Infertility

Females
Based on findings in rats, treatment with XELJANZ/XELJANZ XR may result in reduced fertility in females of reproductive potential. It is not known if this effect is reversible *[see Nonclinical Toxicology (13.1)]*.

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

8.5 Geriatric Use
Of the 3315 patients who enrolled in rheumatoid arthritis Studies I to V, a total of 505 rheumatoid arthritis patients were 65 years of age and older, including 71 patients 75 years and older. The frequency of serious infection among XELJANZ-treated subjects 65 years of age and older was higher than among those under the age of 65.

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

As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly *[see Warnings and Precautions (5.1)]*.

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

8.7 Renal Impairment

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

- Rheumatoid arthritis and psoriatic arthritis patients with moderate or severe renal impairment receiving XELJANZ XR should switch to XELJANZ and adjust the dosage *[see Dosage and Administration (2.2)]*.

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

STATs. JAK enzymes transmit cytokine signaling through pairing of JAKs (e.g., JAK1/JAK3, JAK1/JAK2, JAK1/TyK2, JAK2/JAK2). Tofacitinib inhibited the *in vitro* activities of JAK1/JAK2, JAK1/JAK3, and JAK2/JAK2 combinations with IC_{50} of 406, 56, and 1377 nM, respectively. However, the relevance of specific JAK combinations to therapeutic effectiveness is not known.

12.2 Pharmacodynamics

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

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

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

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

12.3 Pharmacokinetics

XELJANZ

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

XELJANZ XR

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

Absorption

XELJANZ
The absolute oral bioavailability of XELJANZ is 74%. Coadministration of XELJANZ with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. In clinical trials, XELJANZ was administered without regard to meals *[see Dosage and Administration (2.1)]*.

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

Distribution
After intravenous administration, the volume of distribution is 87 L. The protein binding of tofacitinib is approximately 40%. Tofacitinib binds predominantly to albumin and does not appear to bind to α1-acid glycoprotein. Tofacitinib distributes equally between red blood cells and plasma.

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

Pharmacokinetics in Patient Populations
Population pharmacokinetic analyses indicated that pharmacokinetic characteristics were similar between patients with rheumatoid arthritis, psoriatic arthritis, and UC. The coefficient of variation (%) in AUC of tofacitinib were generally similar across different disease patients, ranging from 22% to 34% (Table 6).

Table 6. XELJANZ Exposure in Patient Populations at 5 mg Twice Daily and 10 mg Twice Daily Doses

Pharmacokinetic Parameters[a] Geometric Mean (CV%)	**XELJANZ 5 mg Twice Daily**			**XELJANZ 10 mg Twice Daily**
	Rheumatoid Arthritis	**Psoriatic Arthritis**	**Ulcerative Colitis**	**Ulcerative Colitis**
$AUC_{0\text{-}24,ss}$ (ng·h/mL)	504 (22.0%)	419 (34.1%)	423 (22.6%)	807 (24.6%)

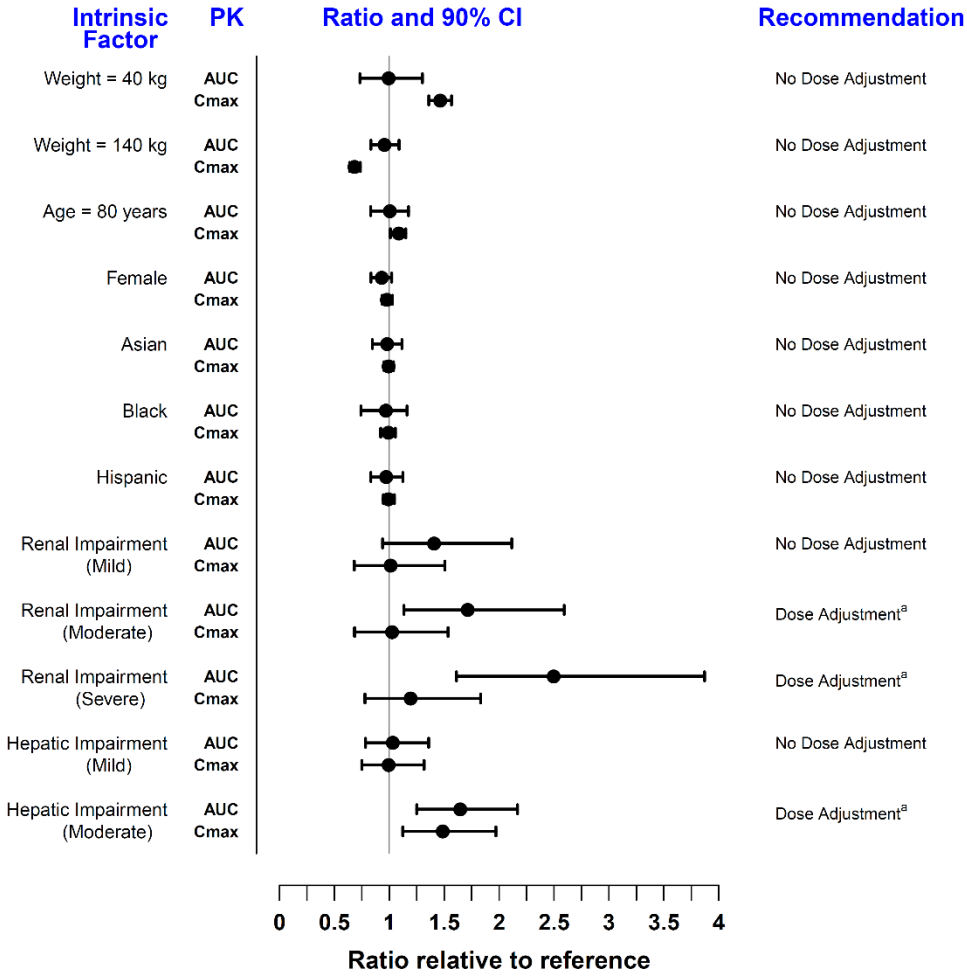
Abbreviations: $AUC_{0\text{-}24,ss}$=area under the plasma concentration-time curve over 24 hours at steady state; CV=coefficient of variation.
[a.] Pharmacokinetic parameters estimated based on population pharmacokinetic analysis.

Specific Populations

Covariate evaluation as part of population PK analyses in patient populations indicated no clinically relevant change in tofacitinib exposure, after accounting for differences in renal function (i.e., creatinine clearance) between patients, based on age, weight, gender and race (Figure 1). An approximately linear relationship between body weight and volume of distribution was observed, resulting in higher peak (C_{max}) and lower trough (C_{min}) concentrations in lighter patients. However, this difference is not considered to be clinically relevant.

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

Figure 1: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics



Note: Reference values for weight, age, gender, and race comparisons are 70 kg, 55 years, male, and white, respectively; reference groups for renal and hepatic impairment data are subjects with normal renal and hepatic function.

[a] *[see Dosage and Administration (2.2, 2.3)]* for dosage adjustment in RA, PsA, and UC patients.

In subjects with ESRD maintained on hemodialysis, mean AUC was approximately 40% higher compared with historical healthy subject data, consistent with approximately 30% contribution of

renal clearance to the total clearance of tofacitinib. Dose adjustment is recommended in ESRD patients maintained on hemodialysis (*[see Dosage and Administration (2.2, 2.3)]* for dosage adjustment in RA, PsA, and UC patients).

Drug Interaction Studies

Potential for XELJANZ/XELJANZ XR to Influence the PK of Other Drugs
In vitro studies indicate that tofacitinib does not significantly inhibit or induce the activity of the major human drug-metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations corresponding to the steady state C_{max} of a 10 mg twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the pharmacokinetics of midazolam, a highly sensitive CYP3A4 substrate, when coadministered with XELJANZ.

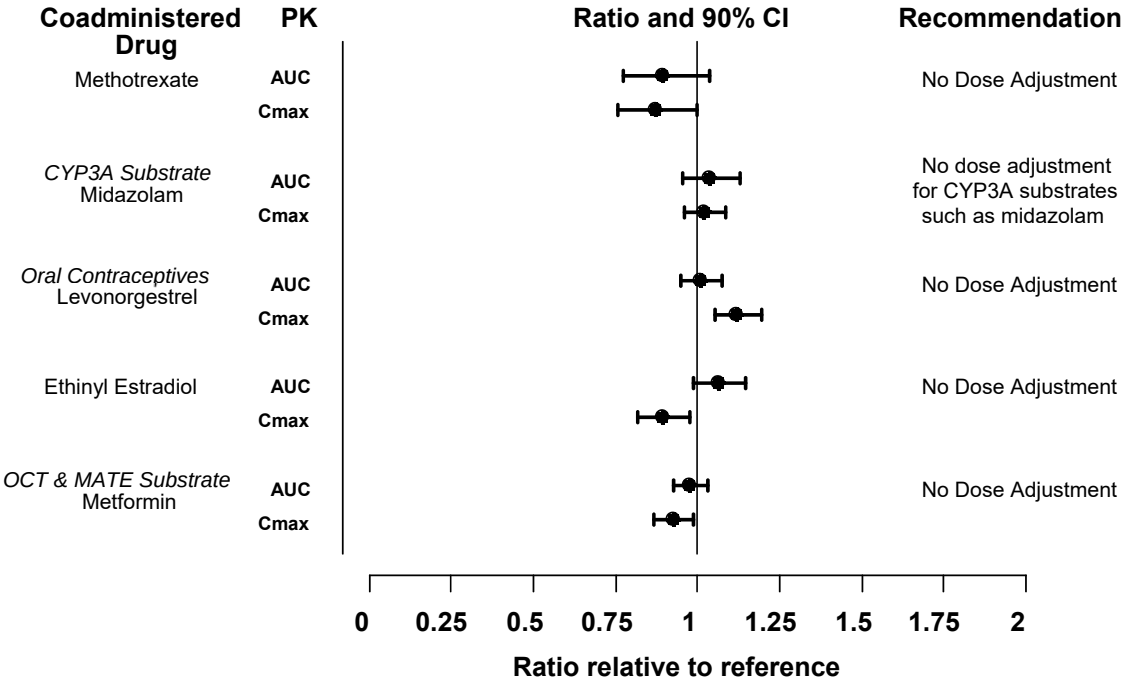
In vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug-metabolizing uridine 5'-diphospho-glucuronosyltransferases (UGTs) [UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7] at concentrations exceeding 250 times the steady state C_{max} of a 10 mg twice daily dose.

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

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

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

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

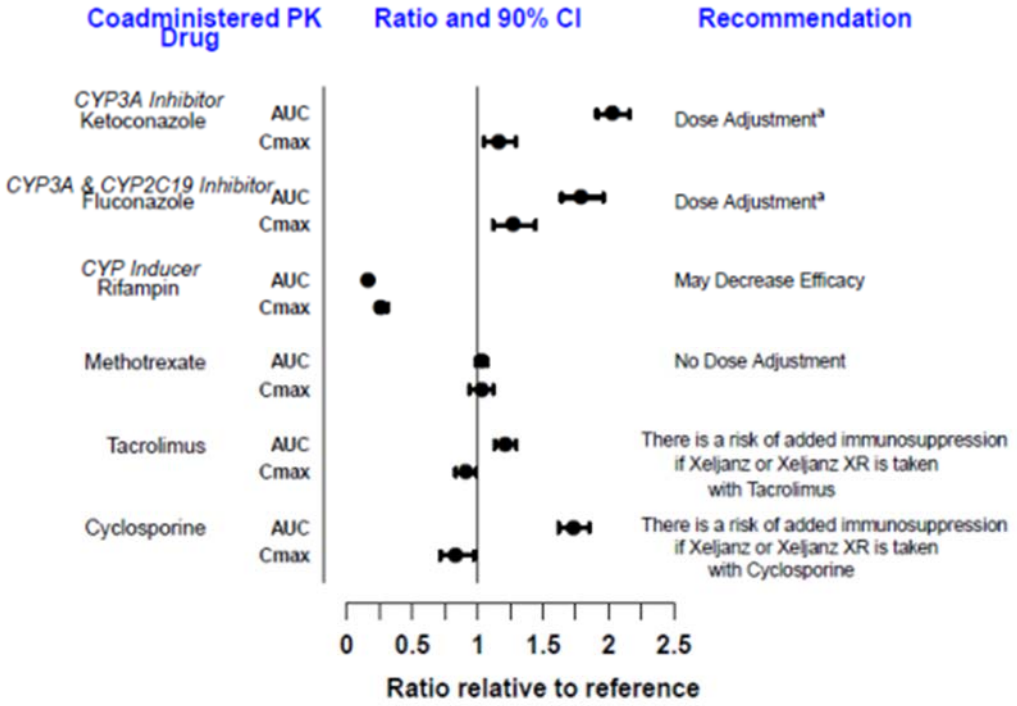


Note: Reference group is administration of concomitant medication alone; OCT = Organic Cationic Transporter; MATE = Multidrug and Toxic Compound Extrusion

Potential for Other Drugs to Influence the Pharmacokinetics of Tofacitinib

Since tofacitinib is metabolized by CYP3A4, interaction with drugs that inhibit or induce CYP3A4 is likely. Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to substantially alter the pharmacokinetics of tofacitinib (see Figure 3).

Figure 3: Impact of Other Drugs on the Pharmacokinetics of Tofacitinib



Note: Reference group is administration of tofacitinib alone.
[a] *[see Dosage and Administration (2.2, 2.3), Drug Interactions (7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 39-week toxicology study in monkeys, tofacitinib at exposure levels approximately 6 times the recommended dose of 5 mg twice daily, and approximately 3 times the 10 mg twice daily dose (on an AUC basis at oral doses of 5 mg/kg twice daily) produced lymphomas. No lymphomas were observed in this study at exposure levels 1 times the recommended dose of 5 mg twice daily, and approximately 0.5 times the 10 mg twice daily dose (on an AUC basis at oral doses of 1 mg/kg twice daily).

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib, at exposure levels approximately 34 times the recommended dose of 5 mg twice daily, and approximately 17 times the 10 mg twice daily dose (on an AUC basis at oral doses of 200 mg/kg/day) was not carcinogenic in mice.

In the 24-month oral carcinogenicity study in Sprague-Dawley rats, tofacitinib caused benign Leydig cell tumors, hibernomas (malignancy of brown adipose tissue), and benign thymomas at doses greater than or equal to 30 mg/kg/day (approximately 42 times the exposure levels at the recommended dose of 5 mg twice daily, and approximately 21 times the 10 mg twice daily dose on an AUC basis). The relevance of benign Leydig cell tumors to human risk is not known.

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

In rats, tofacitinib at exposure levels approximately 17 times the recommended dose of 5 mg twice daily, and approximately 8.3 times the 10 mg twice daily dose (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the recommended dose of 5 mg twice daily, and approximately 0.5 times the 10 mg twice daily dose (on an AUC basis at oral doses of 1 mg/kg/day). Tofacitinib exposure levels at approximately 133 times the recommended dose of 5 mg twice daily, and approximately 67 times the 10 mg twice daily dose (on an AUC basis at oral doses of 100 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis

The XELJANZ clinical development program included two dose-ranging trials and five confirmatory trials. Although other doses have been studied, the recommended dose of XELJANZ is 5 mg twice daily. XELJANZ 10 mg twice daily is not recommended for the treatment of rheumatoid arthritis *[see Dosage and Administration (2.2)]*.

Dose-Ranging Trials

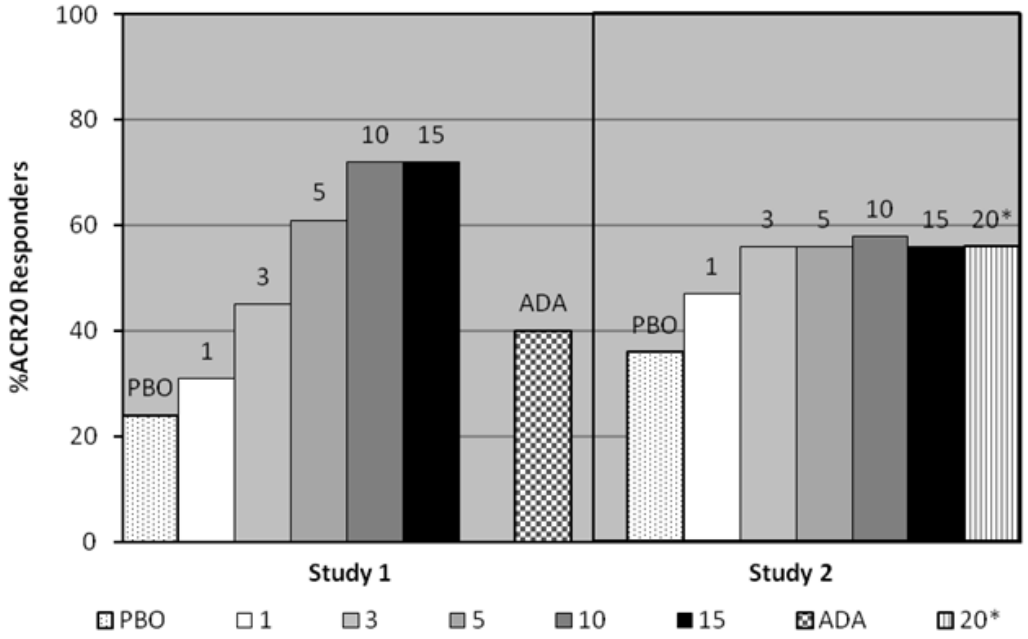
Dose selection for XELJANZ was based on two pivotal dose-ranging trials.

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

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

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

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



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

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

Confirmatory Trials

Study RA-I (NCT00814307) was a 6-month monotherapy trial in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiologic or biologic) received 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 RA-II (NCT00856544) was a 12-month trial in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a nonbiologic DMARD received 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 RA-III (NCT00853385) was a 12-month trial in 717 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX. Patients received XELJANZ 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week, or placebo added to background MTX. Placebo patients were advanced as in Study II. The primary endpoints were the proportion of patients who achieved an ACR20 response at Month 6, HAQ-DI at Month 3, and DAS28-4(ESR) less than 2.6 at Month 6.

Study RA-IV (NCT00847613) was a 2-year trial with a planned analysis at 1 year in which 797 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to MTX received 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 RA-V (NCT00960440) was a 6-month trial in which 399 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to at least one approved TNF blocking biologic agent received 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 RA-VI (NCT01039688) was a 2-year monotherapy trial with a planned analysis at 1 year in which 952 MTX-naïve patients with moderate to severe active rheumatoid arthritis received XELJANZ 5 or 10 mg twice daily or MTX dose-titrated over 8 weeks to 20 mg 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 RA-I, IV, and V are shown in Table 7. Similar results were observed with Studies RA-II and III. In trials RA-I through V, patients treated with 5 mg twice daily XELJANZ had higher ACR20, ACR50, and ACR70 response rates versus placebo, with or without background DMARD treatment, at Month 3 and Month 6. Higher ACR20 response rates were observed within 2 weeks compared to placebo. In the 12-month trials, ACR response rates in XELJANZ-treated patients were consistent at 6 and 12 months.

Table 7: Proportion of Patients with an ACR Response

	Percent of Patients					
	Monotherapy in Nonbiologic or Biologic DMARD Inadequate Responders[c]		MTX Inadequate Responders[d]		TNF Blocker Inadequate Responders[e]	
	Study I		Study IV		Study V	
N[a]	PBO 122	XELJANZ 5 mg Twice Daily 243	PBO + MTX 160	XELJANZ 5 mg Twice Daily + MTX 321	PBO + MTX 132	XELJANZ 5 mg Twice Daily + MTX 133
ACR20 Month 3 Month 6	 26% NA[b]	 59% 69%	 27% 25%	 55% 50%	 24% NA	 41% 51%
ACR50 Month 3 Month 6	 12% NA	 31% 42%	 8% 9%	 29% 32%	 8% NA	 26% 37%
ACR70 Month 3 Month 6	 6% NA	 15% 22%	 3% 1%	 11% 14%	 2% NA	 14% 16%

[a] N is number of randomized and treated patients.
[b] NA Not applicable, as data for placebo treatment is not available beyond 3 months in Studies I and V due to placebo advancement.
[c] Inadequate response to at least one DMARD (biologic or nonbiologic) due to lack of efficacy or toxicity.
[d] Inadequate response to MTX defined as the presence of sufficient residual disease activity to meet the entry criteria.
[e] Inadequate response to a least one TNF blocker due to lack of efficacy and/or intolerance.

In Study RA-IV, a greater proportion of patients treated with XELJANZ 5 mg twice daily plus MTX achieved a low level of disease activity as measured by a DAS28-4(ESR) less than 2.6 at 6 months compared to those treated with MTX alone (Table 8).

Table 8: Proportion of Patients with DAS28-4(ESR) Less Than 2.6 with Number of Residual Active Joints

	Study IV	
DAS28-4(ESR) Less Than 2.6	**Placebo + MTX** **160**	**XELJANZ 5 mg Twice Daily + MTX** **321**
Proportion of responders at Month 6 (n)	1% (2)	6% (19)
Of responders, proportion with 0 active joints (n)	50% (1)	42% (8)
Of responders, proportion with 1 active joint (n)	0	5% (1)
Of responders, proportion with 2 active joints (n)	0	32% (6)
Of responders, proportion with 3 or more active joints (n)	50% (1)	21% (4)

The results of the components of the ACR response criteria for Study RA-IV are shown in Table 9. Similar results were observed for XELJANZ in Studies RA-I, II, III, V, and VI.

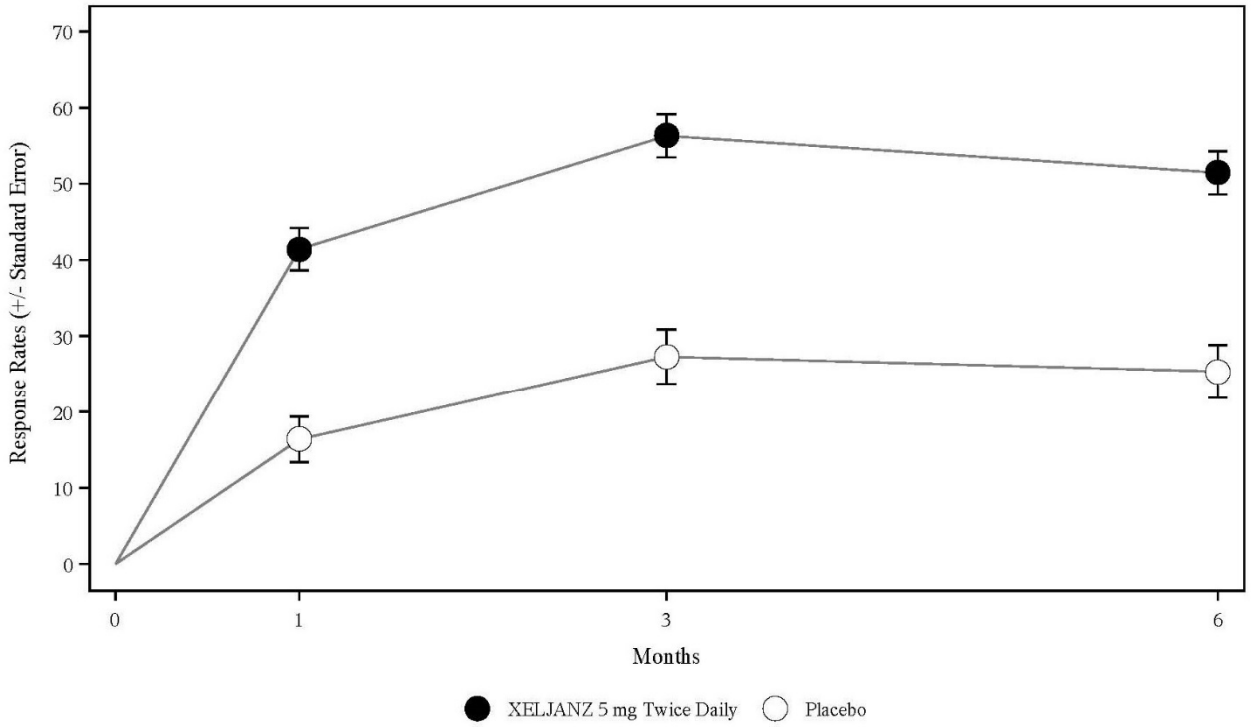
Table 9: Components of ACR Response at Month 3

	Study IV			
	XELJANZ 5 mg Twice Daily + MTX **N=321**		**Placebo + MTX** **N=160**	
Component (mean) [a]	Baseline	Month 3[a]	Baseline	Month 3[a]
Number of tender joints (0-68)	24 (14)	13 (14)	23 (13)	18 (14)
Number of swollen joints (0-66)	14 (8)	6 (8)	14 (9)	10 (9)
Pain[b]	58 (23)	34 (23)	55 (24)	47 (24)
Patient global assessment[b]	58 (24)	35 (23)	54 (23)	47 (24)
Disability index (HAQ-DI)[c]	1.41 (0.68)	0.99 (0.65)	1.32 (0.67)	1.19 (0.68)
Physician global assessment[b]	59 (16)	30 (19)	56 (18)	43 (22)
CRP (mg/L)	15.3 (19.0)	7.1 (19.1)	13.7 (14.9)	14.6 (18.7)

[a] Data shown is mean (Standard Deviation) at Month 3.
[b] Visual analog scale: 0 = best, 100 = worst.
[c] Health Assessment Questionnaire Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

The percent of ACR20 responders by visit for Study RA-IV is shown in Figure 5. Similar responses were observed for XELJANZ in Studies RA-I, II, III, V, and VI.

Figure 5: Percentage of ACR20 Responders by Visit for Study RA-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 at Month 3.

Radiographic Response

Two studies were conducted to evaluate the effect of XELJANZ on structural joint damage. In Study RA-IV and Study RA-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 RA-IV, XELJANZ 5 mg twice daily reduced the mean progression of structural damage (not statistically significant) as shown in Table 10. Analyses of erosion and joint space narrowing scores were consistent with the overall results.

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

In Study RA-VI, XELJANZ monotherapy inhibited the progression of structural damage compared to MTX at Months 6 and 12 as shown in Table 10. 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% of patients treated with XELJANZ 5 mg twice daily.

Table 10: Radiographic Changes at Months 6 and 12

	Study IV		
	Placebo **N=139** **Mean (SD)[a]**	**XELJANZ 5 mg Twice Daily** **N=277** **Mean (SD) [a]**	**XELJANZ 5 mg Twice Daily** **Mean Difference from Placebo[b] (CI)**
mTSS[c] Baseline Month 6	 33 (42) 0.5 (2.0)	 31 (48) 0.1 (1.7)	 - -0.3 (-0.7, 0.0)
	Study VI		
	MTX **N=166** **Mean (SD)[a]**	**XELJANZ 5 mg Twice Daily** **N=346** **Mean (SD) [a]**	**XELJANZ 5 mg Twice Daily** **Mean Difference from MTX[b] (CI)**
mTSS[c] Baseline Month 6 Month 12	 17 (29) 0.8 (2.7) 1.3 (3.7)	 20 (40) 0.2 (2.3) 0.4 (3.0)	 - -0.7 (-1.0, -0.3) -0.9 (-1.4, -0.4)

[a] SD = Standard Deviation
[b] Difference between least squares means XELJANZ minus placebo or MTX (95% CI = 95% confidence interval)
[c] Month 6 and Month 12 data are mean change from baseline.

Physical Function Response

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

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

Other Health-Related Outcomes

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

14.2 Psoriatic Arthritis

The XELJANZ clinical development program to assess efficacy and safety included 2 multicenter, randomized, double-blind, placebo-controlled confirmatory trials in 816 patients 18 years of age and older (PsA-I and PsA-II). Although other doses have been studied, the recommended dose of XELJANZ is 5 mg twice daily. XELJANZ 10 mg twice daily is not recommended for the treatment of psoriatic arthritis *[see Dosage and Administration (2.2)]*. All patients had active psoriatic arthritis for at least 6 months based upon the Classification Criteria for Psoriatic Arthritis (CASPAR), at least 3 tender/painful joints and at least 3 swollen joints, and active plaque psoriasis. Patients randomized and treated across the 2 clinical trials represented different psoriatic arthritis subtypes at screening, including <5 joints or asymmetric

involvement (21%), ≥5 joints involved (90%), distal interphalangeal (DIP) joint involvement (61%), arthritis mutilans (8%), and spondylitis (19%). Patients in these clinical trials had a diagnosis of psoriatic arthritis for a mean (SD) of 7.7 (7.2) years. At baseline, 80% and 53% of patients had enthesitis and dactylitis, respectively. At baseline, all patients were required to receive treatment with a stable dose of a nonbiologic DMARD (79% received methotrexate, 13% received sulfasalazine, 7% received leflunomide, 1% received other nonbiologic DMARDs). In both clinical trials, the primary endpoints were the ACR20 response and the change from baseline in HAQ-DI at Month 3.

Study PsA-I was a 12-month clinical trial in 422 patients who had an inadequate response to a nonbiologic DMARD (67% and 33% were inadequate responders to 1 nonbiologic DMARD and ≥2 nonbiologic DMARDs, respectively) and who were naïve to treatment with a TNF blocker. Patients were randomized in a 2:2:2:1:1 ratio to receive XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, adalimumab 40 mg subcutaneously once every 2 weeks, placebo to XELJANZ 5 mg twice daily treatment sequence, or placebo to XELJANZ 10 mg twice daily treatment sequence, respectively; study drug was added to background nonbiologic DMARD treatment. At the Month 3 visit, all patients randomized to placebo treatment were advanced in a blinded fashion to a predetermined XELJANZ dose of 5 mg or 10 mg twice daily. Study PsA-I was not designed to demonstrate noninferiority or superiority to adalimumab.

Study PsA-II was a 6-month clinical trial in 394 patients who had an inadequate response to at least 1 approved TNF blocker (66%, 19%, and 15% were inadequate responders to 1 TNF blocker, 2 TNF blockers and ≥3 TNF blockers, respectively). Patients were randomized in a 2:2:1:1 ratio to receive XELJANZ 5 mg twice daily, XELJANZ 10 mg twice daily, placebo to XELJANZ 5 mg twice daily treatment sequence, or placebo to XELJANZ 10 mg twice daily treatment sequence, respectively; study drug was added to background nonbiologic DMARD treatment. At the Month 3 visit, placebo patients were advanced in a blinded fashion to a predetermined XELJANZ dose of 5 mg or 10 mg twice daily as in Study PsA-I.

Clinical Response

At Month 3, patients treated with XELJANZ 5 mg twice daily had higher ($p \leq 0.05$) response rates versus placebo for ACR20, ACR50, and ACR70 in Study PsA-I and for ACR20 and ACR50 in Study PsA-II; ACR70 response rates were also higher for XELJANZ 5 mg twice daily versus placebo in Study PsA-II, although the differences versus placebo were not statistically significant ($p > 0.05$) (Tables 11 and 12).

Table 11: Proportion of Patients with an ACR Response in Study PsA-I* [Nonbiologic DMARD Inadequate Responders (TNF Blocker-Naïve)]

Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	
N[a]	105	107	
	Response Rate	Response Rate	Difference (%) 95% CI from Placebo
Month 3			
ACR20	33%	50%	17.1 (4.1, 30.2)
ACR50	10%	28%	18.5 (8.3, 28.7)
ACR70	5%	17%	12.1 (3.9, 20.2)

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

Table 12: Proportion of Patients with an ACR Response in Study PsA-II* (TNF Blocker Inadequate Responders)

Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	
N[a]	131	131	
	Response Rate	Response Rate	Difference (%) 95% CI from Placebo
Month 3			
ACR20	24%	50%	26.0 (14.7, 37.2)
ACR50	15%	30%	15.3 (5.4, 25.2)
ACR70	10%	17%	6.9 (-1.3, 15.1)

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

Improvements from baseline in the ACR response criteria components for both studies are shown in Table 13.

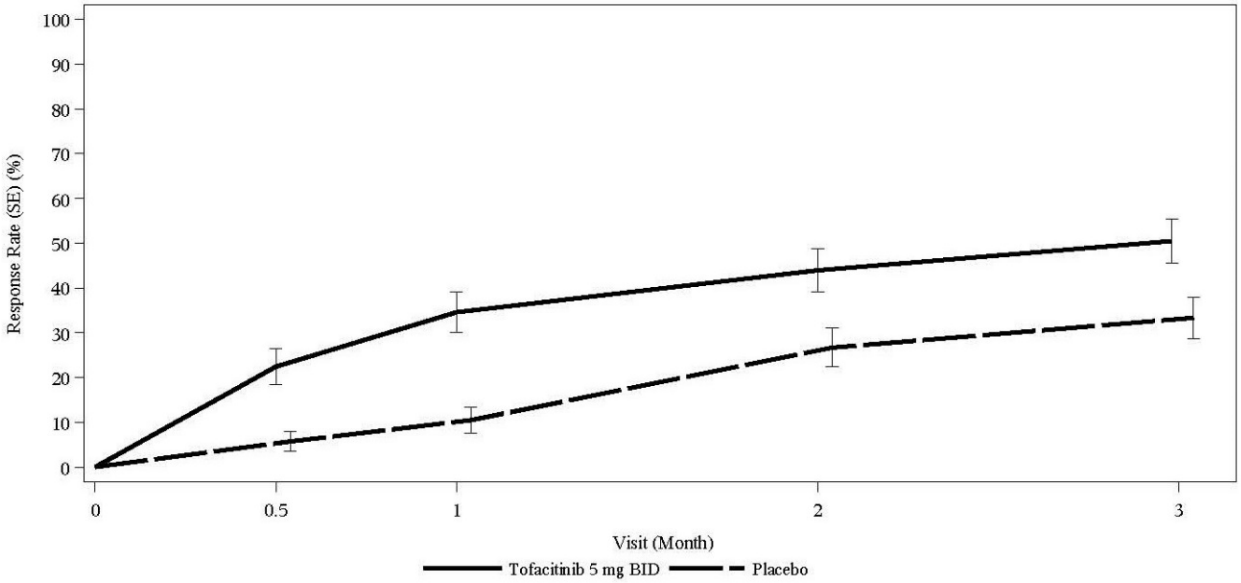
Table 13: Components of ACR Response at Baseline and Month 3 in Studies PsA-I and PsA-II

	Nonbiologic DMARD Inadequate Responders (TNF Blocker-Naïve)		TNF Blocker Inadequate Responders	
	Study PsA-I*		Study PsA-II*	
Treatment Group	Placebo	XELJANZ 5 mg Twice Daily	Placebo	XELJANZ 5 mg Twice Daily
N at Baseline	105	107	131	131
ACR Component[a]				
Number of tender/painful joints (0-68)				
Baseline	20.6	20.5	19.8	20.5
Month 3	14.6	12.2	15.1	11.5
Number of swollen joints (0-66)				
Baseline	11.5	12.9	10.5	12.1
Month 3	7.1	6.3	7.7	4.8
Patient assessment of arthritis pain[b]				
Baseline	53.2	55.7	54.9	56.4
Month 3	44.7	34.7	48.0	36.1
Patient global assessment of arthritis[b]				
Baseline	53.9	54.7	55.8	57.4
Month 3	44.4	35.5	49.2	36.9
HAQ-DI[c]				
Baseline	1.11	1.16	1.25	1.26
Month 3	0.95	0.81	1.09	0.88
Physician's Global Assessment of Arthritis[b]				
Baseline	53.8	54.6	53.7	53.5
Month 3	35.4	29.5	36.4	27.0
CRP (mg/L)				
Baseline	10.4	10.5	12.1	13.8
Month 3	8.6	4.0	11.4	7.7

* Subjects received one concomitant nonbiologic DMARD.
[a] Data shown are mean value at baseline and at Month 3.
[b] Visual analog scale (VAS): 0 = best, 100 = worst.
[c] HAQ-DI = Health Assessment Questionnaire – Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.

The percentage of ACR20 responders by visit for Study PsA-I is shown in Figure 6. Similar responses were observed in Study PsA-II. In both studies, improvement in ACR20 response on XELJANZ was observed at the first visit after baseline (Week 2).

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



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

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

Physical Function

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg twice daily demonstrated significantly greater improvement ($p \leq 0.05$) from baseline in physical functioning compared to placebo at Month 3 (Table 14).

Table 14: Change from Baseline in HAQ-DI in Studies PsA-I and PsA-II

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

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

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

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

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

14.3 Ulcerative Colitis

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

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

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

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

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

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

The efficacy results of Study UC-I and Study UC-II based on the centrally read endoscopy results are shown in Table 15.

Table 15: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints at Week 8 (Induction Study UC-I and Study UC-II, Central Endoscopy Read)

Study UC-I			
Endpoint	**Placebo**	**XELJANZ 10 mg Twice Daily**	**Treatment Difference versus Placebo (95% CI)**
Remission at Week 8[a]			
Total Population	N=122 8%	N=476 18%	10%* (4.3, 16.3)
With Prior TNF Blocker Failure[b]	N=64 2%	N=243 11%	
Without Prior TNF Blocker Failure[c]	N=58 16%	N=233 26%	
Improvement of endoscopic appearance of the mucosa at Week 8[d]			
Total Population	N=122 16%	N=476 31%	16%** (8.1, 23.4)
With Prior TNF Blocker Failure[b]	N=64 6%	N=243 23%	
Without Prior TNF Blocker Failure[c]	N=58 26%	N=233 40%	

Study UC-II			
Endpoint	**Placebo**	**XELJANZ 10 mg Twice Daily**	**Treatment Difference (95% CI)**
Remission at Week 8[a]			
Total Population	N=112 4%	N=429 17%	13%** (8.1, 17.9)
With Prior TNF Blocker Failure[b]	N=60 0%	N=222 12%	
Without Prior TNF Blocker Failure[c]	N=52 8%	N=207 22%	
Improvement of endoscopic appearance of the mucosa at Week 8[d]			
Total Population	N=112 12%	N-429 28%	17%** (9.5, 24.1)
With Prior TNF Blocker Failure[b]	N=60 7%	N=222 22%	
Without Prior TNF Blocker Failure[c]	N=52 17%	N=207 36%	

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

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

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

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

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

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

At baseline of Study UC-III:

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

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

The efficacy results of Study UC-III based on the centrally read endoscopy results are summarized in Table 16.

Table 16: Proportion of Patients Meeting Primary and Key Secondary Efficacy Endpoints in Maintenance Study UC-III (Central Endoscopy Read)

				Treatment Difference versus Placebo (95% CI)	
Endpoint	**Placebo**	**XELJANZ 5 mg Twice Daily**	**XELJANZ 10 mg Twice Daily**	**XELJANZ 5 mg Twice Daily**	**XELJANZ 10 mg Twice Daily**
Remission at Week 52[a]					
Total Population	N=198 11%	N=198 34%	N=197 41%	23%* (15.3, 31.2)	30%* (21.4, 37.6)
With Prior TNF Blocker Failure[b]	N=89 11%	N=83 24%	N=93 37%		
Without Prior TNF Blocker Failure[c]	N=109 11%	N=115 42%	N=104 44%		

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

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

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

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

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

XELJANZ 5 mg twice daily group and 56% in the XELJANZ 10 mg twice daily group maintained remission at Week 52 compared to 10% of placebo patients.

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

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

Of the 905 patients who were assigned to XELJANZ 10 mg twice daily in the 8-week induction studies (Study UC-I or Study UC-II), 322 patients completed the induction studies but did not achieve clinical response. Of these 322 patients, 291 continued to receive XELJANZ 10 mg twice daily (unblinded) and had available data after an additional 8 weeks in Study UC-IV. After 8 additional weeks (a total of 16 weeks treatment), 149 patients achieved clinical response, and 25 patients achieved remission (based on central endoscopy read). Among those 144 patients who achieved clinical response by 16 weeks and had available data at Week 52, 65 patients achieved remission (based on local endoscopy read) after continued treatment with XELJANZ 10 mg twice daily for 52 weeks.

16 HOW SUPPLIED/STORAGE AND HANDLING

	Bottle Size (number of tablets)	**NDC Number**
XELJANZ **5 mg tofacitinib tablets** White, round, immediate-release film-coated tablets, debossed with “Pfizer” on one side, and “JKI 5” on the other side	28	NDC 0069-1001-03
	60	NDC 0069-1001-01
XELJANZ **10 mg tofacitinib tablets** Blue, round, immediate-release film-coated tablets, debossed with “Pfizer” on one side, and “JKI 10” on the other side	28	NDC 0069-1002-03
	60	NDC 0069-1002-01
	180	NDC 0069-1002-02

	Bottle Size (number of tablets)	NDC Number
XELJANZ XR	14	NDC 0069-0501-14
11 mg tofacitinib tablets Pink, oval, extended-release tablet with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet	30	NDC 0069-0501-30

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

XELJANZ/XELJANZ XR
Do not repackage.

17 PATIENT COUNSELING INFORMATION

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

Serious Infections

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

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

Malignancies and Lymphoproliferative Disorders

Inform patients that XELJANZ/XELJANZ XR may increase their risk of certain cancers, and that lymphoma and other cancers have been observed in patients taking XELJANZ. Instruct patients to inform their healthcare provider if they have ever had any type of cancer *[see Warnings and Precautions (5.3)]*.

Thrombosis

Advise patients to stop taking XELJANZ/XELJANZ XR and to call their healthcare provider right away if they experience any symptoms of thrombosis (sudden shortness of breath, chest pain worsened with breathing, swelling of leg or arm, leg pain or tenderness, red or discolored skin in the affected leg or arm) *[see Warnings and Precautions (5.4)]*.

Hypersensitivity
Advise patients to stop taking XELJANZ/XELJANZ XR and to call their healthcare provider right away if they experience any symptoms of allergic reactions while taking XELJANZ/XELJANZ XR *[see Warnings and Precautions (5.6)]*.

Important Information on Laboratory Abnormalities
Inform patients that XELJANZ/XELJANZ XR may affect certain lab test results, and that blood tests are required before and during XELJANZ/XELJANZ XR treatment *[see Warnings and Precautions (5.7)]*.

Pregnancy
Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their prescriber of a known or suspected pregnancy. Inform patients that Pfizer has a registry for pregnant women who have taken XELJANZ/XELJANZ XR during pregnancy. Advise patients to contact the registry at 1-877-311-8972 to enroll *[see Use in Specific Populations (8.1)]*.

Lactation
Advise women not to breastfeed during treatment with XELJANZ/XELJANZ XR and for at least 18 hours after the last dose of XELJANZ or 36 hours after the last dose of XELJANZ XR *[see Use in Specific Populations (8.2)]*.

Infertility
Advise females of reproductive potential that XELJANZ/XELJANZ XR may impair fertility *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*. It is not known if this effect is reversible.

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

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

LAB-0445-17.0

MEDICATION GUIDE

XELJANZ (ZEL' JANS') **(tofacitinib)** **tablets, for oral use**	**XELJANZ XR (ZEL' JANS' EKS-AHR)** **(tofacitinib)** **extended-release tablets, for oral use**

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

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

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

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

People taking the higher dose (10 mg twice daily) of XELJANZ have a higher risk of serious infections and shingles.

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

- think you have an infection or have symptoms of an infection such as:
    - fever, sweating, or chills
    - cough
    - blood in phlegm
    - warm, red, or painful skin or sores on your body
    - burning when you urinate or urinating more often than normal
    - muscle aches
    - shortness of breath
    - weight loss
    - diarrhea or stomach pain
    - feeling very tired
- are being treated for an infection.
- get a lot of infections or have infections that keep coming back.
- have diabetes, chronic lung disease, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
- have TB, or have been in close contact with someone with TB.
- live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidioidomycosis, or blastomycosis). These infections may happen or become more severe if you use XELJANZ/XELJANZ XR. Ask your healthcare provider if you do not know if you have lived in an area where these infections are common.
- have or have had hepatitis B or C.

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

2. Increased risk of death in people 50 years of age and older with rheumatoid arthritis who have at least 1 heart disease (cardiovascular) risk factor and who are taking a higher than recommended dose of XELJANZ/XELJANZ XR. The recommended dose in patients with rheumatoid arthritis and psoriatic arthritis is XELJANZ 5 mg twice daily or XELJANZ XR 11 mg one time each day.

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

- Lymphoma and other cancers including skin cancers can happen in patients taking XELJANZ/XELJANZ XR. People taking the higher dose (10 mg twice daily) of XELJANZ have a higher risk of skin cancers. 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).

4. Blood clots in the lungs, veins of the legs or arms, and arteries. Blood clots in the lungs (pulmonary embolism, PE), veins of the legs (deep vein thrombosis, DVT) and arteries (arterial thrombosis) have happened more often in patients with rheumatoid arthritis who are 50 years of age and older and with at least 1 heart disease (cardiovascular) risk factor taking a higher than recommended dose of XELJANZ/XELJANZ XR. The recommended dose in patients with rheumatoid arthritis and psoriatic arthritis is XELJANZ 5 mg twice daily or XELJANZ XR 11 mg one time each day. Blood clots in the lungs have also happened in patients with ulcerative colitis. Some people have died from these blood clots.

- Stop taking XELJANZ/XELJANZ XR and tell your healthcare provider right away if you develop signs and symptoms of a blood clot, such as sudden shortness of breath or difficulty breathing, chest pain, swelling of the leg or arm, leg pain or tenderness, or redness or discoloration in the leg or arm.

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

- Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking XELJANZ/XELJANZ XR can get tears in their stomach or intestines. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
  Tell your healthcare provider right away if you have fever and stomach-area pain that does not go away, and a change in your bowel habits.

6. Allergic reactions.

- Symptoms such as swelling of your lips, tongue, or throat, or hives (raised, red patches of skin that are often very itchy) that may mean you are having an allergic reaction have been seen in patients taking XELJANZ/XELJANZ XR. Some of these reactions were serious. If any of these symptoms occur while you are taking XELJANZ/XELJANZ XR, stop XELJANZ/XELJANZ XR and call your healthcare provider right away.

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

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

Your healthcare provider should routinely check certain liver tests.
You should not receive XELJANZ/XELJANZ XR if your lymphocyte count, neutrophil count, or red blood cell count is too low or your liver tests are too high.
Your healthcare provider may stop your XELJANZ/XELJANZ XR treatment for a period of time if needed because of changes in these blood test results.
You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving XELJANZ/XELJANZ XR, and as needed after that. Normal cholesterol levels are important to good heart health.
See “What are the possible side effects of XELJANZ/XELJANZ XR?” for more information about side effects.

What is XELJANZ/XELJANZ XR?

XELJANZ/XELJANZ XR is a prescription medicine called a Janus kinase (JAK) inhibitor.
XELJANZ/XELJANZ XR is used to treat adults with moderately to severely active rheumatoid arthritis in whom methotrexate did not work well or cannot be tolerated.
XELJANZ/XELJANZ XR is used to treat adults with active psoriatic arthritis in which methotrexate or other similar medicines called nonbiologic disease-modifying antirheumatic drugs (DMARDs) did not work well or cannot be tolerated.

XELJANZ is used to treat adults with moderately to severely active ulcerative colitis when medicines called tumor necrosis factor (TNF) blockers did not work well or cannot be tolerated.
It is not known if XELJANZ/XELJANZ XR is safe and effective in people with Hepatitis B or C.
XELJANZ/XELJANZ XR is not recommended for people with severe liver problems.
It is not known if XELJANZ/XELJANZ XR is safe and effective in children.

What should I tell my healthcare provider before taking XELJANZ/XELJANZ XR?
Before taking XELJANZ/XELJANZ XR, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection. See "What is the most important information I should know about XELJANZ/XELJANZ XR?"
- have had blood clots in the veins of your legs, arms, or lungs, or clots in the arteries in the past.
- have liver problems.
- have kidney problems.
- have any stomach area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines.
- have had a reaction to tofacitinib or any of the ingredients in XELJANZ/XELJANZ XR.
- have recently received or are scheduled to receive a vaccine. People who take XELJANZ/XELJANZ XR should not receive live vaccines. People taking XELJANZ/XELJANZ XR can receive non-live vaccines.
- plan to become pregnant or are pregnant. XELJANZ/XELJANZ XR may affect the ability of females to get pregnant. It is not known if this will change after stopping XELJANZ/XELJANZ XR. It is not known if XELJANZ/XELJANZ XR will harm an unborn baby.
    - **Pregnancy Registry:** Pfizer has a registry for pregnant women who take XELJANZ/XELJANZ XR. The purpose of this registry is to check the health of the pregnant mother and her baby. If you are pregnant or become pregnant while taking XELJANZ/XELJANZ XR, talk to your healthcare provider about how you can join this pregnancy registry or you may contact the registry at 1-877-311-8972 to enroll.
- plan to breastfeed or are breastfeeding. You and your healthcare provider should decide if you will take XELJANZ/XELJANZ XR or breastfeed. You should not do both. After you stop your treatment with XELJANZ/XELJANZ XR do not start breastfeeding again until:
    - 18 hours after your last dose of XELJANZ or
    - 36 hours after your last dose of XELJANZ XR

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

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

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

How should I take XELJANZ/XELJANZ XR? Take XELJANZ/XELJANZ XR exactly as your healthcare provider tells you to take it.

- Take XELJANZ 2 times a day with or without food.
- Take XELJANZ XR 1 time a day with or without food for rheumatoid or psoriatic arthritis. **Do not take XELJANZ XR for ulcerative colitis.**
- Swallow XELJANZ XR tablets whole and intact. Do not crush, split, or chew.

- When you take XELJANZ XR, you may see something in your stool that looks like a tablet. This is the empty shell from the tablet after the medicine has been absorbed by your body.
- If you take too much XELJANZ/XELJANZ XR, call your healthcare provider or go to the nearest hospital emergency room right away.
- For the treatment of psoriatic arthritis, take XELJANZ/XELJANZ XR in combination with methotrexate, sulfasalazine or leflunomide as instructed by your healthcare provider.

What are possible side effects of XELJANZ/XELJANZ XR?

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

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

Common side effects of XELJANZ/XELJANZ XR in rheumatoid arthritis patients and psoriatic arthritis patients include:

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

Common side effects of XELJANZ in ulcerative colitis patients include:

- nasal congestion, sore throat, and runny nose (nasopharyngitis)
- increased cholesterol levels
- headache
- upper respiratory tract infections (common cold, sinus infections)
- increased muscle enzyme levels
- rash
- diarrhea
- shingles (herpes zoster)

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

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

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

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

How should I store XELJANZ/XELJANZ XR?

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

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

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

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

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

What are the ingredients in XELJANZ 5 mg?
Active ingredient: tofacitinib citrate
Inactive ingredients: croscarmellose sodium, HPMC 2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.
What are the ingredients in XELJANZ 10 mg?
Active ingredient: tofacitinib citrate
Inactive ingredients: croscarmellose sodium, FD&C Blue #1/Brilliant Blue FCF Aluminum Lake, FD&C Blue #2/Indigo Carmine Aluminum Lake, HPMC 2910/Hypromellose 6cP, lactose monohydrate, macrogol/PEG3350, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.
What are the ingredients in XELJANZ XR?
Active ingredient: tofacitinib citrate
Inactive ingredients: cellulose acetate, copovidone, hydroxyethyl cellulose, hydroxypropyl cellulose, HPMC 2910/Hypromellose, magnesium stearate, red iron oxide, sorbitol, titanium dioxide, and triacetin. Printing ink contains ammonium hydroxide, ferrosoferric oxide/black iron, propylene glycol, and shellac glaze.

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