XELJANZ®
(tofacitinib) tablets for oral administration

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XELJANZ® (tofacitinib) tablets, for oral use

Full U.S. Approval: 2012

WARNINGS AND PRECAUTIONS

Serious Infections and Malignancy

See full prescribing information for complete boxed warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ. (5.1)
- If a serious infection develops, interrupt XELJANZ until the infection is controlled. (5.1)
- Prior to starting XELJANZ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)
- Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications. (5.2)

Recent Major Changes

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

Dosage and Administration

Recommended dose of XELJANZ is 5 mg twice daily. (2.1)
- Moderate and severe renal impairment and moderate hepatic impairment: Reduce dose to 5 mg once daily. (2.4, 8.6, 8.7)

Contraindications

None (4)

Warnings and Precautions

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

Adverse Reactions

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

How Supplied/Storage and Handling

Tablets: 5 mg (3)

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Appendix Z: XELJANZ Dosing in Gastrointestinal Perforations

No data are available on the response to vaccination or on the secondary transmission of infection by live vaccines to patients receiving XELJANZ. Avoid use of live vaccines concurrently with XELJANZ. Update immunizations in agreement with current immunization guidelines prior to initiating XELJANZ therapy.
### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trial Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical study of another drug and may not predict the rates observed in a broader patient population in clinical practice.

Although other doses have been studied, the recommended dose of XELJANZ is 5 mg twice daily.

The following data includes two Phase 2 and five Phase 3 double-blind, controlled, multicenter trials. In these trials, patients were randomized to doses of XELJANZ 5 mg twice daily (292 patients) and 10 mg twice daily (308 patients) monotherapy, XELJANZ 5 mg twice daily (1044 patients) and 10 mg twice daily (1043 patients) in combination with DMARDs (including methotrexate) and placebo (809 patients). All seven protocols included provisions for patients taking placebo to receive treatment with XELJANZ at Month 3 or Month 6 either by patient response (based on uncontrolled disease activity) or by design, so that adverse events cannot always be unambiguously attributed to a given treatment. Therefore some analyses that show differences in frequency of adverse events may be changing classification based on uncontrolled disease activity or design.

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

The most common serious adverse reactions were serious infections [see Warnings and Precautions (5.1)]. The proportion of patients who discontinued treatment due to any adverse reaction during the 0 to 3 months exposure in the double-blind, placebo-controlled trials was 4% for patients taking XELJANZ and 3% for placebo-treated patients.

### Infections

In the seven controlled trials, during the 0 to 3 months exposure, the overall frequency of infections was 23% and 22% in the 5 mg twice daily and 10 mg daily groups, respectively, and 18% in the placebo group.

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

### Serious Infections

In the seven controlled trials, during the 0 to 3 months exposure, serious infections were reported in 1 patient (0.5 events per 100 patient-years) who received placebo and 11 patients (1.7 events per 100 patient-years) who received XELJANZ 5 mg or 10 mg twice daily. The rate difference between treatment groups (the corresponding 95% confidence interval) was -0.2 (-0.4, 0.0) events per 100 patient-years for the combined 5 mg twice daily and 10 mg twice daily XELJANZ group minus placebo.

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

The most common serious infections included pneumonia, cellulitis, herpes zoster, and urinary tract infection [see Warnings and Precautions (5.1)].

### Tuberculosis

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

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

Cases of disseminated tuberculosis were also reported. The median XELJANZ exposure prior to diagnosis of tuberculosis was 10 months (range from 152 to 960 days) [see Warnings and Precautions (5.1)].

### Opportunistic Infections (excluding tuberculosis)

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

In the seven controlled trials, during the 0 to 12 months exposure, opportunistic infections were reported in 4 patients (0.4 events per 100 patient-years) who received XELJANZ 5 mg twice daily and 4 patients (0.3 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.3 (-0.1, 0.7) events per 100 patient-years for the combined 5 mg and 10 mg twice daily XELJANZ group minus placebo.

In the seven controlled trials, during the 0 to 12 months exposure, opportunistic infections were not reported in 0 patients who received XELJANZ 5 mg twice daily of XELJANZ and 6 patients (0.5 events per 100 patient-years) who received 10 mg twice daily of XELJANZ. The rate difference between XELJANZ doses (and the corresponding 95% confidence interval) was 0.5 (0.1, 0.9) events per 100 patient-years for 10 mg twice daily XELJANZ minus 5 mg twice daily XELJANZ.

In the long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical trials. There were no confirmed decreases in ANC below 500 cells/mm³ observed in any treatment group.

**Serum Creatinine Elevations**

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

**Other Adverse Reactions**

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

**Table 4: Adverse Reactions Occurring in at Least 2% or More of Patients on 5 mg or 10 mg Twice Daily XELJANZ With or Without DMARD (0-3 months) and at Least 1% Greater Than That Observed in Patients on Placebo**

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>XELJANZ 5 mg Twice Daily</th>
<th>XELJANZ 10 mg Twice Daily *</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1336 (%)</td>
<td>N = 1349 (%)</td>
<td>N = 809 (%)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4.0</td>
<td>2.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Na+ loss</td>
<td>3.6</td>
<td>2.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4.5</td>
<td>3.8</td>
<td>3.3</td>
</tr>
<tr>
<td>Rash</td>
<td>4.3</td>
<td>3.4</td>
<td>2.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.6</td>
<td>2.3</td>
<td>1.1</td>
</tr>
</tbody>
</table>

* N reflects randomized and treated patients from the seven clinical trials
* The recommended dose of XELJANZ is 5 mg twice daily.

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

- **Blood and lymphatic system disorders**: Anemia
- **Metabolism and nutrition disorders**: Dehydration
- **Psychiatric disorders**: Insomnia
- **Nervous system disorders**: Parasthesia
- **Respiratory, thoracic and mediastinal disorders**: Dyspnea, cough, sinus congestion
- **Gastrointestinal disorders**: Abdominal pain, dyspepsia, vomiting, gastritis, nausea
- **Hepatobiliary disorders**: Hepatic steatosis
- **Skin and subcutaneous tissue disorders**: Rash, erythema, pruritus
- **Musculoskeletal, connective tissue and bone disorders**: Musculoskeletal pain, arthralgia, tendinitis, joint swelling
- **Neoplasms benign, malignant and unspecified (including cysts and polyps)**: Non-melanoma skin cancers
- **General disorders and administration site conditions**: Pyrexia, fatigue, peripheral edema

Clinical Experience in Methotrexate-Naive Patients

Study VI was an active-controlled clinical trial in methotrexate-naive patients [see Clinical Studies (14)].

The safety experience in these patients was consistent with Studies I-V.

**7 DRUG INTERACTIONS**

**7.1 Potent CYP3A4 Inhibitors**

Tofacitinib exposure is increased when XELJANZ is coadministered with potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) [see Dosage and Administration (2.3) and Figure 3].

**7.2 Moderate CYP3A4 and Potent CYP2C19 Inhibitors**

Tofacitinib exposure is increased when XELJANZ is coadministered with medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole) [see Dosage and Administration (2.3) and Figure 3].

**7.3 Potent CYP3A4 Inducers**

Tofacitinib exposure is decreased when XELJANZ is coadministered with potent CYP3A4 inducers (e.g., rifampin) [see Dosage and Administration (2.3) and Figure 3].

**7.4 Immunosuppressive Drugs**

There is a risk of added immunosuppression when XELJANZ is coadministered with potent immunosuppressive drugs (e.g., azathioprine, tacrolimus, cyclosporine). Combined use of multiple-dose XELJANZ with potent immunosuppressants has not been studied in rheumatoid arthritis. Use of XELJANZ in combination with biologic DMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
XELJANZ is supplied for oral administration as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) lactose monohydrate, croscarmellose sodium, magnesium stearate, HPMC 2910/Hypromellose 6cP, and titanium dioxide, magenta/Pigment Red 48:2.

12 CLINICAL PHARMACOLOGY

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

12.2 Pharmacokinetics
Following oral administration of XELJANZ, peak concentrations are reached within 0.5-1 hour. AUC ratio-based dose adjustments are performed within 2 weeks after discontinuation of treatment, indicating a longer duration of pharmacodynamic activity compared to the pharmacokinetic half-life.

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

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13.4 Distribution
After intravenous administration, the volume of distribution is 67 L. The protein binding of tofacitinib is approximately 97%. Tofacitinib binds primarily to albumin and does not appear to bind to other plasma proteins. Tofacitinib distributes equally between red blood cells and plasma.

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

13.6 Pharmacokinetics in Rheumatoid Arthritis Patients
13.6.1 PK Analysis in Rheumatoid Arthritis Patients indicated no clinically relevant change in tofacitinib exposure, after accounting for differences in renal function (i.e., creatinine clearance) between patients, based on age, weight, gender, and race (Figure 1). An approximately linear relationship between body weight and volume of distribution was observed, resulting in higher peak (Cmax) and lower trough (Cmin) concentrations in lighter patients. However, this difference is not considered to be clinically relevant. The between-subject variability (% coefficient of variation) in AUC of tofacitinib is estimated to be approximately 27%.

Specific Populations
The effects of renal and hepatic impairment and other intrinsic factors on the pharmacokinetics of tofacitinib is shown in Figure 1.

Figure 1: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics
Drug Interactions
Potential for XELJANZ to Influence the PK of Other Drugs
In vitro studies indicate that tofacitinib does not inhibit or induce the activity of the major human drug-metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2D6, CYP2C19, CYP2B6, and CYP3A4) at concentrations exceeding 185 times the steady state Cmax of a 5 mg twice daily dose. These in vitro results were confirmed by a human drug interaction study showing no changes in the PK of midazolam, a highly sensitive CYP3A4 substrate, when coadministered with XELJANZ.

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

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

Dosing recommendations for coadministered drugs following administration with XELJANZ are shown in Figure 2.

Figure 2: Impact of XELJANZ on PK of Other Drugs

Note: Reference group is administration of tofacitinib alone.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 39-week toxicity study in monkeys, tofacitinib at exposure levels approximately 6 times the MRHD (on an AUC basis at oral doses of 1 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1 times the MRHD (on an AUC basis at oral doses of 1 mg/kg twice daily). The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse studies. Tofacitinib, at exposure levels approximately 34 times the MRHD (on an AUC basis at oral doses of 200 mg/kg/day) was not carcinogenic in mice.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hemibromes (malignancy of brown adipose tissue), and benign thymomas at doses greater than 5 times the MRHD (on an AUC basis at oral doses of 135 mg/kg/day).

In rats, tofacitinib at exposure levels approximately 17 times the MRHD (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the MRHD (on an AUC basis at oral doses of 1 mg/kg/day).

In a 3-month repeat-dose study in rats, tofacitinib was not found to be genotoxic at the administered dose levels as assessed by the CHO/HGPRT assay and the in vitro chromosomal aberration assay with human lymphocytes in the presence of metabolic enzymes, but negative in the absence of the metabolic enzymes. Tofacitinib was negative in the in vivo rat micronucleus assay and the in vivo CHO-HGPRT assay and the in vivo rat hepatocyte unscheduled DNA synthesis assay.

In rats, tofacitinib at exposure levels approximately 17 times the MRHD (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the MRHD (on an AUC basis at oral doses of 1 mg/kg/day).

Although other doses have been studied, the recommended dose of XELJANZ is 5 mg twice daily.

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

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

The results of XELJANZ-treated patients achieving ACR20 responses in Studies 1 and 2 are shown in Figure 4. Although a dose-response relationship was observed in Study 1, the proportion of patients with an ACR20 response did not clearly differ between the 10 mg and 15 mg doses. In Study 2, a smaller proportion of patients achieved an ACR20 response in the placebo and XELJANZ 1 mg groups compared to patients treated with the other XELJANZ doses. However, there was no difference in the proportion of responders among patients treated with XELJANZ 3, 5, 10, 15 mg twice daily or 20 mg once daily doses.

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

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

CONFRIMATORY TRIALS
Study 1 was a 6-month monotherapy trial in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic or biologic) received XELJANZ 5 or 10 mg twice daily or placebo. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of XELJANZ 5 or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, changes in Health Assessment Questionnaire – Disability Index (HAQ-DI), and rates of Disease Activity Score (DAS28-4<ESR) less than 2.6.

Study II was a 12-month trial in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a nonbiologic DMARD received XELJANZ 5 or 10 mg twice daily or placebo added to background DMARD treatment (excluding potent immunosuppressive treatments such as azathioprine or cyclosporine). At the Month 3 visit, nonresponding patients were advanced in a blinded fashion to a second predetermined treatment of XELJANZ 5 or 10 mg twice daily. At the end of Month 6, all placebo patients were advanced to their second predetermined treatment in a blinded fashion. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3, and rates of DAS28-4<ESR) less than 2.6 at Month 6.

Study III was a 12-month trial in 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX. Patients received XELJANZ 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, changes in HAQ-DI at Month 3, and rates of DAS28-4<ESR) less than 2.6 at Month 6.

Study IV was a 2-year trial with a planned analysis at 1 year in which 797 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received XELJANZ 5 or 10 mg twice daily or placebo added to background MTX. Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, mean change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Month 6, HAQ-DI at Month 3, and DAS28-4<ESR) less than 2.6 at Month 6.

Study V was a 6-month trial in which 399 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to at least one approved TNF-inhibiting biologic agent received XELJANZ 5 or 10 mg twice daily or placebo added to background MTX. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a second predetermined treatment of XELJANZ 5 or 10 mg twice daily. The primary endpoints at Month 3 were the proportion of patients who achieved an ACR20 response, HAQ-DI, and DAS28-4<ESR) less than 2.6.

Study VI was a 2-year monotherapy trial with a planned analysis at 1 year in which 952 MTX-naïve patients with moderate to severe active rheumatoid arthritis received XELJANZ 5 or 10 mg twice daily or MTX dose-titrated over 8 weeks to 20 mg weekly. The primary endpoints were mean change from baseline in van der Heijde-modified total Sharp Score (mTSS) at Month 6 and the proportion of patients who achieved an ACR70 response at Month 6.

Clinical Response
The percentages of XELJANZ-treated patients achieving ACR20, ACR50, and ACR70 responses in Studies I, IV, and V are shown in Table 5. Similar results were observed with Studies II and III. In trials IV-V, patients treated with either 5 or 10 mg twice daily XELJANZ had higher ACR20, ACR50, and ACR70 response rates versus placebo, with or without background DMARD treatment, at Month 3 and Month 6. Higher ACR20 response rates were observed within 2 weeks compared to placebo. In the 12-month trials, ACR response rates in XELJANZ-treated patients were consistent at 6 and 12 months.
The percent of ACR20 responders by visit for Study IV is shown in Table 7. Similar responses were observed for XELJANZ in Studies I, II, III, V, and VI.

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

Table 5: Proportion of Patients with an ACR Response

<table>
<thead>
<tr>
<th>Monotherapy in Nonbiologic or Biologic DMARDs</th>
<th>MTX Inadequate Responders</th>
<th>TNF Inhibitor Inadequate Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>Study IV</td>
<td>Study V</td>
</tr>
<tr>
<td>N</td>
<td>PBO</td>
<td>XELJANZ 5 mg Twice Daily</td>
</tr>
<tr>
<td>122</td>
<td>243</td>
<td>245</td>
</tr>
</tbody>
</table>

ACR20
Month 3: 26% 59% 65% 27% 55% 67% 24% 41% 51% 48% 54% 62%
Month 6: 26% 28% 28% 26% 37% 30% 37% 30% 37% 30%

ACR50
Month 3: 12% 31% 36% 9% 32% 44% 8% 37% 37% 37% 37%
Month 6: 22% 42% 46% 32% 36% 36% 26% 30% 30% 30%

ACR70
Month 3: 5% 15% 20% 3% 11% 23% 2% 14% 10% 10%
Month 6: 14% 42% 46% 32% 36% 36% 26% 30% 30% 30%

The recommended dose of XELJANZ is 5 mg twice daily.

In Study IV, a greater proportion of patients treated with XELJANZ 5 mg or 10 mg twice daily plus MTX achieved a low level of disease activity as measured by a DAS28-4(ESR) less than 2.6 at 6 months compared to those treated with MTX alone (Table 6).

Table 6: Proportion of Patients with DAS28-4(ESR) Less Than 2.6 with Number of Residual Active Joints

<table>
<thead>
<tr>
<th>Study IV</th>
<th>DAS28-4(ESR) Less Than 2.6</th>
<th>Placebo</th>
<th>MTX</th>
<th>XELJANZ 5 mg Twice Daily</th>
<th>XELJANZ 10 mg Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 6</td>
<td>NA</td>
<td>69%</td>
<td>70%</td>
<td>66%</td>
<td>67%</td>
</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
<td>62%</td>
<td>63%</td>
<td>61%</td>
<td>62%</td>
</tr>
</tbody>
</table>

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

Table 7: Components of ACR Response at Month 3

<table>
<thead>
<tr>
<th>Component (mean)</th>
<th>Baseline</th>
<th>Month 3</th>
<th>Baseline</th>
<th>Month 3</th>
<th>Baseline</th>
<th>Month 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TENDER joints</td>
<td>(68)</td>
<td>14 (14)</td>
<td>13 (15)</td>
<td>10 (12)</td>
<td>13 (13)</td>
<td>18 (14)</td>
</tr>
<tr>
<td>SWOLLEN joints</td>
<td>(66)</td>
<td>14 (8)</td>
<td>14 (6)</td>
<td>6 (7)</td>
<td>14 (9)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
<td>58 (23)</td>
<td>34 (23)</td>
<td>28 (22)</td>
<td>55 (24)</td>
<td>47 (24)</td>
</tr>
<tr>
<td>Global assessment</td>
<td></td>
<td>58 (24)</td>
<td>35 (23)</td>
<td>27 (22)</td>
<td>54 (24)</td>
<td>47 (24)</td>
</tr>
<tr>
<td>Disability index</td>
<td>(HAD-DI)</td>
<td>1.41 (0.68)</td>
<td>0.99 (0.65)</td>
<td>0.4 (0.64)</td>
<td>0.64 (0.67)</td>
<td>1.19 (0.88)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td></td>
<td>12.3 (19.0)</td>
<td>7.7 (17.1)</td>
<td>7.1 (16.9)</td>
<td>4.4 (14.9)</td>
<td>13.7 (18.7)</td>
</tr>
</tbody>
</table>

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

In Study IV, XELJANZ 10 mg twice daily plus background MTX reduced the progression of structural damage compared to placebo plus MTX at Month 6. When given at a dose of 5 mg twice daily, XELJANZ exhibited similar effects on mean progression of structural damage (not statistically significant). These results are shown in Table 8. Analyses of erosion and joint space narrowing scores were consistent with the overall results.

In the placebo plus MTX group, 74% of patients experienced no radiographic progression at Month 6 compared to 84% and 79% of patients treated with XELJANZ plus MTX 5 or 10 mg twice daily.

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

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

Table 8: Radiographic Changes at Months 6 and 12

<table>
<thead>
<tr>
<th>Component (mean)</th>
<th>Baseline</th>
<th>Month 6</th>
<th>Baseline</th>
<th>Month 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosion score</td>
<td></td>
<td>0.8 (2.7)</td>
<td>0.2 (2.3)</td>
<td>0.7 (1.7)</td>
</tr>
<tr>
<td>Joint space</td>
<td></td>
<td>0.9 (3.7)</td>
<td>0.3 (3.9)</td>
<td>0.9 (3.7)</td>
</tr>
<tr>
<td>MTS S</td>
<td></td>
<td>33 (42)</td>
<td>29 (40)</td>
<td>31 (48)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td>0.5 (2.0)</td>
<td>0.1 (1.7)</td>
<td>-0.3 (-0.7)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td>1.3 (3.7)</td>
<td>0.4 (3.9)</td>
<td>-0.9 (-1.4)</td>
</tr>
</tbody>
</table>

Physical Function Response
Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 and 10 mg twice daily demonstrated greater improvement from baseline in physical functioning compared to placebo at Month 3.

The mean (95% CI) difference from placebo in HAQ-DI improvement from baseline in Study 3 was -0.22 (-0.35, -0.10) in patients receiving 5 mg XELJANZ twice daily and -0.32 (-0.44, -0.19) in patients receiving 10 mg XELJANZ twice daily. Similar results were obtained in Studies I, II, IV, and V. In the 12-month trials, HAQ-D1 results in XELJANZ-treated patients were consistent at 6 and 12 months.

Other Health-Related Outcomes
General health status was assessed by the Short Form health survey (SF-36). In studies I, IV, and VI, patients receiving XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily demonstrated greater improvement from baseline compared to placebo in physical component summary (PCS), mental component summary (MCS) scores and in all 8 domains of the SF-36 at Month 3.

16 HOW SUPPLIED/STORAGE AND HANDLING
XELJANZ is provided as 5 mg tofacitinib (equivalent to 8 mg tofacitinib citrate) tablets: White, round, immediate-release film-coated tablets, debossed with “Pfizer” on one side, and “JKI 5” on the other side.

Bottles of 321: NDC 0069-1001-01
Bottles of 316: NDC 0069-1001-03
Bottles of 60: NDC 0069-1001-01
Bottles of 28: NDC 0069-1001-02

Storage and Handling
Store at 20°C to 25°C (68°F to 77°F).[See USP Controlled Room Temperature.] Do not repackage.

17 PATIENT COUNSELING INFORMATION
See FDA-approved patient labeling (Medication Guide).

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

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

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

Important Information on Laboratory Abnormalities
Inform patients that XELJANZ may affect certain lab test results, and that blood tests are required before and during XELJANZ treatment [see Warnings and Precautions (5.4)].

Pregnancy
Inform patients that XELJANZ should not be used during pregnancy unless clearly necessary, and advise patients to contact the registry at 1-877-311-8972 to enroll [see Pregnancy (8.1)].

Important Information on Laboratory Abnormalities
Inform patients that XELJANZ may affect certain lab test results, and that blood tests are required before and during XELJANZ treatment [see Warnings and Precautions (5.4)].

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

MEDICATION GUIDE
XELJANZ (ZEL' JANS')
(tofacitinib)

Read this Medication Guide before you start taking XELJANZ and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about XELJANZ?
XELJANZ may cause serious side effects including:

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

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

You should not start taking XELJANZ if you have any kind of infection unless your healthcare provider tells you it is okay.

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

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

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

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

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

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

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

- changes in lymphocyte counts. Lymphocytes are white blood cells that help the body fight off infections.
- low neutrophil counts. Neutrophils are white blood cells that help the body fight off infections.
- low red blood cell count. This may mean that you have anemia, which may make you feel weak and tired.
Your healthcare provider should routinely check certain liver tests. You should not receive XELJANZ if your lymphocyte count, neutrophil count, or red blood cell count is too low or your liver tests are too high. Your healthcare provider may stop your XELJANZ treatment for a period of time if needed because of changes in these blood test results.

You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 6 weeks after you start receiving XELJANZ, and as needed after that. Normal cholesterol levels are important to good heart health.

See “What are the possible side effects of XELJANZ?” for more information about side effects.

What is XELJANZ?

XELJANZ is a prescription medicine called a Janus kinase (JAK) inhibitor. XELJANZ is used to treat adults with moderately to severely active rheumatoid arthritis in which methotrexate did not work well. It is not known if XELJANZ is safe and effective in people with Hepatitis B or C. XELJANZ is not for people with severe liver problems. It is not known if XELJANZ is safe and effective in children.

What should I tell my healthcare provider before taking XELJANZ? XELJANZ may not be right for you. Before taking XELJANZ, tell your healthcare provider if you:

- have an infection. See “What is the most important information I should know about XELJANZ?”
- have liver problems
- have kidney problems
- have any stomach area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines
- have had a reaction to tofacitinib or any of the ingredients in XELJANZ
- have recently received or are scheduled to receive a vaccine. People who take XELJANZ should not receive live vaccines. People taking XELJANZ can receive non-live vaccines.
- have any other medical conditions
- plan to become pregnant or are pregnant. It is not known if XELJANZ will harm an unborn baby.
- have any other conditions that make you more likely to have infections
- have a history of liver problems
- have a history of kidney problems
- have a history of stomach or intestine problems
- have liver problems
- have had a reaction to tofacitinib or any of the ingredients in XELJANZ
- have recently received or are scheduled to receive a vaccine. People who take XELJANZ should not receive live vaccines. People taking XELJANZ can receive non-live vaccines.
- have any other medical conditions
- plan to become pregnant or are pregnant. It is not known if XELJANZ will harm an unborn baby.

Pregnancy Registry: Pfizer has a registry for pregnant women who take XELJANZ. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking XELJANZ, talk to your healthcare provider about how you can join this registry or you may contact the registry at 1-877-311-8972 to enroll.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. XELJANZ and other medicines may affect each other causing side effects. Especially tell your healthcare provider if you take:

- any other medicines to treat your rheumatoid arthritis. You should not take tocilizumab (Actemra®), etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®), rituximab (Rituxan®), abatacept (Orencia®), anakinra (Kineret®), certolizumab (Cimzia®), golimumab (Simponi®), azathioprine, cyclosporine, or other immunosuppressive drugs while you are taking XELJANZ. Taking XELJANZ with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XELJANZ?

- Take XELJANZ as your healthcare provider tells you to take it.
- Take XELJANZ 2 times a day with or without food.
- If you take too much XELJANZ, call your healthcare provider or go to the nearest hospital emergency room right away.

What are possible side effects of XELJANZ? XELJANZ may cause serious side effects, including:

- See “What is the most important information I should know about XELJANZ?”

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

Common side effects of XELJANZ include:

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

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all the possible side effects of XELJANZ. For more information, ask your healthcare provider or pharmacist.

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

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

How should I store XELJANZ? Store XELJANZ at 68°F to 77°F (room temperature). Safely throw away medicine that is out of date or no longer needed. Keep XELJANZ and all medicines out of the reach of children.

General information about the safe and effective use of XELJANZ.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use XELJANZ for a condition for which it was not prescribed. Do not give XELJANZ to other people, even if they have the same symptoms you have. It may harm them. This Medication Guide summarizes the most important information about XELJANZ. If you would like more information, talk to your healthcare provider. You can ask your pharmacist or healthcare provider for information about XELJANZ that is written for health professionals.

What are the ingredients in XELJANZ?

Active ingredient: tofacitinib citrate

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.