral Developmental Peri/Postnatal Reproduction including Postnatal Behavioral/Functional Evaluation in Rats (LIA00468)</td>
<td>GD 6 - DL 21 (or GD 24 for rats not delivering a litter)</td>
<td>Rat/Sprague-Dawley</td>
<td>25F/dose</td>
<td>Oral gavage, QD, 2 mL/kg</td>
<td>10 mg/kg/day: No effect 50 mg/kg/day: ↓ Delivered pups, ↓ liveborn pups, ↓ pup survival, ↓ pup body weight.</td>
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<tr>
<td>Developmental and Reproductive - Juvenile</td>
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<tr>
<td>Oral Fertility Study in Juvenile Rats (10GR250)</td>
<td>PND 21-70 (M) PND 21-55 (F)</td>
<td>Rat/Sprague-Dawley</td>
<td>20/sex/dose</td>
<td>1, 10, 100</td>
<td>1 mg/kg/day: No effect. 10 mg/kg/day: ↓ BW (M), ↓ BW gain (M). 100 mg/kg/day: Same as above (M&amp;F).</td>
</tr>
<tr>
<td>Oral Toxicity Study in Juvenile Rats with a 2-Month Recovery (10GR307)</td>
<td>PND 21-49</td>
<td>Rat/Sprague Dawley</td>
<td>16/sex/dose</td>
<td>1, 10, 100</td>
<td>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.</td>
</tr>
<tr>
<td>Study Type</td>
<td>Treatment Duration</td>
<td>Species/Test system</td>
<td>Animals/Group</td>
<td>Dose (mg/kg/day)a</td>
<td>Results</td>
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<tr>
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<tr>
<td>39-Week Oral Toxicity in Juvenile Monkeys with a 26-Week Recovery (Interim Report) (2501-010)</td>
<td>39 Weeks</td>
<td>Monkey/Cynomolgus</td>
<td>4/sex/dose</td>
<td>0.5, 2, 10</td>
<td>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.</td>
</tr>
</tbody>
</table>

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, 33.3 mg/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; NaHCO3 = 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.
REFERENCES


PART III: CONSUMER INFORMATION

PrXEJLANZ™
Tofacitinib tablets

This leaflet is part III of a three-part "Product Monograph" published when XELJANZ 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. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

XELJANZ

What the medication is used for:
XELJANZ (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 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 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, you should not take XELJANZ (See What the nonmedicinal ingredients are).

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

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

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

WARNINGS AND PRECAUTIONS

Serious Warning and Precautions:
• XELJANZ is a medicine that affects your immune system and can lower the ability of your immune system to fight infections such as tuberculosis, and infections caused by 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 immunosuppressants at the same time such as methotrexate or corticosteroids. You should not be using XELJANZ if you have any kind of infection.
• If a serious infection develops, stop XELJANZ and contact your doctor.

• Your doctor will closely monitor you for the signs and symptoms of infection during and after the treatment with XELJANZ.
• Lymphoma and other serious conditions have been reported in patients treated with XELJANZ.

Before taking XELJANZ, 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, and may adjust your dose of XELJANZ 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 level cells.
• 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.
• are pregnant or planning to become pregnant
• are breastfeeding or planning to breastfeed. Women should not breastfeed while being treated with XELJANZ.
• 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.
• if you are planning to get vaccinated, tell your doctor. Certain types of vaccines should not be given when taking
XELJANZ. Before you start XELJANZ, you should be up to date with all recommended vaccinations

- have chest pain or any heart problems.

INTERACTIONS WITH THIS MEDICATION

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

- Tell your doctor if you are taking immunosuppressants (e.g. tacrolimus, sirolimus, cyclosporine), antiarrhythmics, beta-blockers, calcium channel blockers, cholinesterase inhibitors, HIV protease inhibitors, rifampin, ketoconazole, fluconazole.
- Avoid grapefruit juice
- St. John’s Wort (Hypericum perforatum) may reduce the response to XELJANZ.

PROPER USE OF THIS MEDICATION

Usual adult dose:
The recommended dose is 5 mg taken by mouth twice daily. Patients taking XELJANZ are usually also prescribed methotrexate.

XELJANZ 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 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, 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

Like all medicines, XELJANZ can have side effects. The following information describes the most important side effects which you should know of. If you experience any symptom that bothers you or does not go away, contact your healthcare provider or get medical attention as soon as possible.

The most common side effects of XELJANZ include:

- High blood pressure
- Diarrhea
- Nausea (upset stomach)
- Indigestion

The uncommon side effects of XELJANZ include:

- Bronchitis, cough
- Shingles/ Herpes Zoster (painful skin rash with blisters)
- Anemia (low count of red blood cells)
- Dizziness
- Vomiting
- Gastritis, abdominal pain, loss of appetite
- Back pain
- Swelling of legs and ankles or the arms and hands (Peripheral edema)
- Influenza (Flu)
- Congestive heart failure. Your heart isn’t able to pump enough blood to meet your body needs.

<table>
<thead>
<tr>
<th>Symptom / effect</th>
<th>Talk with your doctor or pharmacist</th>
<th>Stop taking drug and call your doctor or pharmacist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>Only if severe</td>
<td>In all cases</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>Only if severe</td>
<td>In all cases</td>
</tr>
<tr>
<td>Uncommon</td>
<td></td>
<td></td>
</tr>
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<td>Shingles/ Herpes Zoster (painful skin rash with blisters)</td>
<td>Only if severe</td>
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</tr>
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</tr>
</tbody>
</table>
This is not a complete list of side effects. For any unexpected effects while taking XELJANZ, contact your doctor or pharmacist.

HOW TO STORE IT
Store between 15°C and 30°C.
Keep out of reach of children

REPORTING SUSPECTED SIDE EFFECTS
You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

$ Report online at www.healthcanada.gc.ca/medeffect
$ Call toll-free at 1-866-234-2345
$ Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
            Health Canada
            Postal Locator 0701E
            Ottawa, Ontario
            K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION
This document plus the full product monograph, prepared for health professionals can be found at:
http://www.Pfizer.ca
or by contacting the sponsor, Pfizer Canada Inc., at:
1-800-463-6001.

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