PRODUCT INFORMATION

XELJANZ® tofacitinib (as citrate) tablet

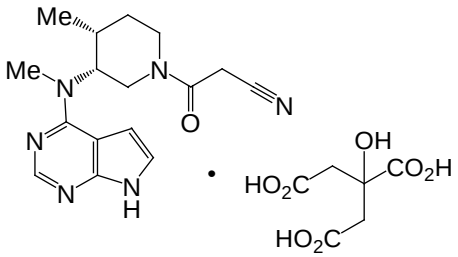
NAME OF THE MEDICINE

Chemical name: (3*R*,4*R*)-4-methyl-3-(methyl-7*H*-pyrrolo [2,3-*d*]pyrimidin-4-ylamino)-ß-oxo-1-piperidinepropanenitrile, 2-hydroxy-1,2,3-propanetricarboxylate

Molecular weight: 504.5 (312.4 for tofacitinib free base)

Molecular formula: $C_{16}H_{20}N_6O \bullet C_6H_8O_7$

Chemical structure:



CAS Registry Number: 540737-29-9 (citrate salt); 477600-75-2 (free base)

DESCRIPTION

Tofacitinib citrate is a white to off-white powder with a pKa of 5.07. Tofacitinib citrate is freely soluble in *N*,*N*-Dimethylacetamide, slightly soluble in water, and very slightly soluble in ethanol (99.5% ethanol). The partition coefficient is 14.3 (Log P = 1.15)

XELJANZ is supplied for oral administration as follows:

· 5 mg - white, round, immediate release, film-coated tablet debossed with "Pfizer" on one side, and "JKI 5" on the other side. Each 5 mg tablet contains 8.078 mg of tofacitinib citrate equivalent to 5 mg of tofacitinib free base active pharmaceutical ingredient.

XELJANZ also contains the following inactive ingredients: cellulose - microcrystalline, lactose, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, macrogol 3350, and glycerol triacetate.

PHARMACOLOGY

Mechanism of Action

Tofacitinib is a selective inhibitor of the Janus kinase (JAK) family of kinases with a high degree of selectivity against other kinases in the human genome. In kinase assays, tofacitinib,

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

Pharmacodynamics

Treatment with tofacitinib was associated with dose-dependent reductions of circulating CD16/56+ natural killer cells, with estimated maximum reductions occurring at approximately 8-10 weeks after initiation of therapy. These changes generally resolved within 2-6 weeks after discontinuation of treatment. Treatment with tofacitinib 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.

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

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

Pharmacokinetics

The PK profile of tofacitinib is characterised by rapid absorption (peak plasma concentrations are reached within 0.5-1 hour), rapid elimination (half-life of ~3 hours) and dose-proportional increases in systemic exposure. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after twice daily administration.

Absorption and Distribution

Tofacitinib is well-absorbed, with an oral bioavailability of 74%. Coadministration of tofacitinib with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. In clinical trials, tofacitinib was administered without regard to meal.

After intravenous administration, the volume of distribution is 87 L. The protein binding of tofacitinib is ~40%. Tofacitinib binds predominantly to albumin and does not appear to bind to a1-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 drug, 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.

Special Populations

Rheumatoid Arthritis (RA), Elderly (>65 years) patients, Gender, Race

Population PK analysis in rheumatoid arthritis patients indicated that systemic exposure (AUC) of tofacitinib in the extremes of body weight (40 kg, 140 kg) were similar to that of a 70 kg patient. Elderly patients 80 years of age were estimated to have < 5% higher AUC relative to the mean age of 55 years. Women were estimated to have 7% lower AUC compared to men. The available data have also shown that there are no major differences in tofacitinib AUC between races. An approximate linear relationship between body weight and volume of distribution was observed, resulting in higher peak (C_{max}) and lower trough (C_{min}) concentrations in lighter patients. However, this difference is not considered to be clinically relevant. The between-subject variability (percentage coefficient of variation) in AUC of tofacitinib is estimated to be approximately 27%.

Children and Adolescents

The pharmacokinetics, safety and efficacy of tofacitinib in paediatric patients have not been established.

Renal Impairment

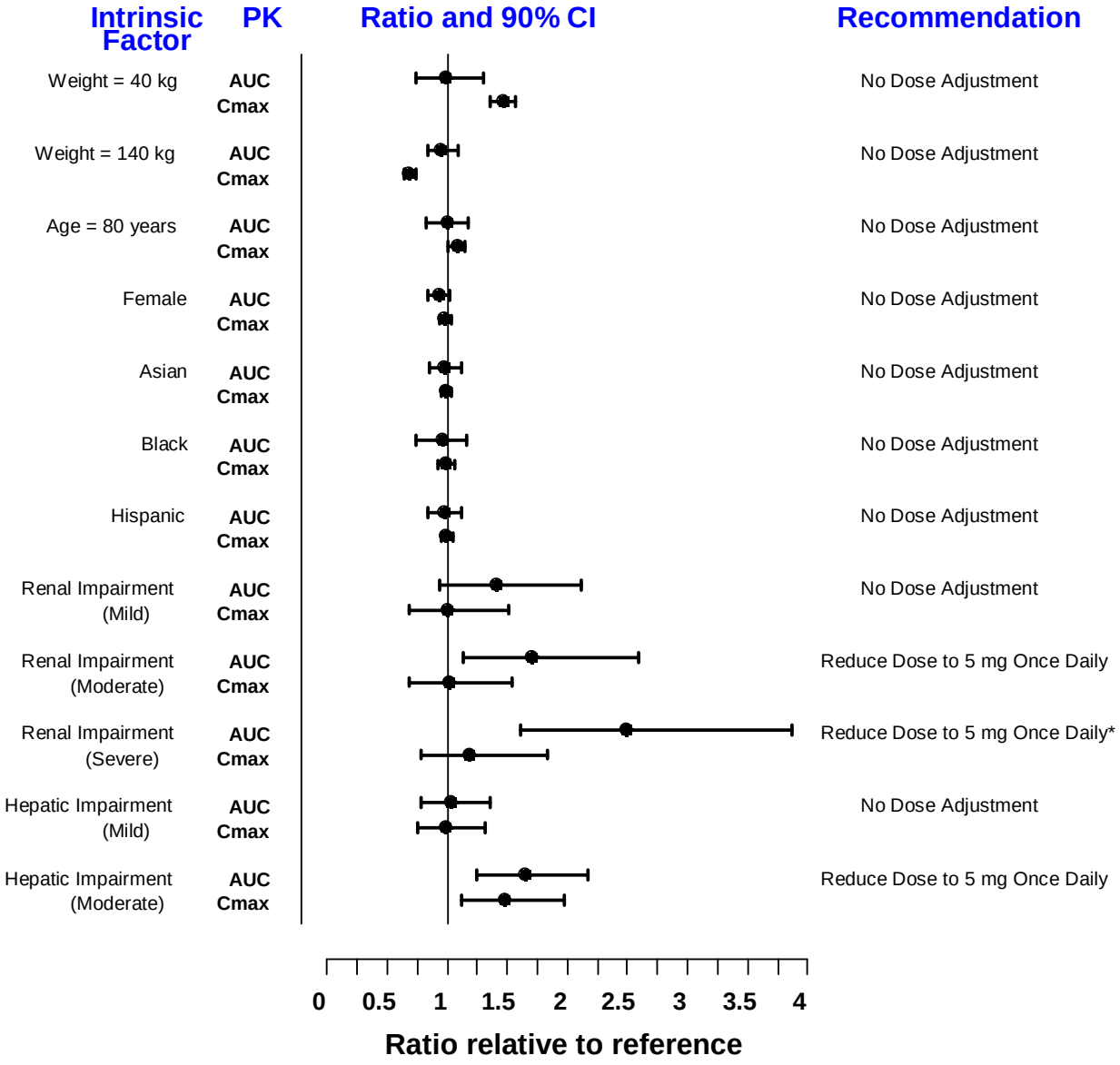
Subjects with mild (creatinine clearance 51-80 mL/min), moderate (30-50 mL/min), and severe (<30 mL/min) renal impairment (estimated GFR (Cockcroft–Gault formula)) had 37%, 43% and 123% higher AUC, respectively, compared with healthy subjects (see DOSAGE AND ADMINISTRATION). In subjects with end-stage renal disease, the contribution of dialysis to the total clearance of tofacitinib was relatively small.

Hepatic Impairment

Subjects with mild and moderate hepatic impairment had 3%, and 65% higher AUC, respectively, compared with healthy subjects (see DOSAGE AND ADMINISTRATION). Subjects with severe hepatic impairment were not studied. Therefore XELJANZ should not be used in patients with severe hepatic impairment (see CONTRAINDICATIONS).

The impact of intrinsic factors on tofacitinib pharmacokinetics is summarised in Figure 1 with dosage adjustment recommendations.

Figure 1: Impact of Intrinsic Factors on Tofacitinib Pharmacokinetics



*Supplemental doses are not necessary in patients after dialysis

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

CLINICAL TRIALS

The efficacy and safety of XELJANZ were assessed in five randomised, double-blind, paired placebo controlled, multicentre studies in patients ≥18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 6 tender and 6 swollen joints at randomisation (4 swollen and tender joints for Study II). XELJANZ, 5 or 10 mg twice daily, was given as monotherapy (Study I) and in combination

with nonbiological disease-modifying antirheumatic drugs (DMARDs) (Study II) in patients with an inadequate response to DMARDs. XELJANZ, 5 or 10 mg twice daily was given in combination with methotrexate (MTX) in patients with either an inadequate response to MTX (Study III and Study IV) or inadequate response or intolerance to at least one approved tumor necrosis factor (TNF)-inhibiting biological agent (Study V).

Study I (A3921045/ORAL Solo) was a 6-month monotherapy study in which 610 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a DMARD (nonbiological or biological) received XELJANZ 5 or 10 mg twice daily or placebo. At the Month 3 visit, all patients randomised 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) < 2.6.

Study II (A3921046/ORAL Sync) was a 12-month study in which 792 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to a nonbiological 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 randomised to placebo treatment 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) < 2.6 at month 6.

Study III (A3921064/ORAL Standard) was a 12-month study 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) < 2.6 at Month 6.

Study IV (A3921044/ORAL Scan) was a 2-year study 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) < 2.6 at Month 6.

Study V (A3921032/ORAL Step) was a 6-month study in which 399 patients with moderate to severe active rheumatoid arthritis who had an inadequate response to at least one approved TNF-inhibiting biological agent received XELJANZ 5 or 10 mg twice daily or placebo added to background MTX. At the Month 3 visit, all patients randomised 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) < 2.6.

Clinical Response

The percentages of XELJANZ-treated patients achieving ACR20, ACR50 and ACR70 responses in Studies I, II, III, IV, and V are shown in Table 1. Results are provided for XELJANZ 5 mg twice daily.

In Studies I and V, patients treated with 5 mg twice daily XELJANZ had statistically superior ACR20, ACR50, and ACR70 response rates at Month 3 vs. placebo-treated patients. In Studies II, III and IV, patients treated with 5 mg twice daily XELJANZ had statistically superior ACR20, ACR50, and ACR70 response rates at Month 3 and 6 vs placebo-treated patients (Table 1).

In Studies I, II, and V, improvement in ACR20 response rate vs. placebo was observed within 2 weeks. In Studies II, III and IV, ACR response rates were maintained to 12 months in XELJANZ-treated patients. ACR response was maintained for 3 years in the ongoing open-label extension studies.

In Study III the proportion achieving an ACR20 response at Month 6; change in HAQ-DI at Month 3, and DAS28-4(ESR) < 2.6 at Month 6 were 51.5, 47.2 and 28.3%; -0.55, -0.49 and -0.24; and 6.2%, 6.7% and 1.1% for the 5 mg twice daily XELJANZ, adalimumab 40 mg subcutaneously every other week and placebo groups, respectively. For a pre-specified secondary endpoint, the ACR70 response rates at month 6 for the 5 mg twice daily XELJANZ group was significantly greater than adalimumab (19.9% and 9.1%, respectively).

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race or disease status. Time to onset was rapid (as early as Week 2 in Studies I, II and V) and the magnitude of response continued to improve with duration of treatment. As with the overall ACR response, each of the components of the ACR response was consistently improved from baseline, including: tender and swollen joint counts; patient and physician global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs in all studies.

Patients in the Phase 3 studies had a mean Disease Activity Score (DAS28-4(ESR)) of 6.1–6.7 at baseline. Significant reductions in DAS28-4(ESR) from baseline (mean improvement) of 1.8-2.0 were observed in 5 mg XELJANZ-treated patients compared to placebo-treated patients (0.7-1.1) at 3 months. The proportion of patients achieving a DAS28 clinical remission (DAS28-4(ESR) < 2.6) in Studies II, III and IV was significantly higher in patients receiving 5 mg XELJANZ (6–9%) compared to placebo (1–3%) patients at 6 months. In Study III, similar percentages of patients achieving DAS28-4(ESR) < 2.6 were observed for adalimumab and XELJANZ 5 mg twice daily at Month 6.

Table 1: Proportion of Patients with an ACR Response

	Percent of Patients										
	Monotherapy in DMARD Inadequate Responders		**DMARD Inadequate Responders**		**MTX Inadequate Responders**			**MTX Inadequate Responders**		**TNF Inhibitor Inadequate Responders**	
	Study I (SOLO)		**Study II (SYNC)**		**Study III (Standard)**			**Study IV (SCAN)**		**Study V (STEP)**	
Response Rate	Placebo N=120	XELJANZ 5 mg Twice Daily N=241	Placebo + DMARD N=157	XELJANZ 5 mg Twice Daily + DMARD N=311	Placebo + MTX N=106	XELJANZ 5 mg Twice Daily + MTX N=196	Adalimumab 40mg q2 Weeks + MTX N=199	Placebo + MTX N=154	XELJANZ 5 mg Twice Daily + MTX N=309	Placebo + MTX N=131	XELJANZ 5 mg Twice Daily + MTX N=132
ACR20											
Month 3	27%	60%***	27%	56%***	26%	61%***	56%***	27%	56%***	24%	42%*†
Month 6	NA	69%	31%	53%***	28%	52%***	47%**	25%	51%***†	NA	52%
Month 12	NA	NA	NA	51%	NA	49%	49%	NA	49%	NA	NA
ACR50											
Month 3	13%	31%***	10%	27%***	7%	34%***	24%***	8%	29%***	8%	27%***
Month 6	NA	42%	13%	34%***	12%	37%***	28%**	8%	32%***††	NA	37%
Month 12	NA	NA	NA	33%	NA	37%	34%	NA	33%	NA	NA
ACR70											
Month 3	6%	15%*	2%	8%**	2%	12%**	9%*	3%	11%**	2%	14%**
Month 6	NA	22%	3%	13%***	2%	20%***	9%*	1%	15%***	NA	16%
Month 12	NA	NA	NA	19%	NA	23%	17%	NA	19%	NA	NA

* *p<0.05,* XELJANZ *vs. placebo*
** *p<0.001,* XELJANZ *vs. placebo*
*** *p<0.0001,* XELJANZ *vs. placebo*

The results of the components of the ACR response criteria for Studies IV and V are shown in Table 2. Similar results were observed in Studies I, II and III.

Table 2: Components of ACR Response at Month 3

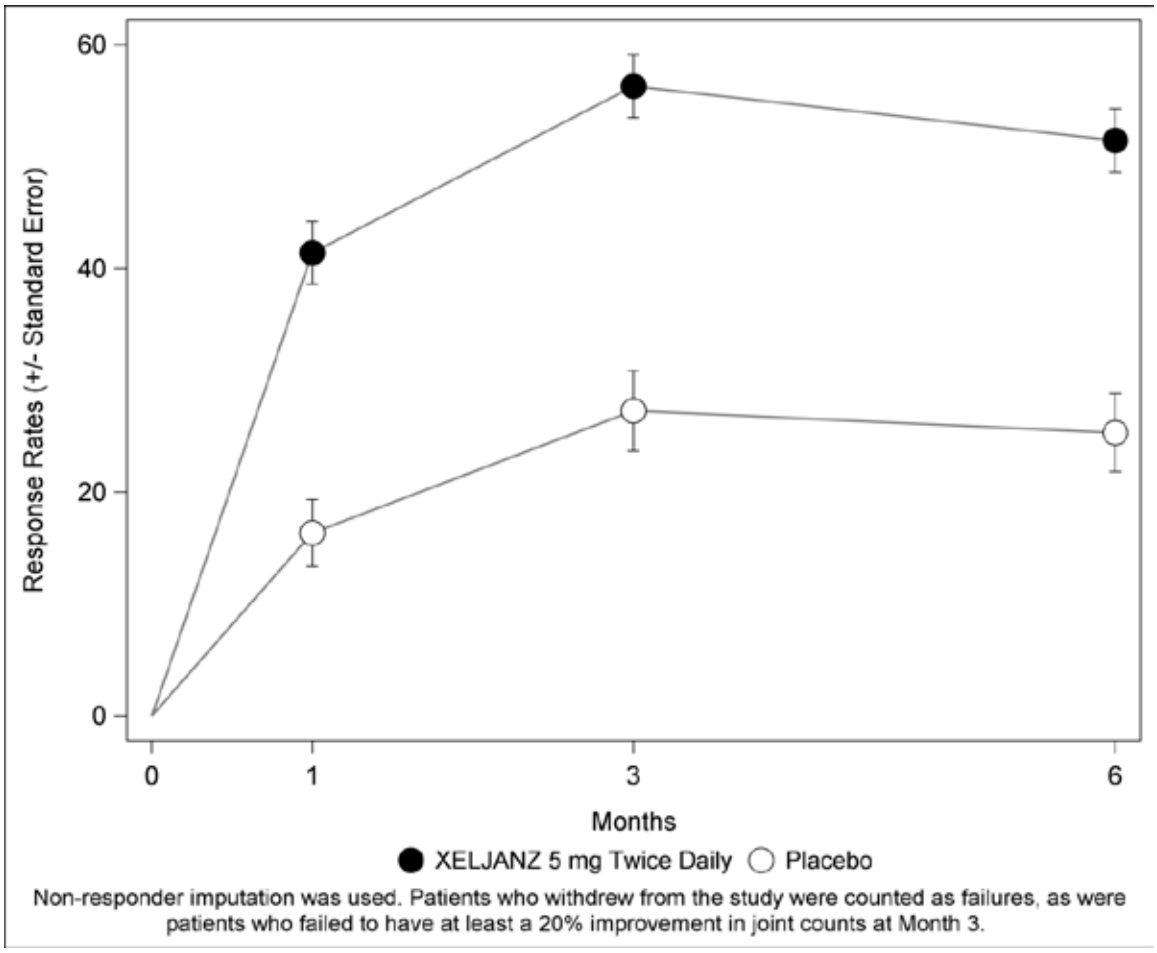
	Study IV (SCAN) MTX Inadequate Responders				**Study V (STEP) TNF Inhibitor Inadequate Responders**			
	XELJANZ 5 mg Twice Daily + MTX N=316		**Placebo + MTX N=156**		**XELJANZ 5 mg Twice Daily + MTX N=133**		**Placebo + MTX N=132**	
Component (mean)	Base- line	Month 3	Base- line	Month 3	Base- line	Month 3	Base- line	Month 3
Number of tender joints (0-68)	24	13	23	18	28	16	28	21
Number of swollen joints (0-66)	14	6	14	10	16	8	17	12
Pain[a]	58	35	55	47	66	39	61	53
Patient global assessment[a]	58	35	54	47	65	41.2	62	53
Disability index (HAQ-DI)[b]	1.41	1.00	1.31	1.19	1.60	1.20	1.63	1.44
Physician global assessment[a]	59	30	56	43	65	35	64	44
CRP (mg/L)	15.5	6.9	13.7	14.6	19.3	6.2	16.7	18.2

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

[b]Health Assessment Questionnaire Disability Index: 0 = best, 3 = worst; 20 questions; categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities

The percent of ACR20 responders by visit for Study IV is shown in Figure 2. Similar responses were observed in Studies I, II, III and V.

Figure 2: Percentage of ACR20 Responders by Visit for Study IV



Physical Function Response and Health Related Outcomes

Improvements in physical function have been shown with and without MTX.

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg twice daily demonstrated significantly greater improvement from baseline in physical functioning compared to placebo at Month 3 (Studies I, II, III, and V) and Month 6 (Studies II and III). XELJANZ 5 mg twice daily treated patients exhibited significantly greater improved physical functioning compared to placebo as early as Week 2 in Studies I and II. In Study III, mean HAQ-DI improvements were maintained to 12 months in XELJANZ-treated patients. Mean HAQ-DI improvements were maintained for 36 months in the ongoing open-label extension studies. Compared with adalimumab-treated patients, at Month 3, patients in the XELJANZ 5 mg twice daily group had similar decreases from baseline in HAQ-DI values.

Health-related quality of life was assessed by the Short Form Health Survey (SF-36) in all 5 studies. XELJANZ-treated patients exhibited significantly greater improvement from baseline compared to placebo in all 8 domains of the SF-36 as well as the Physical Component Summary (PCS) and the Mental Component Summary (MCS) at Month 3 in

Studies I, IV, and V. In Studies III and IV, mean SF-36 improvements were maintained to 12 months in XELJANZ-treated patients.

Improvement in fatigue was evaluated by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale at Month 3 in all studies. Patients receiving XELJANZ 5 mg twice daily demonstrated significantly greater improvement from baseline in fatigue compared to placebo in all 5 studies. In Studies III and IV, mean FACIT-F improvements were maintained to 12 months in XELJANZ-treated patients.

Improvement in sleep was assessed using the Sleep Problems Index I and II summary scales of the Medical Outcomes Study Sleep (MOS-Sleep) measure at Month 3 in all studies. Patients receiving XELJANZ 5 mg twice daily demonstrated significantly greater improvement from baseline in both scales compared to placebo in Studies II, III, and IV. In Studies III and IV, mean improvements in both scales were maintained to 12 months in XELJANZ-treated patients.

INDICATIONS

XELJANZ is indicated for the treatment of the signs and symptoms of moderate to severe active rheumatoid arthritis in adults who have had an inadequate response or are intolerant to methotrexate. XELJANZ can be used alone or in combination with nonbiological DMARDs, including methotrexate.

Therapy with XELJANZ should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.

CONTRAINDICATIONS

Hypersensitivity to tofacitinib citrate or to any of the excipients.

XELJANZ must not be used in combination with biological DMARDs or other potent immunosuppressive agents such as azathioprine and cyclosporin.

XELJANZ should not be used in patients with severe hepatic impairment.

PRECAUTIONS

Therapy with XELJANZ should be initiated and monitored by a rheumatologist or specialist physician with expertise in the management of rheumatoid arthritis.

Serious Infections

Patients treated with XELJANZ are at increased risk for developing serious infections that may lead to hospitalisation or death, especially in those taking concomitant immunosuppressants.

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral or other opportunistic pathogens have been reported in rheumatoid arthritis patients receiving immunomodulatory agents (these include biological DMARDs as well as XELJANZ). The

most common serious infections reported with XELJANZ included pneumonia, cellulitis, herpes zoster and urinary tract infection. Among opportunistic infections, tuberculosis and other mycobacterial infections, cryptococcus, oesophageal candidiasis, pneumocystosis, multidermatomal herpes zoster, cytomegalovirus and BK virus were reported with XELJANZ. Some patients have presented with disseminated rather than localised disease, and were often taking concomitant immunomodulating agents such as methotrexate or corticosteroids which, in addition to rheumatoid arthritis may predispose them to infections. Other serious infections, that were not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, and listeriosis).

XELJANZ should not be administered in patients with an active infection, including localised infections. The risks and benefits of treatment should be considered prior to initiating XELJANZ in patients with chronic or recurrent infections, or those who have been exposed to tuberculosis, or with a history of a serious or an opportunistic infection, or have resided or travelled in areas of endemic tuberculosis or endemic mycoses; or have underlying conditions that may predispose them to infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. XELJANZ should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis (see DOSAGE AND ADMINISTRATION). A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

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

Tuberculosis

Patients should be evaluated and tested for latent or active infection prior to administration of XELJANZ.

Antituberculosis therapy should be considered prior to administration of XELJANZ in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but who have risk factors for tuberculosis infection. Consultation with a health care professional with expertise in the treatment of tuberculosis is recommended to aid in the decision about whether initiating antituberculosis therapy is appropriate for an individual patient.

Patients should be closely monitored for the development of signs and symptoms of tuberculosis, including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

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

Viral Reactivation

Viral reactivation has been reported with DMARD treatment and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. The

impact of XELJANZ on chronic viral hepatitis reactivation is unknown. Patients who screened positive for hepatitis B or C were excluded from clinical trials. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ.

Malignancy and Lymphoproliferative Disorder (excluding Nonmelanoma Skin Cancer [NMSC])

The possibility exists for XELJANZ to affect host defenses against malignancies. The impact of treatment with XELJANZ on the development and course of malignancies is not known, but malignancies were observed in clinical studies.

In the controlled clinical studies in rheumatoid arthritis patients, 13 malignancies (excluding NMSC) were diagnosed in patients receiving XELJANZ, compared to 0 malignancies (excluding NMSC) in patients in the placebo/placebo plus DMARD group. Over 3000 patients (2098 patient-years of observation) were treated with XELJANZ for durations up to 1 year while approximately 680 patients (203 patient-years of observation) were treated with placebo for a maximum of 6 months. The exposure-adjusted incidence rate for malignancies was 0.62 events per 100 patient-years in the XELJANZ groups.

In the long-term safety population, the rate of malignancies (excluding NMSC) was 1.12 events per 100 patient-years, consistent with the rate observed in the controlled period.

Lymphomas have been observed in patients treated with XELJANZ. While patients with rheumatoid arthritis, particularly those with highly active disease, are at a higher risk than the general population (up to several-fold) for the development of lymphoma, the role of JAK inhibition in the development of lymphoma is not known

Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications (see PRECAUTIONS, Renal Transplant).

Skin Cancer

Melanoma and nonmelanoma skin cancers have been reported in patients treated with XELJANZ. Regular skin examinations are recommended, particularly for patients with an increased risk for, or a prior history of, skin cancer.

Renal Transplant

In studies in renal transplant patients treated with XELJANZ (15 mg twice daily for 3 to 6 months then reduced) and concomitant immunosuppressive agents (induction therapy with basiliximab, high dose corticosteroids, mycophenolic acid products) for prophylaxis of organ rejection, serious infections and Epstein Barr Virus-associated post-transplant lymphoproliferative disorder were observed at an increased rate compared to patients treated with cyclosporine and concomitant immunosuppressive agents.

XELJANZ should not be used in combination with potent immunosuppressants because of the possibility of an increased risk of serious infection and post-transplant lymphoproliferative disorder.

Cardiovascular

XELJANZ causes a decrease in heart rate and a prolongation of the PR interval. Caution should be observed in patients with a low heart rate at baseline (< 60 beats per minute), a history of syncope or arrhythmia, sick sinus syndrome, sinoatrial block, atrioventricular (AV) block, ischemic heart disease, or congestive heart failure. Concomitant medications that result in a decrease in heart rate and/or PR interval prolongation should be avoided to the extent possible during treatment with XELJANZ (see INTERACTIONS WITH OTHER MEDICINES).

Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials in rheumatoid arthritis patients, although the role of JAK inhibition in these events is not known. The incidence rate of gastrointestinal perforation across all studies (phase 2, phase 3 and long-term extension) was 0.177 events per 100 patient-years with XELJANZ therapy. Events were primarily reported as diverticular perforation, peritonitis, abdominal abscess and appendicitis. All patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids. The relative contribution of these concomitant medications vs. XELJANZ to the development of gastrointestinal perforations is not known.

XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Patients presenting with new onset abdominal symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Vaccinations

No data are available on the response to live vaccination or on the secondary transmission of infection by live vaccines to patients receiving XELJANZ. Live vaccines should not be given concurrently with XELJANZ. It is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines prior to initiating XELJANZ therapy. In a controlled clinical trial, the humoral response to concurrent vaccination with influenza and pneumococcal polysaccharide vaccines in patients with rheumatoid arthritis initiating tofacitinib 10 mg twice daily or placebo was evaluated. A similar percentage of patients achieved a satisfactory humoral response to influenza vaccine (≥4-fold increase in ≥2 of 3 antigens) in the tofacitinib (57%) and placebo (62%) treatment groups. A modest reduction in the percentage of patients who achieved a satisfactory humoral response to pneumococcal polysaccharide vaccine (≥2-fold increase in ≥6 of 12 serotypes) was observed in patients treated with tofacitinib monotherapy (62%) and MTX monotherapy (62%) as compared with placebo (77%), with a greater reduction in the response rate of patients receiving both tofacitinib and methotrexate (32%). The clinical significance of this is unknown.

A separate vaccine study evaluated the humoral response to concurrent vaccination with influenza and pneumococcal polysaccharide vaccines in patients receiving tofacitinib 10 mg twice daily for a median of approximately 22 months. Greater than 60% of patients treated with tofacitinib (with or without MTX) had satisfactory responses to influenza and pneumococcal vaccines. Consistent with the controlled trial, patients receiving both

tofacitinib and MTX had a lower response rate to pneumococcal polysaccharide vaccine as compared with tofacitinib monotherapy (66% vs 89%).

Interstitial Lung Disease

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

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

Asian Patients

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

Effects on Fertility

In rats, tofacitinib had no effects on male fertility, sperm motility, or sperm concentration at doses up to 100 mg/kg/day (>100 times the human unbound drug AUC at 5 mg twice daily; extrapolated from values from other rat studies). Treatment-related effects on female fertility were noted at ³10 mg/kg/day in rats (>20 times the human unbound AUC at 5 mg twice daily; based on extrapolation from values from other rat studies).

Use in Pregnancy: Category D

There are no adequate and well-controlled studies on the use of XELJANZ in pregnant women. Tofacitinib has been shown to be teratogenic in rats and rabbits, and to have effects in rats on parturition, and peri/postnatal development.

In an embryo-fetal development (EFD) study in rats given 30, 100, or 300 mg/kg/day, maternal toxicity was observed at doses ³100 mg/kg/day. Observations included postimplantation loss, consisting of early and late resorptions and consequently a reduced number of viable fetuses, and decreased uterine weight. Fetal developmental effects were observed at 100 mg/kg/day (³200 times the unbound drug human AUC at 5 mg twice daily). Teratogenic effects consisted of external and soft tissue malformations of anasarca and membranous ventricular septal defects, respectively, and skeletal malformations or variations (absent cervical arch; bent femur, fibula, humerus, radius, scapula, tibia, and ulna; sternoschisis; absent rib; misshapen femur; branched rib; fused rib; fused sternebra; and hemicentric thoracic centrum). The no observed adverse effect level (NOAEL) for maternal and developmental toxicity in this study was 30 mg/kg/day, a dose at which the unbound drug AUC was ~81-fold the human AUC at 5 mg twice daily.

In an EFD study in rabbits given 10, 30, or 100 mg/kg/day, maternal toxicity was not observed. Fetal developmental effects were observed at ≥30 mg/kg/day. Teratogenic effects included thoracogastroschisis, omphalocele, membranous ventricular septal defects, and cranial/skeletal malformations (microstomia, microphthalmia), mid-line and tail defects. The NOAELs for maternal and developmental toxicity in this study were 100 and 10 mg/kg/day,

doses at which the total drug AUCs were ~63- and 3-fold, respectively, the human AUC at 5 mg twice daily.

In a perinatal/postnatal rat study, there were reductions in live litter size, postnatal survival, and pup body weights at 50 mg/kg/day (~100 times the unbound exposure in humans at 5 mg twice daily, based on extrapolation from values from other rat studies). At 10 mg/kg/day (~20 times the unbound exposure in humans at 5 mg twice daily, based on extrapolation from values from other rat studies), no effect occurred on sexual maturation or the ability of the F1 generation rats to learn, mate, and produce viable F2 generation fetuses.

In the Phase 2, Phase 3 and long-term extension studies in rheumatoid arthritis (RA) patients, 14 maternal pregnancies were reported in patients treated with tofacitinib. Pregnancy outcomes comprised full-term normal newborn (6 cases), spontaneous abortion (3), elective termination (2), lost to follow up (2) and low birth weight (1). A spontaneous abortion occurred in the only maternal pregnancy in patients treated with placebo.

XELJANZ should not be used during pregnancy or by women attempting to become pregnant.

Use in Lactation

Tofacitinib was secreted in the milk of lactating rats. It is not known whether tofacitinib is secreted in human milk. Women should not breastfeed while being treated with XELJANZ.

Paediatric Use

The safety and efficacy of XELJANZ in children aged from neonates to < 18 years of age has not yet been established.

Use in the Elderly

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

Use in Renal Impairment

No dose adjustment is required in patients with mild (creatinine clearance 51-80 mL/min) renal impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with moderate (creatinine clearance 30-50 mL/min) and severe (creatinine clearance < 30 mL/min) renal impairment (see DOSAGE AND ADMINISTRATION and PHARMACOLOGY, Pharmacokinetics).

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

Use in Hepatic Impairment

Subjects with moderate hepatic impairment had 65% higher AUC compared with healthy subjects (see PHARMACOLOGY, Pharmacokinetics). XELJANZ has not been studied in patients with severe hepatic impairment, or in patients with positive hepatitis B virus or hepatitis C virus serology. No dose adjustment is required in patients with mild hepatic impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with moderate

hepatic impairment (see DOSAGE AND ADMINISTRATION). XELJANZ should not be used in patients with severe hepatic impairment (see CONTRAINDICATIONS).

Genotoxicity

Tofacitinib is not mutagenic or genotoxic based on the weight of evidence from a series of *in vitro* and *in vivo* tests for gene mutations and chromosomal aberrations.

Carcinogenicity

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib was not carcinogenic in mice up to a high dose of 200 mg/kg/day (unbound drug AUC of ~38-fold the human AUC at 5 mg twice daily). Benign Leydig cell tumours were observed in rats: benign Leydig cell tumours in rats are not associated with a risk of Leydig cell tumours in humans. Hibernomas (malignancy of brown adipose tissue) were observed in female rats at doses ≥ 30 mg/kg (unbound drug AUC of ~83-fold the human AUC at 5 mg twice daily). Benign thymomas were observed in female rats dosed only at the 100 reduced to 75 mg/kg/day dose (unbound drug AUC of ~187-fold the human AUC at 5 mg twice daily).

Lymphoma was observed in 3 of 8 adult and 0 of 14 juvenile monkeys dosed with tofacitinib at 5 mg/kg twice daily. The NOAEL for the lymphomas was 1 mg/kg twice daily. The unbound AUC at 1 mg/kg twice daily was 341 ng•h/mL, which is similar to the unbound AUC at 5 mg twice daily in humans.

Effects on Ability to Drive and Use of Machines

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

Effects on Laboratory Parameters

Lymphocytes

Treatment with XELJANZ was associated with initial lymphocytosis at one month of exposure followed by a gradual decrease in mean lymphocyte counts below the baseline of approximately 10% during 12 months of therapy (see PHARMACOLOGY, Pharmacodynamics).

Lymphocyte counts < 0.5 x 10^9 cells/L were associated with an increased incidence of treated and serious infections. Avoid initiatation of XELJANZ treatment in patients with a low lymphocyte count (i.e., < 0.5 x 10^9 cells/L). In patients who develop a confirmed absolute lymphocyte count < 0.5 x 10^9 cells/L treatment with XELJANZ is not recommended. Lymphocytes should be monitored at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts see DOSAGE AND ADMINISTRATION.

Neutrophils

Treatment with XELJANZ was associated with an increased incidence of neutropaenia (<2.0 x 10^9 cells/L) compared to placebo.

Avoid initiation of XELJANZ treatment in patients with a low neutrophil count (i.e., <1.0 x 10^9 cells/L). For patients who develop a persistent absolute neutrophil count (ANC) of 0.5-

1.0 x 10^9 cells/L, interrupt XELJANZ dosing until ANC is >1.0 x 10^9 cells/L. In patients who develop a confirmed ANC <0.5 x 10^9 cells/L treatment with XELJANZ is not recommended. Neutrophils should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter (see DOSAGE AND ADMINISTRATION and ADVERSE EFFECTS).

Haemoglobin

Avoid initiation of XELJANZ treatment in patients with low haemoglobin values (i.e., <90 g/L). Treatment with XELJANZ should be interrupted in patients who develop haemoglobin levels <80 g/L or whose haemoglobin level drops >20 g/L on treatment. Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter (see DOSAGE AND ADMINISTRATION).

Lipids

Treatment with XELJANZ was associated with increases in lipid parameters such as total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol (see ADVERSE EFFECTS). Maximum effects were generally observed within 6 weeks. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been established. Assessment of lipid parameters should be performed approximately 4 to 8 weeks following initiation of XELJANZ therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia. Increases in total and LDL cholesterol associated with XELJANZ may be decreased to pretreatment levels with statin therapy.

Liver Enzyme Elevations

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

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

INTERACTIONS WITH OTHER MEDICINES

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

Potential for Other Medicines to Influence the Pharmacokinetics of Tofacitinib

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

Methotrexate: Concomitant administration with methotrexate (15-25 mg MTX once weekly) had no effect on the PK of tofacitinib.

Ketoconazole: Co-administration of ketoconazole, a strong CYP3A4 inhibitor, with a single dose of tofacitinib increased the AUC and C_{max} of tofacitinib by 103% and 16%, respectively (see DOSAGE AND ADMINISTRATION).

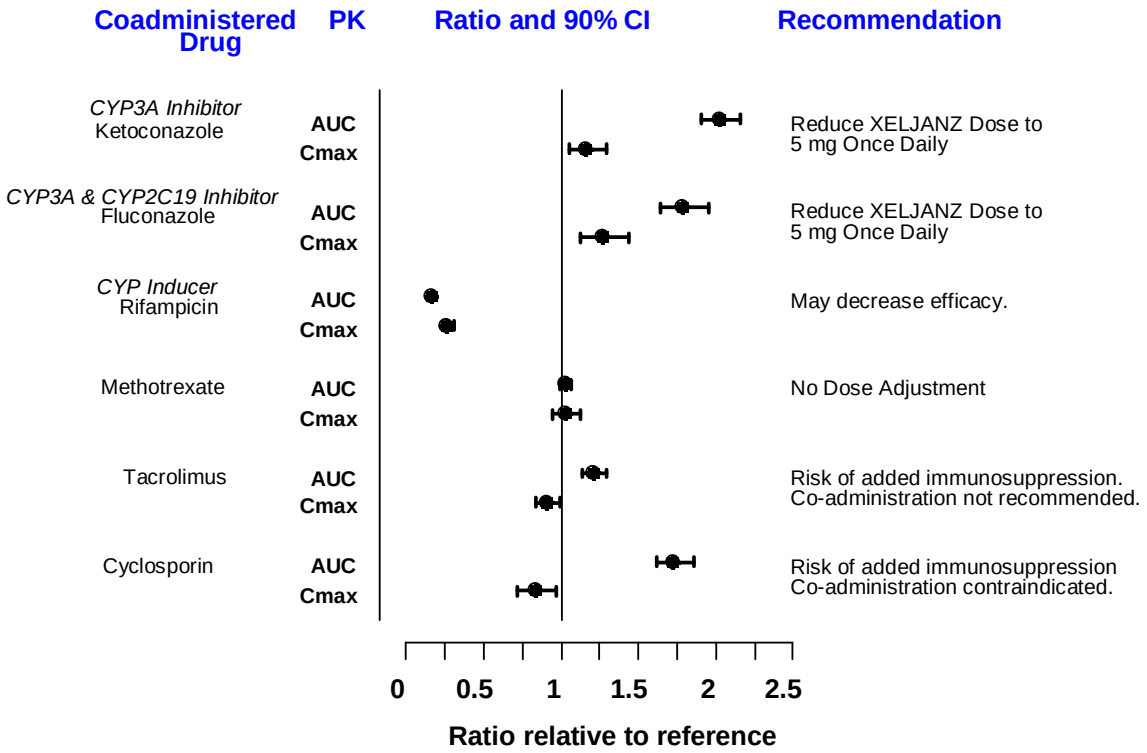
Fluconazole: Co-administration of fluconazole, a moderate inhibitor of CYP3A4 and a strong inhibitor of CYP2C19, increased the AUC and C_{max} of tofacitinib by 79% and 27%, respectively (see DOSAGE AND ADMINISTRATION).

Cyclosporin: Co-administration of cyclosporin, a moderate inhibitor of CYP3A4, increased the AUC of tofacitinib by 73% and decreased C_{max} of tofacitinib by 17%. The combined use of multiple-dose tofacitinib with this potent immunosuppressive has not been studied in patients with rheumatoid arthritis and is contraindicated.

Tacrolimus: Co-administration of tacrolimus, a mild inhibitor of CYP3A4, increased the AUC of tofacitinib by 21% and decreased the C_{max} of tofacitinib by 9%. The combined use of multiple-dose tofacitinib with this potent immunosuppressive has not been studied in patients with rheumatoid arthritis and is not recommended.

Rifampicin: Coadministration of rifampicin, a strong CYP3A4 inducer, decreased the AUC and C_{max} of tofacitinib by 84% and 74%, respectively (see DOSAGE AND ADMINISTRATION).

Figure 3. Impact of Other Medicines on the Pharmacokinetics of Tofacitinib



Potential for Tofacitinib to Influence the Pharmacokinetics of Other Medicines

In vitro studies indicate that tofacitinib does not significantly inhibit or induce the activity of the major human drug metabolising CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations exceeding 185 times the steady state C_{max} of a 5 mg twice daily dose. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the PK of midazolam, a highly sensitive CYP3A4 substrate, when coadministered with tofacitinib.

In RA patients, the oral clearance of tofacitinib does not vary with time, indicating that tofacitinib does not normalise CYP enzyme activity in RA patients. Therefore, coadministration with tofacitinib is not expected to result in clinically relevant increases in the metabolism of CYP substrates in RA 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 also low.

Oral Contraceptives: Coadministration of tofacitinib did not have an effect on the PK of oral contraceptives, levonorgestrel and ethinyloestradiol, in healthy female volunteers.

Methotrexate: Coadministration of tofacitinib with methotrexate 15-25 mg once weekly decreased the AUC and C_{max} of methotrexate by 10% and 13% respectively. The extent of decrease in methotrexate exposure does not warrant modifications to the individualized dosing of methotrexate.

Metformin: Coadministration of tofacitinib did not have an effect on the PK of metformin, indicating that tofacitinib does not interfere with the organic cationic transporter (OCT2) in healthy volunteers.

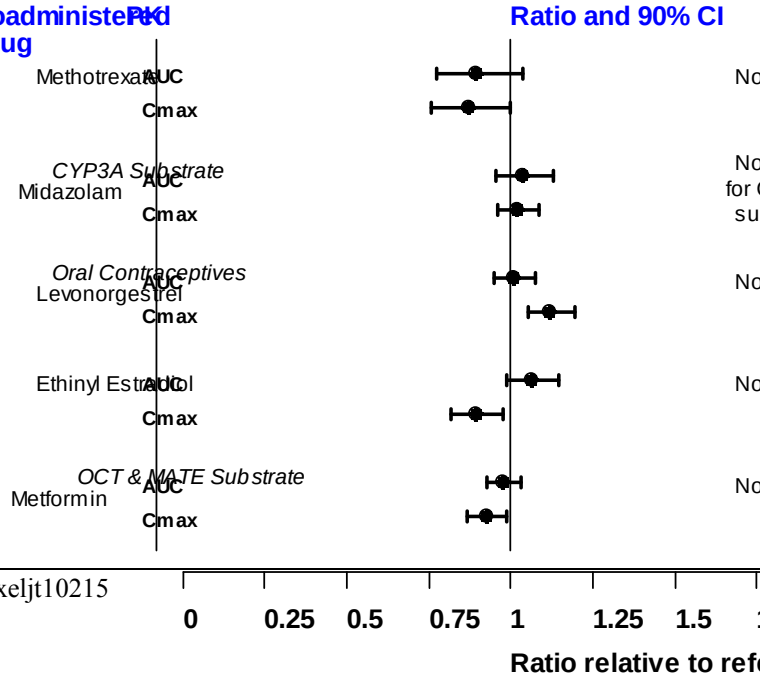


Figure 4. Impact of Tofacinib on the Pharmacokinetics of Other

Medicines

Medicines that Decrease Heart Rate (HR) and/or Prolong the PR Interval

XELJANZ results in a decrease in heart rate and an increase in the PR interval (see PRECAUTIONS, Cardiovascular). Caution should be observed if XELJANZ is used concomitantly with medicines that lower heart rate and/or prolong the PR interval, such as antiarrhythmics, beta blockers, alpha2 adrenoceptor agonists, non-dihydropyridine calcium channel blockers, digitalis glycosides, cholinesterase inhibitors, sphingosine-1 phosphate receptor modulators, and some HIV protease inhibitors.

ADVERSE EFFECTS

The following data includes 5 double-blind, controlled, multicenter studies. In these studies, patients were randomised and treated with doses of XELJANZ 5 mg twice daily (243 patients) or 10 mg twice daily (245 patients) monotherapy and XELJANZ 5 mg twice daily (973 patients) or 10 mg twice daily (969 patients) in combination with DMARDs (including methotrexate).

Of the 3030 patients who received XELJANZ in these 5 clinical studies, including those who advanced from placebo to XELJANZ, 1871 received treatment for at least 6 months and 580 for at least one year.

The long-term safety population includes all patients who participated in a double-blind, controlled study (including earlier development phase studies) and then participated in one of two long-term safety studies.

Of the 3227 patients who received XELJANZ in the long-term studies, 1689 received open-label treatment for at least 6 months, 970 for at least 1 year, 659 received treatment for at least 2 years, and 62 for at least 3 years.

All patients in these studies had moderate to severe active rheumatoid arthritis. The study population had a mean age of 54 years and 84% were female. The highest proportions of patients in the clinical studies were either White (62%) or Asian (25%).

Clinical Trial Experience

The most common serious adverse reactions were serious infections (see PRECAUTIONS).

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

The proportion of patients who discontinued treatment due to any adverse reactions during first 3 months of the double-blind, placebo-controlled studies was 4.2% for patients taking XELJANZ and 3.2% for placebo-treated patients. The most common adverse reactions that resulted in discontinuation of XELJANZ were infections. The most common infections resulting in discontinuation of therapy were herpes zoster and pneumonia.

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

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

Body System / Adverse Event	XELJANZ 5mg BD (N=1216)	XELJANZ 10 mg BD (N=1214)	Placebo (N=681)	Adalimumab 40 mg SC q2w (N=204)
Infections and infestations				
Upper respiratory tract infection	53 (4.4)	47 (3.9)	23 (3.4)	7 (3.4)
Nasopharyngitis	48 (3.9)	35 (2.9)	19 (2.8)	7 (3.4)
Urinary tract infection	25 (2.1)	24 (2.0)	12 (1.8)	7 (3.4)
Bronchitis	14 (1.2)	13 (1.1)	10 (1.5)	4 (2.0)
Herpes zoster	5 (0.4)	16 (1.3)	2 (0.3)	0
Blood and lymphatic system disorders				
Anaemia	15 (1.2)	13 (1.1)	8 (1.2)	0
Metabolism and nutrition disorders				
Hypercholesterolaemia	12 (1.0)	13 (1.1)	3 (0.4)	1 (0.5)
Nervous system disorders				
Headache	54 (4.4)	39 (3.2)	15 (2.2)	5 (2.5)

Body System / Adverse Event	XELJANZ 5mg BD (N=1216)	XELJANZ 10 mg BD (N=1214)	Placebo (N=681)	Adalimumab 40 mg SC q2w (N=204)
Dizziness	13 (1.1)	12 (1.0)	8 (1.2)	3 (1.5)
Vascular disorders				
Hypertension	20 (1.6)	27 (2.2)	7 (1.0)	0
Respiratory, thoracic and mediastinal disorders				
Cough	11 (0.9)	16 (1.3)	11 (1.6)	4 (2.0)
Gastrointestinal disorders				
Diarrhoea	45 (3.7)	34 (2.8)	16 (2.3)	2 (1.0)
Nausea	32 (2.6)	25 (2.1)	18 (2.6)	3 (1.5)
Dyspepsia	19 (1.6)	25 (2.1)	11 (1.6)	3 (1.5)
Abdominal pain upper	23 (1.9)	13 (1.1)	5 (0.7)	3 (1.5)
Vomiting	21 (1.7)	9 (0.7)	10 (1.5)	0
Constipation	16 (1.3)	17 (1.4)	6 (0.9)	2 (1.0)
Gastritis	12 (1.0)	16 (1.3)	7 (1.0)	0
Abdominal pain	10 (0.8)	13 (1.1)	7 (1.0)	2 (1.0)
Gastroenteritis	12 (1.0)	13 (1.1)	5 (0.7)	0
Hepatobiliary Disorders				
Alanine aminotransferase increased	14 (1.2)	15 (1.2)	7 (1.0)	1 (0.5)
Musculoskeletal and connective tissue disorders				
Rheumatoid arthritis	17 (1.4)	5 (0.4)	17 (2.5)	1 (0.5)
Back pain	18 (1.5)	20 (1.6)	5 (0.7)	1 (0.5)
Arthralgia	13 (1.1)	9 (0.7)	16 (2.3)	4 (2.0)
General disorders and administration site conditions				
Oedema peripheral	17 (1.4)	21 (1.7)	16 (2.3)	3 (1.5)
Influenza	9 (0.7)	14 (1.2)	5 (0.7)	2 (1.0)
Pyrexia	13 (1.1)	7 (0.6)	5 (0.7)	1 (0.5)
Investigations				
Blood creatine phosphokinase increased	9 (0.7)	26 (2.1)	3 (0.4)	1 (0.5)
Weight increased	11 (0.9)	13 (1.1)	4 (0.6)	2 (1.0)
Injury, Poisoning and Procedural Complications				
Fall	7 (0.6)	13 (1.1)	4 (0.6)	1 (0.5)

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

Blood and lymphatic system disorders:

Uncommon: Neutropenia, lymphopenia

Hepatobiliary Disorders:

Uncommon: Hepatic steatosis

Infections and infestations:

Uncommon: Sepsis, bacterial pneumonia, pneumococcal pneumonia, pyelonephritis, cellulitis, viral gastroenteritis, viral infection, herpes simplex.

Rare: Tuberculosis of central nervous system, encephalitis, necrotising fasciitis, meningitis cryptococcal, disseminated tuberculosis, urosepsis, *Pneumocystis jiroveci* pneumonia, staphylococcal bacteraemia, tuberculosis, arthritis bacterial, atypical mycobacterial infection, *Mycobacterium avium* complex infection, cytomegalovirus infection, bacteraemia.

Injury, Poisoning and Procedural Complications:

Uncommmon: Muscle strain

Investigations:

Uncommmon: Transaminases increased, blood creatinine increased, gamma glutamyltransferase increased, liver function test abnormal

Metabolism and nutrition disorders:

Uncommmon: Dehydration

Musculoskeletal and connective tissue disorders:

Uncommon: Tendonitis, joint swelling

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

Uncommmon: Nonmelanoma skin cancers

Nervous system disorders:

Uncommmon: Paraesthesia

Respiratory, thoracic and mediastinal disorders:

Uncommmon: Sinus congestion

Skin and subcutaneous tissue disorders:

Uncommmon: Erythema, pruritus

Overall Infections

In the controlled portion of the phase 3 monotherapy study (0-3 months), the rate of infections in the 5 mg twice daily and 10 mg twice daily XELJANZ monotherapy groups were 16.5% and 19.2%, respectively, compared to 18.9% in the placebo group. In the controlled portion of the phase 3 studies (0-3 months or 0-6 months) with background DMARDs, the rates of infections in the 5 mg twice daily and 10 mg twice daily XELJANZ plus DMARD groups were 20.9% and 21.7%, respectively, compared to 18.2% in the placebo plus DMARD group.

The most commonly reported infections were upper respiratory tract infections and nasopharyngitis (4.1% and 3.4%, respectively).

The overall rate of infections with XELJANZ in the long-term safety all exposure population was 41.5 events per 100 patient-years (31.5 and 66.9 events for 5 mg and 10 mg twice daily, respectively). For patients on monotherapy, the rates were 35.5 and 55.8 events per 100 patient-years for 5 mg and 10 mg twice daily, respectively. For patients on background DMARDs, the rates were 28.8 and 78.4 events per 100 patient-years for 5 mg and 10 mg twice daily, respectively.

Serious Infections

In the controlled portion of the phase 3 monotherapy study (0-3 months), the rate of serious infections in the 5 mg twice daily XELJANZ monotherapy group was 0.85 events per 100 patient-years. In the 10 mg twice daily XELJANZ monotherapy group, the rate was 3.5 events per 100 patient-years, and the rate was 0 events per 100 patient-years for the placebo group.

In the controlled portion of the phase 3 studies (0-3 months or 0-6 months) with background DMARDs, the rates of serious infections in the 5 mg twice daily and 10 mg twice daily XELJANZ plus DMARD groups were 3.6 and 2.9 events per 100 patient-years, respectively, compared to 1.7 events per 100 patient-years in the placebo plus DMARD group.

In the long-term safety all exposure population, the overall rates of serious infections were 2.3 and 4.9 events per 100 patient-years for 5 mg and 10 mg twice daily XELJANZ, respectively. The most common serious infections reported with XELJANZ included pneumonia, herpes zoster, and urinary tract infection. Cases of opportunistic infections have been reported (see PRECAUTIONS).

Of the 3315 patients who enrolled in 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 those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Laboratory Parameters

Lymphocytes

In the controlled clinical studies, confirmed decreases in lymphocyte counts below 0.5 x 10^9 cells/L occurred in 0.21% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

In the long term safety population, confirmed decreases in lymphocyte counts below 0.5 x 10^9 cells/L occurred in 0.31% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

Confirmed lymphocyte counts < 0.5 x 10^9 cells/L were associated with an increased incidence of treated and serious infections (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Neutrophils

In the controlled clinical studies, confirmed decreases in ANC below 1.0 x 10^9 cells/L occurred in 0.08% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. There were no confirmed decreases in ANC below 0.5 x 10^9 cells/L observed in any treatment group. There was no clear relationship between neutropaenia and the occurrence of serious infections.

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

Liver Enzyme Tests

Confirmed increases in liver enzymes > 3x upper limit of normal (ULN) were uncommonly observed. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of XELJANZ, or reduction in XELJANZ dose, resulted in decrease or normalisation of liver enzymes.

In the controlled portion of the phase 3 monotherapy study (0-3 months), ALT elevations > 3x ULN were observed in 1.65%, 0.41%, and 0% of patients receiving placebo, 5 mg and 10 mg twice daily, respectively. In this study, AST elevations > 3x ULN were observed in 1.65%, 0.41% and 0% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively.

In the controlled portion of the phase 3 studies on background DMARDs (0-3 months), ALT elevations > 3x ULN were observed in 0.9%, 1.24% and 1.25% of patients receiving placebo, 5 mg, and 10 mg twice daily, respectively. In these studies, AST elevations > 3x ULN were observed in 0.72%, 0.5% and 0.42% of patients receiving placebo, 5 mg and 10 mg twice daily, respectively.

One patient treated with tofacitinib 10 mg twice daily and MTX had possible drug-induced liver injury (DILI). Despite discontinuation of both drugs, 2-3 months later she developed further increases in transaminase levels. The elevated liver tests responded to prednisolone and azathioprine, possibly consistent with autoimmune hepatitis, but DILI cannot be ruled out.

Lipids

Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were first assessed at one month following initiation of XELJANZ in the controlled double-blind clinical trials. Increases were observed at this time point and remained stable thereafter. Changes in lipid parameters from baseline through the end of the study (6-12 months) in the controlled clinical studies are summarised below:

- Mean LDL cholesterol increased by 14% in the XELJANZ 5 mg twice daily arm and 20% in the XELJANZ 10 mg twice daily arm.
- Mean HDL cholesterol increased by 16% in the XELJANZ 5 mg twice daily arm and 18% in the XELJANZ 10 mg twice daily arm.
- Mean LDL cholesterol/HDL cholesterol ratios were essentially unchanged in XELJANZ-treated patients.
- Apolipoprotein B (ApoB)/ApoA1 ratios were essentially unchanged in XELJANZ-treated patients.

In a controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy.

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

Serum Creatinine

In the controlled clinical trials, dose-related elevations in serum creatinine were observed with XELJANZ treatment. The mean increase in serum creatinine was <8.84 µmol/L in the 12-month pooled safety analysis; however, with increasing duration of exposure in the long-term extensions, up to 2% of patients were discontinued from XELJANZ treatment due to the protocol-specified discontinuation criterion of an increase in creatinine by more than 50% of baseline. The clinical significance of the observed serum creatinine elevations is unknown.

DOSAGE AND ADMINISTRATION

XELJANZ may be used as monotherapy or in combination with methotrexate or other nonbiological DMARDs. The recommended dosage is 5 mg administered twice daily.

XELJANZ treatment should be interrupted if a patient develops a serious infection until the infection is controlled.

XELJANZ is given orally with or without food.

Dose Adjustments Due to Laboratory Abnormalities (see PRECAUTIONS)

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopaenia, neutropaenia and anaemia as described in Tables 4, 5 and 6 below.

It is recommended that XELJANZ not be initiated in patients with a lymphocyte count less than 0.5 x 10^9 cells/L.

Table 4: Dose Adjustments for Lymphopaenia

Low Lymphocyte Count (see PRECAUTIONS)	
Lab Value (x 10^9 cells/L)	**Recommendation**
Lymphocyte count ≥0.5	Maintain dose.
Lymphocyte count <0.5 (Confirmed by repeat testing)	Discontinue XELJANZ.

It is recommended that XELJANZ not be initiated in patients with an absolute neutrophil count (ANC) <1.0 x 10^9 cells/L.

Table 5: Dose Adjustments for Neutropaenia

Low ANC (see PRECAUTIONS)	
Lab Value (x 10^9 cells/L)	**Recommendation**
ANC >1.0	Maintain dose.
ANC 0.5-1.0	For persistent decreases in this range, interrupt XELJANZ dosing until ANC is >1.0. When ANC is >1.0, resume XELJANZ 5 mg twice daily.
ANC <0.5 (Confirmed by repeat testing)	Discontinue XELJANZ.

It is recommended that XELJANZ not be initiated in patients with haemoglobin < 90 g/L.

Table 6: Dose Adjustments for Anaemia

Low Haemoglobin Value (see PRECAUTIONS)	
Lab Value (g/L)	**Recommendation**
≤20 g/L decrease and ≥90 g/L	Maintain dose.
>20 g/L decrease or <80 g/L (Confirmed by repeat testing)	Interrupt the administration of XELJANZ until haemoglobin values have normalised.

Dosage Adjustment in Renal Impairment

No dose adjustment is required in patients with mild (creatinine clearance 51-80 mL/min) renal impairment. XELJANZ dosage should be reduced to 5 mg once daily in patients with moderate (creatinine clearance 30-50 mL/min) and severe (creatinine clearance <30 mL/min) renal impairment (see PRECAUTIONS, and PHARMACOLOGY, Pharmacokinetics).

Dosage Adjustment in Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment. XELJANZ dosage should be reduced to 5 mg once daily in patients with moderate hepatic impairment (see PRECAUTIONS, and PHARMACOLOGY, Pharmacokinetics). XELJANZ should not be used in patients with severe hepatic impairment (see CONTRAINDICATIONS and PHARMACOLOGY, Pharmacokinetics).

Dose Adjustment due to Interactions with Other Medicines

XELJANZ dosage should be reduced to 5 mg once daily in patients receiving potent inhibitors of CYP3A4 (e.g., ketoconazole). XELJANZ dosage should be reduced to 5 mg once daily in patients receiving one or more concomitant medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole). Coadministration of XELJANZ with potent CYP inducers (e.g., rifampicin) may result in loss of or reduced clinical response (see INTERACTIONS WITH OTHER MEDICINES).

Dosage Adjustment in the Elderly

No dosage adjustment is required in patients aged 65 years and older.

Children and Adolescents

The safety and efficacy of XELJANZ in children aged from neonates to < 18 years of age has not yet been established.

OVERDOSAGE

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

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

XELJANZ 5 mg film-coated tablets

White, round, immediate release, film-coated tablet debossed with "Pfizer" on one side, and "JKI 5" on the other side.

HDPE bottles with desiccant and child-resistant caps containing 60 or 180 film-coated tablets.

Al/PVC-backed Al blisters containing 14 or 56 film-coated tablets.

Not all pack sizes may be marketed.

Store below 30°C.

NAME AND ADDRESS OF THE SPONSOR

Pfizer Australia Pty Ltd
A.B.N. 5000 8422 348
38-42 Wharf Road
WEST RYDE NSW 2114

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

05 Feb 2015

Ò Registered trademark