ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. **NAME OF THE MEDICINAL PRODUCT**

XELJANZ 5 mg film-coated tablets

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film-coated tablet contains tofacitinib citrate, equivalent to 5 mg tofacitinib.

Excipient with known effect
Each tablet contains 59.44 mg lactose.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Film-coated tablet.
White, round tablet of 7.9 mm diameter, debossed “Pfizer” on one side and “JKI 5” on the reverse.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indication**

**Rheumatoid arthritis**
XELJANZ in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. XELJANZ can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is inappropriate (see sections 4.4 and 4.5).

**Psoriatic arthritis**
XELJANZ in combination with MTX is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy (see section 5.1).

4.2 **Posology and method of administration**

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of conditions for which XELJANZ is indicated.

**Posology**
The recommended dose is 5 mg administered twice daily.

**Dose adjustment**
No dose adjustment is required when used in combination with MTX.

**Dose interruption and discontinuation**
XELJANZ treatment should be interrupted if a patient develops a serious infection until the infection is controlled.
Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia, and anaemia. As described in Tables 1, 2 and 3 below, recommendations for temporary dose interruption or permanent discontinuation of treatment are made according to the severity of laboratory abnormalities (see section 4.4).

It is recommended not to initiate dosing in patients with an absolute lymphocyte count (ALC) less than 750 cells/mm³.

**Table 1: Low Absolute Lymphocyte Count**

<table>
<thead>
<tr>
<th>Lab Value (cells/mm³)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALC greater than or equal to 750</td>
<td>Dose should be maintained.</td>
</tr>
<tr>
<td>ALC 500-750</td>
<td>For persistent (2 sequential values in this range on routine testing) decrease in this range, dosing should be interrupted until ALC is greater than 750. When ALC is greater than 750, resume 5 mg twice daily.</td>
</tr>
<tr>
<td>ALC less than 500</td>
<td>If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.</td>
</tr>
</tbody>
</table>

It is recommended not to initiate dosing in patients with an absolute neutrophil count (ANC) less than 1,000 cells/mm³.

**Table 2: Low Absolute Neutrophil Count**

<table>
<thead>
<tr>
<th>Lab Value (cells/mm³)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC greater than 1,000</td>
<td>Dose should be maintained.</td>
</tr>
<tr>
<td>ANC 500-1,000</td>
<td>For persistent (2 sequential values in this range on routine testing) decreases in this range, dosing should be interrupted until ANC is greater than 1,000. When ANC is greater than 1,000, resume 5 mg twice daily.</td>
</tr>
<tr>
<td>ANC less than 500</td>
<td>If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.</td>
</tr>
</tbody>
</table>

It is recommended not to initiate dosing in patients with haemoglobin less than 9 g/dL.

**Table 3: Low Haemoglobin Value**

<table>
<thead>
<tr>
<th>Lab Value (g/dL)</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL</td>
<td>Dose should be maintained.</td>
</tr>
<tr>
<td>Greater than 2 g/dL decrease or less than 8.0 g/dL (Confirmed by repeat testing)</td>
<td>Dosing should be interrupted until haemoglobin values have normalised.</td>
</tr>
</tbody>
</table>
Special populations

Renal impairment
No dose adjustment is required in patients with mild (creatinine clearance 50-80 mL/min) or moderate (creatinine clearance 30-49 mL/min) renal impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with severe (creatinine clearance <30 mL/min) renal impairment (see section 5.2). Patients with severe renal impairment should remain on a reduced dose of 5 mg once daily even after haemodialysis.

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A). The dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment (Child Pugh B) (see sections 4.4 and 5.2). XELJANZ should not be used in patients with severe hepatic impairment (Child Pugh C) (see section 4.3).

Elderly
No dose adjustment is required in patients aged 65 years and older. There are limited data in patients aged 75 years and older.

Paediatric population
The safety and efficacy of XELJANZ in children aged from 2 years to less than 18 years of age have not yet been established. No data are available.

There is no relevant use of XELJANZ in patients aged less than 2 years for the indication of juvenile idiopathic arthritis.

Drug-drug interactions
XELJANZ dose should be reduced to 5 mg once daily in patients receiving potent inhibitors of cytochrome (CYP) P450 3A4 (e.g., ketoconazole). XELJANZ dosage should be reduced to 5 mg once daily in patients receiving one or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g., fluconazole) (see sections 4.4 and 4.5).

Method of administration
Oral use.

XELJANZ is given orally with or without food.

For patients who have difficulties swallowing, XELJANZ 5 mg tablets may be crushed and taken with water.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Active tuberculosis (TB), serious infections such as sepsis, or opportunistic infections (see section 4.4).
- Severe hepatic impairment (see section 4.2).
- Pregnancy and lactation (see section 4.6).

4.4 Special warnings and precautions for use

Combination with other therapies
XELJANZ has not been studied and its use should be avoided in combination with biological disease-modifying antirheumatic drugs (DMARDs) such as tumour necrosis factor (TNF) antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, selective co-stimulation modulators and potent...
immunosuppressants such as azathioprine, ciclosporine and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

There was a higher incidence of adverse events for the combination of XELJANZ with MTX versus XELJANZ as monotherapy in RA clinical studies.

The use of XELJANZ in combination with phosphodiesterase 4 inhibitors has not been studied in XELJANZ clinical studies.

**Serious infections**

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving XELJANZ. The risk of opportunistic infections is higher in Asian geographic regions (see section 4.8).

XELJANZ should not be initiated in patients with active infections, including localised infections.

The risks and benefits of treatment should be considered prior to initiating XELJANZ in patients:

- with recurrent infections,
- with a history of a serious or an opportunistic infection,
- who have resided or travelled in areas of endemic mycoses,
- who 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. Treatment should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes (see section 4.8).

Risk of infection may be higher with increasing degrees of lymphopenia and consideration should be given to lymphocyte counts when assessing individual patient risk of infection. Discontinuation and monitoring criteria for lymphopenia are discussed in section 4.2.

**Tuberculosis**

The risks and benefits of treatment should be considered prior to initiating XELJANZ in patients:

- who have been exposed to TB,
- who have resided or travelled in areas of endemic TB.

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

Patients with latent TB, who test positive, should be treated with standard antimycobacterial therapy before administering XELJANZ.

Antituberculosis therapy should also be considered prior to administration of XELJANZ in patients who test negative for TB but who have a past history of latent or active TB and where an adequate course of treatment cannot be confirmed; or those who test negative but who have risk factors for TB infection. Consultation with a healthcare professional with expertise in the treatment of TB 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 TB, including patients who tested negative for latent TB infection prior to initiating therapy.
Viral reactivation
Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. In patients treated with XELJANZ, the incidence of herpes zoster appears to be increased in:

- Japanese or Korean patients.
- patients with an ALC less than 1,000 cells/mm³ (see section 4.2).
- patients with long standing RA who have previously received two or more biological disease modifying antirheumatic drugs (DMARDs).

The impact of XELJANZ on chronic viral hepatitis reactivation is unknown. Patients 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
The risks and benefits of XELJANZ treatment should be considered prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. The possibility exists for XELJANZ to affect host defences against malignancies.

Lymphomas have been observed in patients treated with XELJANZ. Patients with RA, particularly those with highly active disease may be at a higher risk (up to several-fold) than the general population for the development of lymphoma. The effect of XELJANZ on the development of lymphoma is uncertain.

Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.

The effect of XELJANZ on the development and course of malignancies is not known.

Non-melanoma skin cancer
NMSCs have been reported in patients treated with XELJANZ. Periodic skin examination is recommended for patients who are at increased risk for skin cancer (see Table 4 in section 4.8).

Interstitial lung disease
Caution is also recommended in patients with a history of chronic lung disease as they may be more prone to infections. Events of interstitial lung disease (some of which had a fatal outcome) have been reported in patients treated with XELJANZ in RA clinical trials and in the post-marketing setting although the role of Janus kinase (JAK) inhibition in these events is not known. Asian RA patients are known to be at higher risk of interstitial lung disease, thus caution should be exercised in treating these patients.

Gastrointestinal perforations
Events of gastrointestinal perforation have been reported in clinical trials although the role of JAK inhibition in these events 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 with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory drugs). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Cardiovascular risk
RA and PsA patients have an increased risk for cardiovascular disorders. Patients treated with XELJANZ should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care.

Liver enzymes
Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation in some patients (see section 4.8 liver enzyme tests). Caution should be exercised when considering
initiation of XELJANZ treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST), particularly when initiated in combination with potentially hepatotoxic medicinal products such as MTX. Following initiation, routine monitoring of liver tests and prompt investigation of the causes of any observed liver enzyme elevations are recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of XELJANZ should be interrupted until this diagnosis has been excluded.

**Hypersensitivity**
In post-marketing experience, cases of drug hypersensitivity associated with tofacitinib administration have been reported. Allergic reactions included angioedema and urticaria; serious reactions have occurred. If any serious allergic or anaphylactic reaction occurs, tofacitinib should be discontinued immediately.

**Laboratory parameters**

**Lymphocytes**
Treatment with XELJANZ was associated with an increased incidence of lymphopenia compared to placebo. Lymphocyte counts less than 750 cells/mm$^3$ were associated with an increased incidence of serious infections. It is not recommended to initiate or continue XELJANZ treatment in patients with a confirmed lymphocyte count less than 750 cells/mm$^3$. Lymphocytes should be monitored at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts, see section 4.2.

**Neutrophils**
Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2,000 cells/mm$^3$) compared to placebo. It is not recommended to initiate XELJANZ treatment in patients with an ANC less than 1,000 cells/mm$^3$. ANC should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on ANC, see section 4.2.

**Haemoglobin**
Treatment with XELJANZ has been associated with decreases in haemoglobin levels. It is not recommended to initiate XELJANZ treatment in patients with a haemoglobin value less than 9 g/dL. Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on haemoglobin level, see section 4.2.

**Lipid monitoring**
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. Maximum effects were generally observed within 6 weeks. Assessment of lipid parameters should be performed after 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.

**Vaccinations**
Prior to initiating XELJANZ, it is recommended that all patients be brought up to date with all immunisations in agreement with current immunisation guidelines. It is recommended that live vaccines not be given concurrently with XELJANZ. The decision to use live vaccines prior to XELJANZ treatment should take into account the pre-existing immunosuppression in a given patient.

Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular consideration should be given to patients with longstanding RA who have previously received two or more biological DMARDs. If live zoster vaccine is administered; it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus (VZV). If the history of chickenpox is considered doubtful or unreliable it is recommended to test for antibodies against VZV.
Vaccination with live vaccines should occur at least 2 weeks but preferably 4 weeks prior to initiation of XELJANZ or in accordance with current vaccination guidelines regarding immunomodulatory medicinal products. No data are available on the secondary transmission of infection by live vaccines to patients receiving XELJANZ.

**Elderly**
The elderly population in general has an increased risk of adverse events, of increased severity; caution should be used when treating the elderly, see section 4.8.

**Lactose**
XELJANZ contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

### 4.5 Interaction with other medicinal products and other forms of interaction

**Potential for other medicinal products to influence the pharmacokinetics (PK) of XELJANZ**

Since XELJANZ is metabolised by CYP3A4, interaction with medicinal products that inhibit or induce CYP3A4 is likely. XELJANZ 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) (see section 4.2).

XELJANZ exposure is decreased when coadministered with potent CYP inducers (e.g., rifampicin). Inhibitors of CYP2C19 alone or P-glycoprotein are unlikely to significantly alter the PK of XELJANZ.

Coadministration with ketoconazole (strong CYP3A4 inhibitor), fluconazole (moderate CYP3A4 and potent CYP2C19 inhibitor), tacrolimus (mild CYP3A4 inhibitor) and ciclosporine (moderate CYP3A4 inhibitor) increased XELJANZ AUC, while rifampicin (potent CYP inducer) decreased XELJANZ AUC. Coadministration of XELJANZ with potent CYP inducers (e.g., rifampicin) may result in a loss of or reduced clinical response (see Figure 1). Coadministration of potent inducers of CYP3A4 with XELJANZ is not recommended. Coadministration with ketoconazole and fluconazole increased XELJANZ C\(_{\text{max}}\), while tacrolimus, ciclosporine and rifampicin decreased XELJANZ C\(_{\text{max}}\). Concomitant administration with MTX 15-25 mg once weekly had no effect on the PK of XELJANZ in RA patients (see Figure 1).
Figure 1. Impact of Other Drugs on PK of XELJANZ

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>PK</th>
<th>Ratio and 90% CI</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A Inhibitor</td>
<td>AU</td>
<td>0.5</td>
<td>Reduce XELJANZ Dose 5 mg Once Daily</td>
</tr>
<tr>
<td></td>
<td>Cma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketoconazol</td>
<td>AU</td>
<td>0.5</td>
<td>Reduce XELJANZ Dose 5 mg Once Daily</td>
</tr>
<tr>
<td></td>
<td>Cma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A &amp; CYP2C19 Inhibitor</td>
<td>AU</td>
<td>0.5</td>
<td>Reduce XELJANZ Dose 5 mg Once Daily</td>
</tr>
<tr>
<td></td>
<td>Cma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazol</td>
<td>AU</td>
<td>0.5</td>
<td>May Decrease</td>
</tr>
<tr>
<td></td>
<td>Cma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP Inducer</td>
<td>AU</td>
<td>0.5</td>
<td>No Dose Adjustment</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Cma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>AU</td>
<td>0.5</td>
<td>Combined use of XELJANZ with Tacrolimus should be</td>
</tr>
<tr>
<td></td>
<td>Cma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>AU</td>
<td>0.5</td>
<td>Combined use of XELJANZ with Ciclosporine should be avoided</td>
</tr>
<tr>
<td></td>
<td>Cma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciclosporine</td>
<td>AU</td>
<td>0.5</td>
<td>Combined use of XELJANZ with Ciclosporine should be avoided</td>
</tr>
<tr>
<td></td>
<td>Cma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Reference group is administration of XELJANZ alone

Potential for XELJANZ to influence the PK of other medicinal products

*In vitro* studies indicate that tofacitinib does not significantly inhibit or induce the activity of the major human drug metabolizing CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) at concentrations exceeding 160 and 268 times the respective steady state total and free C\text{max}, respectively, of a 5 mg twice daily dose in patients treated with tofacitinib. These *in vitro* results were confirmed by a human drug interaction study showing no changes in the PK of midazolam, a highly sensitive CYP3A4 substrate, when coadministered with XELJANZ.

*In 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 535 and 893 times the steady state total and free C\text{max} of a 5 mg twice daily dose in patients treated with tofacitinib.

*In vitro* data indicate that the potential for XELJANZ to inhibit transporters such as multidrug resistance (MDR1), organic anion transporting polypeptide (OATP1B1/1B3), organic anionic (OAT1/3), organic cationic (OCT2), or multidrug resistance-associated protein (MRP2) transporters at therapeutic concentrations is also low.

Coadministration of XELJANZ did not have an effect on the PK of oral contraceptives, levonorgestrel and ethinyl estradiol, in healthy female volunteers.

In RA patients, coadministration of XELJANZ with MTX 15-25 mg once weekly decreased the AUC and C\text{max} of MTX by 10% and 13%, respectively. The extent of decrease in MTX exposure does not warrant modifications to the individualised dosing of MTX.

Coadministration of XELJANZ did not have an effect on the PK of metformin, indicating that XELJANZ does not interfere with the OCT2 in healthy volunteers.
4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate and well-controlled studies on the use of tofacitinib in pregnant women. Tofacitinib has been shown to be teratogenic in rats and rabbits, and to affect parturition and peri/postnatal development (see section 5.3).

As a precautionary measure, the use of XELJANZ during pregnancy is contraindicated (see section 4.3).

Women of childbearing potential/contraception in females
Women of childbearing potential should be advised to use effective contraception during treatment with XELJANZ and for at least 4 weeks after the last dose.

Breast-feeding
It is not known whether XELJANZ is secreted in human milk. A risk to the breast-fed child cannot be excluded. Tofacitinib was secreted in the milk of lactating rats (see section 5.3). As a precautionary measure, the use of XELJANZ during breast-feeding is contraindicated (see section 4.3).

Fertility
Formal studies of the potential effect on human fertility have not been conducted. Tofacitinib impaired female fertility but not male fertility in rats (see section 5.3).

4.7 Effects on ability to drive and use machines

XELJANZ has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Rheumatoid arthritis
The safety data includes 6 double-blind, controlled, multicentre studies of varying durations from 6-24 months (Studies I-VI, see section 5.1). A total of 6,194 patients (Phases 1, 2, 3 and long-term extension studies) were treated with any dose of XELJANZ, with a mean duration of 3.13 years, with 19,405.8 patient-years of accumulated total drug exposure based on up to 8 years of continuous exposure to XELJANZ.

All patients in these studies had moderate to severe RA. The study XELJANZ population had a mean age of 52.1 years and 83.2% were female.

The most common serious adverse reactions were serious infections (see section 4.4). The most common serious infections reported with XELJANZ were pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus, BK virus infections and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localised disease. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

The most commonly reported adverse reactions during the first 3 months in controlled clinical trials were headache, upper respiratory tract infections, nasopharyngitis, diarrhoea, nausea and hypertension (see Table 4, Adverse Drug Reactions [ADRs] based on all study durations).

The proportion of patients who discontinued treatment due to adverse reactions during first 3 months of the double-blind, placebo or MTX controlled studies was 3.8% for patients taking XELJANZ. The most common infections resulting in discontinuation of therapy were herpes zoster and pneumonia.
**Psoriatic arthritis**

The safety data include 2 double-blind, controlled, multicentre studies: Study PsA-I with a 12-month duration and Study PsA-II with a 6-month duration; both included a 3-month, placebo-controlled period (see section 5.1). All patients in the clinical studies were required to receive treatment with a stable dose of a conventional synthetic disease-modifying antirheumatic drug (csDMARD) (the majority received MTX [78.2%]). An additional long-term, open-label clinical study was conducted and included patients with PsA who originally participated in either of the 2 double-blind, controlled clinical studies.

Overall, the safety profile observed in patients with active PsA treated with XELJANZ was consistent with the safety profile observed in patients with RA treated with XELJANZ.

Tabulated list of adverse reactions

The ADRs listed in the table below are from clinical studies in patients with RA and PsA and are presented by System Organ Class (SOC) and frequency categories, defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), or not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

**Table 4: Adverse Drug Reactions**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
<th>Very Rare</th>
<th>Not Known (cannot be estimated from the available data)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥1/100 to &lt;1/10</td>
<td>≥1/1,000 to &lt;1/100</td>
<td>≥1/10,000 to &lt;1/100</td>
<td>&lt;1/10,000</td>
<td>TB of central nervous system Meningitis cryptococcal Mycobacterium avium complex infection</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Nasopharyngitis Pharyngitis</td>
<td>Tuberculosis Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection</td>
<td>Sepsis Urosepsis Disseminated TB Necrotizing fasciitis Bacteraemia Staphylococcal bacteraemia <em>Pneumocystis jirovecii</em> pneumonia Pneumonia pneumococcal Pneumonia bacterial Encephalitis Atypical mycobacterial infection Cytomegalovirus infection Arthritis bacterial</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia</td>
<td>Leukopenia Lymphopenia Neutropenia</td>
<td></td>
<td></td>
<td>Drug hypersensitivity* Angioedema* Urticaria*</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Common</td>
<td>Uncommon</td>
<td>Rare</td>
<td>Very Rare</td>
<td>Not Known</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>≥1/100 to &lt;1/10</td>
<td>≥1/1,000 to &lt;1/100</td>
<td>≥1/10,000 to &lt;1/1,000</td>
<td>&lt;1/10,000</td>
<td>(cannot be estimated from the available data)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Paraesthesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>Dyspnoea</td>
<td>Sinus congestion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
<td>Vomiting</td>
<td>Diarrhoea</td>
<td>Nausea</td>
<td>Gastritis</td>
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<tr>
<td>Hepatobiliary disorders</td>
<td></td>
<td></td>
<td>Hepatic steatosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td></td>
<td>Erythema</td>
<td>Pruritus</td>
<td></td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>Musculoskeletal pain</td>
<td>Joint swelling</td>
<td>Tendonitis</td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Oedema peripheral</td>
<td></td>
<td>Pyrexia</td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Blood creatine phosphokinase increased</td>
<td>Hepatic enzyme increased</td>
<td>Transaminases increased</td>
<td>Liver function test abnormal</td>
<td>Gamma glutamyl-transferase increased</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Ligament sprain</td>
<td>Muscle strain</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Spontaneous reporting data

Description of selected adverse reactions

Overall infections

**Rheumatoid arthritis**
In controlled Phase 3 clinical studies, the rates of infections over 0-3 months in the 5 mg twice daily (total 616 patients) and 10 mg twice daily (total 642 patients) XELJANZ monotherapy groups were 16.2% (100 patients) and 17.9% (115 patients), respectively, compared to 18.9% (23 patients) in the placebo group (total 122 patients). In controlled Phase 3 clinical studies with background DMARDs, the rates of infections over 0-3 months in the 5 mg twice daily (total 973 patients) and 10 mg twice daily (total 969 patients) XELJANZ plus DMARD group were 21.3% (207 patients) and 21.8% (211 patients), respectively, compared to 18.4% (103 patients) in the placebo plus DMARD group (total 559 patients).
The most commonly reported infections were upper respiratory tract infections and nasopharyngitis (3.7% and 3.2%, respectively).

The overall incidence rate of infections with XELJANZ in the long-term safety all exposure population (total 4,867 patients) was 46.1 patients with events per 100 patient-years (43.8 and 47.2 patients with events for 5 mg and 10 mg twice daily, respectively). For patients (total 1,750) on monotherapy, the rates were 48.9 and 41.9 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively. For patients (total 3,117) on background DMARDs, the rates were 41.0 and 50.3 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively.

**Serious infections**

*Rheumatoid arthritis*

In the 6-month and 24-month, controlled clinical studies, the rate of serious infections in the 5 mg twice daily XELJANZ monotherapy group was 1.7 patients with events per 100 patient-years. In the 10 mg twice daily XELJANZ monotherapy group the rate was 1.6 patients with events per 100 patient-years, the rate was 0 events per 100 patient-years for the placebo group, and the rate was 1.9 patients with events per 100 patient-years for the MTX group.

In studies of 6-, 12-, or 24-month duration, the rates of serious infections in the 5 mg twice daily and 10 mg twice daily XELJANZ plus DMARD groups were 3.6 and 3.4 patients with events per 100 patient-years, respectively, compared to 1.7 patients with 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 2.4 and 3.0 patients with events per 100 patient-years for 5 mg and 10 mg twice daily XELJANZ groups, respectively. The most common serious infections included pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis and diverticulitis. Cases of opportunistic infections have been reported (see section 4.4).

**Serious infections in the elderly**

Of the 4,271 patients who enrolled in RA Studies I-VI (see section 5.1), a total of 608 RA patients were 65 years of age and older, including 85 patients 75 years and older. The frequency of serious infection among XELJANZ-treated patients 65 years of age and older was higher than those under the age of 65 (4.8 per 100 patient-years versus 2.4 per 100 patient-years, respectively). As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly (see section 4.4).

**Viral reactivation**

Patients treated with XELJANZ who are Japanese or Korean, or patients with long standing RA who have previously received two or more biological DMARDs or patients with an ALC less than 1,000 cells/mm³ may have an increased risk of herpes zoster (see section 4.4).

**Laboratory tests**

*Lymphocytes*

In the controlled RA clinical studies, confirmed decreases in ALC below 500 cells/mm³ occurred in 0.3% of patients and for ALC between 500 and 750 cells/mm³ in 1.9% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

In the RA long-term safety population, confirmed decreases in ALC below 500 cells/mm³ occurred in 1.3% of patients and for ALC between 500 and 750 cells/mm³ in 8.4% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

Confirmed ALC less than 750 cells/mm³ were associated with an increased incidence of serious infections (see section 4.4).
Neutrophils
In the controlled RA clinical studies, confirmed decreases in ANC below 1,000 cells/mm³ 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 500 cells/mm³ observed in any treatment group. There was no clear relationship between neutropenia and the occurrence of serious infections.

In the RA 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 section 4.4).

Liver enzyme tests
Confirmed increases in liver enzymes greater than 3 times the upper limit of normal (3x ULN) were uncommonly observed in RA patients. In those 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 RA Phase 3 monotherapy study (0-3 months), (Study I, see section 5.1), ALT elevations greater than 3x ULN were observed in 1.65%, 0.41%, and 0% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 1.65%, 0.41% and 0% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively.

In the RA Phase 3 monotherapy study (0-24 months) (Study VI, see section 5.1), ALT elevations greater than 3x ULN were observed in 7.1%, 3.0%, and 3.0% of patients receiving MTX, XELJANZ 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 3.3%, 1.6% and 1.5% of patients receiving MTX, XELJANZ 5 mg and 10 mg twice daily, respectively.

In the controlled portion of the RA Phase 3 studies on background DMARDs (0-3 months), (Study II-V, see section 5.1), ALT elevations greater than 3x ULN were observed in 0.9%, 1.24% and 1.14% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively. In these studies, AST elevations greater than 3x ULN were observed in 0.72%, 0.5% and 0.31% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively.

In the RA long-term extension studies, on monotherapy, ALT elevations greater than 3x ULN were observed in 1.1% and 1.4% of patients receiving XELJANZ 5 mg and 10 mg twice daily, respectively. AST elevations greater than 3x ULN were observed in <1.0% in both the tofacitinib 5 mg and 10 mg twice daily groups.

In the RA long-term extension studies, on background DMARDs, ALT elevations greater than 3x ULN were observed in 1.8% and 1.6% of patients receiving XELJANZ 5 mg and 10 mg twice daily, respectively. AST elevations greater than 3x ULN were observed in <1.0% in both the XELJANZ 5 mg and 10 mg twice daily groups.

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 of RA. Increases were observed at this time point and remained stable thereafter.

Changes in lipid parameters from baseline through the end of the study (6-24 months) in the controlled clinical studies in RA are summarised below:

- Mean LDL cholesterol increased by 15% in the XELJANZ 5 mg twice daily arm and 20% in the XELJANZ 10 mg twice daily arm at Month 12, and increased by 16% in the XELJANZ 5 mg twice daily arm and 19% in the XELJANZ 10 mg twice daily arm at Month 24.
Mean HDL cholesterol increased by 17% in the XELJANZ 5 mg twice daily arm and 18% in the XELJANZ 10 mg twice daily arm at Month 12, and increased by 19% in the XELJANZ 5 mg twice daily arm and 20% in the XELJANZ 10 mg twice daily arm at Month 24.

Upon withdrawal of XELJANZ treatment, lipid levels returned to baseline.

Mean LDL cholesterol/HDL cholesterol ratios and Apolipoprotein B (ApoB)/ApoA1 ratios were essentially unchanged in XELJANZ-treated patients.

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

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

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective Immunosuppressants; ATC code: L04AA29

Mechanism of action
Tofacitinib is a potent, selective inhibitor of the JAK family. In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent Tyk2. In contrast, tofacitinib has a high degree of selectivity against other kinases in the human genome. In human cells, tofacitinib preferentially inhibits signalling by heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib attenuates signalling of interleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which will result in modulation of the immune and inflammatory response.

Pharmacodynamic effects
In patients with RA, treatment up to 6 months with XELJANZ was associated with dose-dependent reductions of circulating CD16/56+ natural killer (NK) 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.

Following long-term treatment (median duration of XELJANZ treatment of approximately 5 years), CD4+ and CD8+ counts showed median reductions of 28% and 27%, respectively, from baseline. In contrast to the observed decrease after short-term dosing, CD16/56+ natural killer cell counts showed
a median increase of 73% from baseline. CD19+ B cell counts showed no further increases after long-term XELJANZ treatment. All these lymphocyte subset changes returned toward baseline after temporary discontinuation of treatment. There was no evidence of a relationship between serious or opportunistic infections or herpes zoster and lymphocyte subset counts (see section 4.2 for absolute lymphocyte count monitoring).

Changes in total serum IgG, IgM, and IgA levels over 6-month XELJANZ dosing in patients with RA were small, not dose-dependent and similar to those seen on placebo, indicating a lack of systemic humoral suppression.

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

**Vaccine studies**
In a controlled clinical trial of patients with RA initiating XELJANZ 10 mg twice daily or placebo, the number of responders to influenza vaccine was similar in both groups: XELJANZ (57%) and placebo (62%). For pneumococcal polysaccharide vaccine the number of responders was as follows: 32% in patients receiving both XELJANZ and MTX; 62% for XELJANZ monotherapy; 62% for MTX monotherapy; and 77% for placebo. The clinical significance of this is unknown, however, similar results were obtained in a separate vaccine study with influenza and pneumococcal polysaccharide vaccines in patients receiving long-term XELJANZ 10 mg twice daily.

A controlled study was conducted in patients with RA on background MTX immunised with a live attenuated virus vaccine (Zostavax®) 2 to 3 weeks before initiating a 12-week treatment with XELJANZ 5 mg twice daily or placebo. Evidence of humoral and cell-mediated responses to VZV was observed in both XELJANZ and placebo-treated patients at 6 weeks. These responses were similar to those observed in healthy volunteers aged 50 years and older. A patient with no previous history of varicella infection and no anti-varicella antibodies at baseline experienced dissemination of the vaccine strain of varicella 16 days after vaccination. XELJANZ was discontinued and the patient recovered after treatment with standard doses of antiviral medication. This patient subsequently made a robust, though delayed, humoral and cellular response to the vaccine (see section 4.4).

**Clinical efficacy and safety**

**Rheumatoid arthritis**
The efficacy and safety of XELJANZ were assessed in 6 randomised, double-blind, controlled multicentre studies in patients greater than 18 years of age with active RA diagnosed according to American College of Rheumatology (ACR) criteria. Table 5 provides information regarding the pertinent study design and population characteristics.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Study I (ORAL Solo)</th>
<th>Study II (ORAL Sync)</th>
<th>Study III (ORAL Standard)</th>
<th>Study IV (ORAL Scan)</th>
<th>Study V (ORAL Step)</th>
<th>Study VI (ORAL Start)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>DMARD-IR</td>
<td>DMARD-IR</td>
<td>MTX-IR</td>
<td>MTX-IR</td>
<td>TNFi-IR</td>
<td>MTX-naïve</td>
</tr>
<tr>
<td>Control</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
<td>MTX</td>
</tr>
<tr>
<td>Background treatment</td>
<td>None</td>
<td>csDMARDs</td>
<td>MTX</td>
<td>MTX</td>
<td>MTX</td>
<td>None</td>
</tr>
<tr>
<td>Key features</td>
<td>Monotherapy</td>
<td>Various csDMARDs</td>
<td>Active control (adalimumab)</td>
<td>X-Ray</td>
<td>TNFi-IR</td>
<td>Monotherapy, Active comparator (MTX), X-Ray</td>
</tr>
</tbody>
</table>
**Clinical response**

**ACR response**

The percentages of tofacitinib-treated patients achieving ACR20, ACR50 and ACR70 responses in Studies ORAL Solo, ORAL Sync, ORAL Standard, ORAL Scan, ORAL Step, and ORAL Start are shown in Table 6. In all studies, patients treated with either 5 or 10 mg twice daily tofacitinib had statistically significant ACR20, ACR50 and ACR70 response rates at Month 3 and Month 6 versus placebo (or versus MTX in ORAL Start) treated patients.

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 ORAL Solo, ORAL Sync, and ORAL Step) and the magnitude of response continued to improve with duration of treatment. As with the overall ACR response in patients treated with 5 mg or 10 mg twice daily tofacitinib, 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.
Table 6: Proportion (%) of Patients with an ACR Response

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Time</th>
<th>Placebo N=122</th>
<th>Tofacitinib 5 mg Twice Daily Monotherapy N=241</th>
<th>Tofacitinib 10 mg Twice Daily Monotherapy N=243</th>
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<tbody>
<tr>
<td>ORAL Solo: DMARD Inadequate Responders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACR20</td>
<td>Month 3</td>
<td>26</td>
<td>60***</td>
<td>65***</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>NA</td>
<td>69</td>
<td>71</td>
</tr>
<tr>
<td>ACR50</td>
<td>Month 3</td>
<td>12</td>
<td>31***</td>
<td>37***</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>NA</td>
<td>42</td>
<td>47</td>
</tr>
<tr>
<td>ACR70</td>
<td>Month 3</td>
<td>6</td>
<td>15*</td>
<td>20***</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>NA</td>
<td>22</td>
<td>29</td>
</tr>
</tbody>
</table>

<p>| ORAL Sync: DMARD Inadequate Responders |</p>
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Time</th>
<th>Placebo + DMARD(s) N=158</th>
<th>Tofacitinib 5 mg Twice Daily + DMARD(s) N=312</th>
<th>Tofacitinib 10 mg Twice Daily + DMARD(s) N=315</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>Month 3</td>
<td>27</td>
<td>56***</td>
<td>63***</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>31</td>
<td>53***</td>
<td>57***</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>51</td>
<td>56</td>
</tr>
<tr>
<td>ACR50</td>
<td>Month 3</td>
<td>9</td>
<td>27***</td>
<td>33***</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>13</td>
<td>34***</td>
<td>36***</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>33</td>
<td>42</td>
</tr>
<tr>
<td>ACR70</td>
<td>Month 3</td>
<td>2</td>
<td>8**</td>
<td>14***</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>3</td>
<td>13***</td>
<td>16***</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>19</td>
<td>25</td>
</tr>
</tbody>
</table>

<p>| ORAL Standard: MTX Inadequate Responders |</p>
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Time</th>
<th>Placebo N=105</th>
<th>Tofacitinib Twice Daily + MTX 5 mg N=198</th>
<th>10 mg N=197</th>
<th>Adalimumab 40 mg QOW + MTX N=199</th>
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</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>Month 3</td>
<td>26</td>
<td>59***</td>
<td>57***</td>
<td>56***</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>28</td>
<td>51***</td>
<td>51***</td>
<td>46**</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>48</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>ACR50</td>
<td>Month 3</td>
<td>7</td>
<td>33***</td>
<td>27***</td>
<td>24***</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>12</td>
<td>36***</td>
<td>34***</td>
<td>27**</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>NA</td>
<td>36</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>ACR70</td>
<td>Month 3</td>
<td>2</td>
<td>12**</td>
<td>15***</td>
<td>9*</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>2</td>
<td>19***</td>
<td>21***</td>
<td>9*</td>
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<td>Month 12</td>
<td>NA</td>
<td>22</td>
<td>23</td>
<td>17</td>
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## ORAL Scan: MTX Inadequate Responders

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Time</th>
<th>Placebo + MTX N=156</th>
<th>Tofacitinib 5 mg Twice Daily + MTX N=316</th>
<th>Tofacitinib 10 mg Twice Daily + MTX N=309</th>
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<tbody>
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<td>ACR20</td>
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<td>55***</td>
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<td>Month 6</td>
<td>25</td>
<td>50***</td>
<td>62***</td>
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<td></td>
<td>Month 12</td>
<td>NA</td>
<td>47</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>NA</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>ACR50</td>
<td>Month 3</td>
<td>8</td>
<td>28***</td>
<td>36***</td>
</tr>
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<td></td>
<td>Month 6</td>
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<td></td>
<td>Month 24</td>
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<td>28</td>
<td>40</td>
</tr>
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<td>3</td>
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<td>17***</td>
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</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>NA</td>
<td>17</td>
<td>26</td>
</tr>
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</table>

## ORAL Step: TNF Inhibitor Inadequate Responders

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Time</th>
<th>Placebo + MTX N=132</th>
<th>Tofacitinib 5 mg Twice Daily + MTX N=133</th>
<th>Tofacitinib 10 mg Twice Daily + MTX N=134</th>
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</thead>
<tbody>
<tr>
<td>ACR20</td>
<td>Month 3</td>
<td>24</td>
<td>41*</td>
<td>48***</td>
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<tr>
<td></td>
<td>Month 6</td>
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<td>51</td>
<td>54</td>
</tr>
<tr>
<td>ACR50</td>
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<td>26***</td>
<td>28***</td>
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<tr>
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<td>37</td>
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<td>10*</td>
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<td></td>
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<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

## ORAL Start: MTX-naïve

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Time</th>
<th>MTX N=184</th>
<th>Tofacitinib 5 mg Twice Daily Monotherapy N=370</th>
<th>Tofacitinib 10 mg Twice Daily Monotherapy N=394</th>
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<tbody>
<tr>
<td>ACR20</td>
<td>Month 3</td>
<td>52</td>
<td>60***</td>
<td>77***</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>51</td>
<td>71***</td>
<td>75***</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>51</td>
<td>67**</td>
<td>71**</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>42</td>
<td>62***</td>
<td>64**</td>
</tr>
<tr>
<td>ACR50</td>
<td>Month 3</td>
<td>20</td>
<td>40***</td>
<td>49***</td>
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<td></td>
<td>Month 6</td>
<td>27</td>
<td>46***</td>
<td>56***</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>33</td>
<td>49**</td>
<td>55**</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>28</td>
<td>48***</td>
<td>49**</td>
</tr>
<tr>
<td>ACR70</td>
<td>Month 3</td>
<td>5</td>
<td>20***</td>
<td>26***</td>
</tr>
<tr>
<td></td>
<td>Month 6</td>
<td>12</td>
<td>25***</td>
<td>37***</td>
</tr>
<tr>
<td></td>
<td>Month 12</td>
<td>15</td>
<td>28**</td>
<td>38***</td>
</tr>
<tr>
<td></td>
<td>Month 24</td>
<td>15</td>
<td>34***</td>
<td>37***</td>
</tr>
</tbody>
</table>

*p<0.05, **p<0.001, ***p<0.0001 verses placebo (versus MTX for ORAL Start), QOW=every other week, N=number of subjects analysed, ACR20/50/70=American College of Rheumatology ≥20, 50, 70% improvement, NA=not applicable.

### DAS28-4(ESR) response

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 and 1.9-2.2 were observed in patients treated with 5 mg and 10 mg twice daily doses, respectively, compared to placebo-treated patients (0.7-1.1) at Month 3. The proportion of patients achieving a DAS28 clinical remission (DAS28-4(ESR) < 2.6) in ORAL Step, ORAL Sync, and ORAL Standard is shown in Table 7.
Table 7: Number (%) of Subjects Achieving DAS28-4(ESR) < 2.6 Remission at Months 3 and 6

<table>
<thead>
<tr>
<th></th>
<th>Time Point</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL Step: TNF Inhibitor Inadequate Responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tofacitinib 5 mg twice daily + MTX</td>
<td>Month 3</td>
<td>133</td>
<td>6</td>
</tr>
<tr>
<td>Tofacitinib 10 mg twice daily + MTX</td>
<td>Month 3</td>
<td>134</td>
<td>8*</td>
</tr>
<tr>
<td>Placebo + MTX</td>
<td>Month 3</td>
<td>132</td>
<td>2</td>
</tr>
<tr>
<td><strong>ORAL Sync: DMARD Inadequate Responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tofacitinib 5 mg twice daily</td>
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<td>Tofacitinib 10 mg twice daily</td>
<td>Month 6</td>
<td>315</td>
<td>11***</td>
</tr>
<tr>
<td>Placebo</td>
<td>Month 6</td>
<td>158</td>
<td>3</td>
</tr>
<tr>
<td><strong>ORAL Standard: MTX Inadequate Responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tofacitinib 5 mg twice daily + MTX</td>
<td>Month 6</td>
<td>198</td>
<td>6*</td>
</tr>
<tr>
<td>Tofacitinib 10 mg twice daily + MTX</td>
<td>Month 6</td>
<td>197</td>
<td>11***</td>
</tr>
<tr>
<td>Adalimumab 40 mg SC QOW + MTX</td>
<td>Month 6</td>
<td>199</td>
<td>6*</td>
</tr>
<tr>
<td>Placebo + MTX</td>
<td>Month 6</td>
<td>105</td>
<td>1</td>
</tr>
</tbody>
</table>

*p <0.05, ***p<0.0001 versus placebo, SC=subcutaneous, QOW=every other week, N=number of subjects analysed, DAS28=Disease Activity Scale 28 joints, ESR=Erythrocyte Sedimentation Rate.

**Radiographic response**

In ORAL Scan and ORAL Start, inhibition of progression of structural joint damage was assessed radiographically and expressed as mean change from baseline in mTSS and its components, the erosion score and joint space narrowing (JSN) score, at Months 6 and 12.

In ORAL Scan, tofacitinib 10 mg twice daily plus background MTX resulted in significantly greater inhibition of the progression of structural damage compared to placebo plus MTX at Months 6 and 12. When given at a dose of 5 mg twice daily, tofacitinib plus MTX exhibited similar effects on mean progression of structural damage (not statistically significant). Analysis of erosion and JSN scores were consistent with overall results.

In the placebo plus MTX group, 78% of patients experienced no radiographic progression (mTSS change less than or equal to 0.5) at Month 6 compared to 89% and 87% of patients treated with tofacitinib 5 or 10 mg (plus MTX) twice daily respectively, (both significant versus placebo plus MTX).

In ORAL Start, tofacitinib monotherapy resulted in significantly greater inhibition of the progression of structural damage compared to MTX at Months 6 and 12 as shown in Table 8, which was also maintained at Month 24. Analyses of erosion and JSN scores were consistent with overall results.

In the MTX group, 70% of patients experienced no radiographic progression at Month 6 compared to 83% and 90% of patients treated with tofacitinib 5 or 10 mg twice daily respectively, both significant versus MTX.
### Table 8: Radiographic Changes at Months 6 and 12

<table>
<thead>
<tr>
<th></th>
<th>Placebo + MTX</th>
<th>Tofacitinib 5 mg Twice Daily + MTX</th>
<th>Tofacitinib 5 mg Twice Daily + MTX Mean Difference from Placebo&lt;sup&gt;b&lt;/sup&gt; (CI)</th>
<th>Tofacitinib 10 mg Twice Daily + MTX</th>
<th>Tofacitinib 10 mg Twice Daily + MTX Mean Difference from Placebo&lt;sup&gt;b&lt;/sup&gt; (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORAL Scan: MTX Inadequate Responders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>N=139 Mean (SD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>33 (42)</td>
<td>31 (48)</td>
<td>-0.3 (-0.7, 0.0)</td>
<td>37 (54)</td>
</tr>
<tr>
<td>Tofacitinib 5 mg</td>
<td>N=277 Mean (SD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.5 (2.0)</td>
<td>0.1 (1.7)</td>
<td>-0.6 (-1.3, 0.0)</td>
<td>0.1 (2.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 6</td>
<td>1.0 (3.9)</td>
<td></td>
<td>-0.9 (-1.5, -0.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 12</td>
<td>0.3 (3.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORAL Start: MTX-naive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MTX</td>
<td>N=168 Mean (SD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>16 (29)</td>
<td>20 (41)</td>
<td>-0.7 (-1.0, -0.3)</td>
<td>19 (39)</td>
</tr>
<tr>
<td>Tofacitinib 5 mg</td>
<td>N=344 Mean (SD)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.9 (2.7)</td>
<td>0.2 (2.3)</td>
<td>-0.9 (-1.4, -0.4)</td>
<td>0.0 (1.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 6</td>
<td>1.3 (3.7)</td>
<td></td>
<td>-0.8 (-1.2, -0.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Month 12</td>
<td>0.4 (3.0)</td>
<td></td>
<td>-1.3 (-1.8, -0.8)</td>
</tr>
</tbody>
</table>

<sup>a</sup> SD = Standard Deviation  
<sup>b</sup> Difference between least squares means tofacitinib minus placebo (95% CI = 95% confidence interval)  
<sup>c</sup> Month 6 and Month 12 data are mean change from baseline  
<sup>d</sup> Difference between least squares means tofacitinib minus MTX (95% CI = 95% confidence interval)

### Physical function response and health-related outcomes

XELJANZ, alone or in combination with MTX, has shown improvements in physical function, as measured by the HAQ-DI. Patients receiving tofacitinib 5 or 10 mg twice daily demonstrated significantly greater improvement from baseline in physical functioning compared to placebo at Month 3 (Studies ORAL Solo, ORAL Sync, ORAL Standard, and ORAL Step) and Month 6 (Studies ORAL Sync and ORAL Standard). Tofacitinib 5 or 10 mg twice daily-treated patients demonstrated significantly greater improvement in physical functioning compared to placebo as early as Week 2 in ORAL Solo and ORAL Sync. Changes from baseline in HAQ-DI in studies ORAL Standard, ORAL Step and ORAL Sync are shown in Table 9.
Health-related quality of life was assessed by the Short Form Health Survey (SF-36). Patients receiving either 5 or 10 mg tofacitinib twice daily experienced significantly greater improvement from baseline compared to placebo in all 8 domains as well as the Physical Component Summary and Mental Component Summary scores at Month 3 in ORAL Solo, ORAL Scan and ORAL Step. In ORAL Scan, mean SF-36 improvements were maintained to 12 months in tofacitinib-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 tofacitinib 5 or 10 mg twice daily demonstrated significantly greater improvement from baseline in fatigue compared to placebo in all 5 studies. In ORAL Standard and ORAL Scan, mean FACIT-F improvements were maintained to 12 months in tofacitinib-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 tofacitinib 5 or 10 mg twice daily demonstrated significantly greater improvement from baseline in both scales compared to placebo in ORAL Sync, ORAL Standard and ORAL Scan. In ORAL Standard and ORAL Scan, mean improvements in both scales were maintained to 12 months in tofacitinib-treated patients.

Durability of clinical responses
Durability of effect was assessed by ACR20, ACR50, ACR70 response rates in studies of duration of up to two years. Changes in mean HAQ-DI and DAS28-4(ESR) were maintained in both tofacitinib treatment groups through to the end of the studies.

Evidence of persistence of efficacy with tofacitinib treatment for up to 7 years is also provided from data in the one ongoing and one completed open-label, long-term follow-up studies.

Psoriatic arthritis
The efficacy and safety of XELJANZ were assessed in 2 randomised, double-blind, placebo-controlled Phase 3 studies in adult patients with active PsA (≥ 3 swollen and ≥ 3 tender joints). Patients were required to have active plaque psoriasis at the screening visit. For both studies, the primary endpoints were ACR20 response rate and change from baseline in HAQ-DI at Month 3.

Study PsA-I (OPAL BROADEN) evaluated 422 patients who had a previous inadequate response (due to lack of efficacy or intolerance) to a csDMARD (MTX for 92.7% of patients); 32.7% of the patients in this study had a previous inadequate response to > 1 csDMARD or 1 csDMARD and a targeted
synthetic DMARD (tsDMARD). In OPAL BROADEN, previous treatment with TNF inhibitor was not allowed. All patients were required to have 1 concomitant csDMARD; 83.9% of patients received concomitant MTX, 9.5% of patients received concomitant sulfaalazine, and 5.7% of patients received concomitant leflunomide. The median PsA disease duration was 3.8 years. At baseline, 79.9% and 56.2% of patients had enthesitis and dactylitis, respectively. Patients randomised to XELJANZ received 5 mg twice daily or XELJANZ 10 mg twice daily for 12 months. Patients randomised to placebo were advanced in a blinded manner at Month 3 to either XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily and received treatment until Month 12. Patients randomised to adalimumab (active-control arm) received 40 mg subcutaneously every 2 weeks for 12 months.

Study PsA-II (OPAL BEYOND) evaluated 394 patients who had discontinued a TNF inhibitor due to lack of efficacy or intolerance; 36.0% had a previous inadequate response to > 1 biological DMARD. All patients were required to have 1 concomitant csDMARD; 71.6% of patients received concomitant MTX, 15.7% of patients received concomitant sulfaalazine, and 8.6% of patients received concomitant leflunomide. The median PsA disease duration was 7.5 years. At baseline, 80.7% and 49.2% of patients had enthesitis and dactylitis, respectively. Patients randomised to XELJANZ received 5 mg twice daily or XELJANZ 10 mg twice daily for 6 months. Patients randomised to placebo were advanced in a blinded manner at Month 3 to either XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily and received treatment until Month 6.

**Signs and symptoms**

Treatment with XELJANZ resulted in significant improvements in some signs and symptoms of PsA, as assessed by the ACR20 response criteria compared to placebo at Month 3. The efficacy results for important endpoints assessed are shown in Table 10.

**Table 10: Proportion (%) of PsA Patients Who Achieved Clinical Response and Mean Change from Baseline in OPAL BROADEN and OPAL BEYOND Studies**

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo</th>
<th>XELJANZ 5 mg Twice Daily</th>
<th>Adalimumab 40 mg SC q2W</th>
<th>Placebo</th>
<th>XELJANZ 5 mg Twice Daily</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>105</td>
<td>107</td>
<td>106</td>
<td>131</td>
<td>131</td>
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<tr>
<td>ACR20</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>33%</td>
<td>50%&lt;sup&gt; d,* &lt;/sup&gt;</td>
<td>52%&lt;sup&gt;* &lt;/sup&gt;</td>
<td>24%</td>
<td>50%&lt;sup&gt;d,*** &lt;/sup&gt;</td>
</tr>
<tr>
<td>Month 6</td>
<td>NA</td>
<td>59%</td>
<td>64%</td>
<td>NA</td>
<td>60%</td>
</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
<td>68%</td>
<td>60%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ACR50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>10%</td>
<td>28%&lt;sup&gt; e,** &lt;/sup&gt;</td>
<td>33%&lt;sup&gt;*** &lt;/sup&gt;</td>
<td>15%</td>
<td>30%&lt;sup&gt;e,* &lt;/sup&gt;</td>
</tr>
<tr>
<td>Month 6</td>
<td>NA</td>
<td>38%</td>
<td>42%</td>
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</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
<td>45%</td>
<td>41%</td>
<td>-</td>
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<tr>
<td>ACR70</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Month 3</td>
<td>5%</td>
<td>17%&lt;sup&gt; e,* &lt;/sup&gt;</td>
<td>19%&lt;sup&gt;* &lt;/sup&gt;</td>
<td>10%</td>
<td>17%</td>
</tr>
<tr>
<td>Month 6</td>
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<td>18%</td>
<td>30%</td>
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</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
<td>23%</td>
<td>29%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>∆LEIf</td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Month 3</td>
<td>-0.4</td>
<td>-0.8</td>
<td>-1.1&lt;sup&gt; &lt;/sup&gt;</td>
<td>-0.5</td>
<td>-1.3&lt;sup&gt; * &lt;/sup&gt;</td>
</tr>
<tr>
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<td>Month 12</td>
<td>NA</td>
<td>-1.7</td>
<td>-1.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>∆DSS&lt;sup&gt;f&lt;/sup&gt;</td>
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<td></td>
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<td>-3.5</td>
<td>-4.0</td>
<td>-1.9</td>
<td>-5.2&lt;sup&gt; * &lt;/sup&gt;</td>
</tr>
<tr>
<td>Month 6</td>
<td>NA</td>
<td>-5.2</td>
<td>-5.4</td>
<td>NA</td>
<td>-6.0</td>
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<tr>
<td>Month 12</td>
<td>NA</td>
<td>-7.4</td>
<td>-6.1</td>
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</table>
Both TNF inhibitor naïve and TNF inhibitor inadequate responder XELJANZ 5 mg BID -treated patients had significantly higher ACR20 response rates compared to placebo at Month 3. Examination of age, sex, race, baseline disease activity and PsA subtype did not identify differences in response to XELJANZ. The number of patients with arthritis mutilans or axial involvement was too small to allow meaningful assessment. Statistically significant ACR20 response rates were observed with XELJANZ 5 mg BID in both studies as early as Week 2 (first post-baseline assessment) in comparison to placebo.

In OPAL BROADEN, Minimal Disease Activity (MDA) response was achieved by 26.2%, 25.5% and 6.7% of XELJANZ 5 mg BID, adalimumab and placebo treated patients, respectively (XELJANZ 5 mg BID treatment difference from placebo 19.5% [95% CI: 9.9, 29.1]) at Month 3. In OPAL BEYOND, MDA was achieved by 22.9% and 14.5% of XELJANZ 5 mg BID and placebo treated patients, respectively, however XELJANZ 5 mg BID did not achieve nominal statistical significance (treatment difference from placebo 8.4% [95% CI: -1.0, 17.8] at Month 3).

**Radiographic response**

In Study OPAL BROADEN, the progression of structural joint damage was assessed radiographically utilising the van der Heijde modified Total Sharp Score (mTSS) and the proportion of patients with radiographic progression (mTSS increase from baseline greater than 0.5) was assessed at Month 12. At Month 12, 96% and 98% of patients receiving XELJANZ 5 mg twice daily, and adalimumab 40 mg subcutaneously every 2 weeks, respectively, did not have radiographic progression (mTSS increase from baseline less than or equal to 0.5).

**Physical function and health-related quality of life**

Improvement in physical functioning was measured by the HAQ-DI. Patients receiving XELJANZ 5 mg twice daily demonstrated greater improvement (p≤ 0.05) from baseline in physical functioning compared to placebo at Month 3 (see Table 11).
Table 11: Change From Baseline in HAQ-DI in PsA Studies OPAL BROADEN and OPAL BEYOND

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo</th>
<th>XELJANZ 5 mg Twice Daily</th>
<th>Adalimumab 40 mg SC q2W</th>
<th>Placebo</th>
<th>XELJANZ 5 mg Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>104</td>
<td>107</td>
<td>106</td>
<td>131</td>
<td>129</td>
</tr>
<tr>
<td>Month 3</td>
<td>-0.18</td>
<td>-0.35&lt;sup&gt;c&lt;/sup&gt;,*</td>
<td>-0.38&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-0.14</td>
<td>-0.39&lt;sup&gt;c&lt;/sup&gt;,***</td>
</tr>
<tr>
<td>Month 6</td>
<td>NA</td>
<td>-0.45</td>
<td>-0.43</td>
<td>NA</td>
<td>-0.44</td>
</tr>
<tr>
<td>Month 12</td>
<td>NA</td>
<td>-0.54</td>
<td>-0.45</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

<sup>a</sup> Inadequate response to at least one conventional synthetic DMARD (csDMARD) due to lack of efficacy and/or intolerability.

<sup>b</sup> Inadequate response to at least one TNF inhibitor (TNFi) due to lack of efficacy and/or intolerability.

<sup>c</sup> Achieved statistical significance globally at p < 0.05 per the pre-specified step-down testing procedure.

The HAQ-DI responder rate (response defined as having decrease from baseline of ≥ 0.35) at Month 3 in Studies OPAL BROADEN and OPAL BEYOND was 53% and 50%, respectively in patients receiving XELJANZ 5 mg twice daily, 31% and 28%, respectively in patients receiving placebo, and 53% in patients receiving adalimumab 40 mg subcutaneously once every 2 weeks (OPAL BROADEN only).

Health-related quality of life was assessed by SF-36v2, fatigue was assessed by the FACIT-F. Patients receiving XELJANZ 5 mg twice daily demonstrated greater improvement from baseline compared to placebo in the SF-36v2 physical functioning domain, the SF-36v2 physical component summary score, and FACIT-F scores at Month 3 in Studies OPAL BROADEN and OPAL BEYOND (nominal p < 0.05). Improvements from baseline in SF-36v2 and FACIT-F were maintained through Month 6 (OPAL BROADEN and OPAL BEYOND) and Month 12 (OPAL BROADEN).

Patients receiving XELJANZ 5 mg twice daily demonstrated a greater improvement in arthritis pain (as measured on a 0-100 visual analogue scale) from baseline at Week 2 (first post-baseline assessment) through Month 3 compared to placebo in studies OPAL BROADEN and OPAL BEYOND (nominal p < 0.05).

**Paediatric population**

The European Medicines Agency has deferred the obligation to submit results of studies in XELJANZ in one or more subsets of the paediatric population in juvenile idiopathic arthritis (see section 4.2 for information on paediatric use).

### 5.2 Pharmacokinetic properties

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<sub>max</sub> was reduced by 32%. In clinical trials, tofacitinib was administered without regard to meal.
After intravenous administration, the volume of distribution is 87 L. Approximately 40% of circulating tofacitinib is bound to plasma proteins. 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 elimination
Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged active substance, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. All metabolites have been observed in animal species and are predicted to have less than 10-fold potency than tofacitinib for JAK1/3 inhibition. No evidence of stereo conversion in human samples was detected. The pharmacologic activity of tofacitinib is attributed to the parent molecule. In vitro, tofacitinib is a substrate for MDR1, but not for breast cancer resistance protein (BCRP), OATP1B1/1B3, or OCT1/2, and is not an inhibitor of MDR1, OATP1B1/1B3, OCT2, OAT1/3, or MRP at clinically meaningful concentrations.

Pharmacokinetics in patients
The enzymatic activity of CYP enzymes is reduced in RA patients due to chronic inflammation. In RA patients, the oral clearance of XELJANZ does not vary with time, indicating that treatment with XELJANZ does not normalise CYP enzyme activity.

Population PK analysis in RA patients indicated that systemic exposure (AUC) of tofacitinib in the extremes of body weight (40 kg, 140 kg) were similar (within 5%) to that of a 70 kg patient. Elderly patients 80 years of age were estimated to have less than 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 White, Black and Asian patients. 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%.

Results from population PK analysis in patients with active PsA were consistent with those in patients with RA.

Renal impairment
Subjects with mild (creatinine clearance 50-80 mL/min), moderate (creatinine clearance 30-49 mL/min), and severe (creatinine clearance < 30 mL/min) renal impairment had 37%, 43% and 123% higher AUC, respectively, compared to subjects with normal renal function (see section 4.2). In subjects with end-stage renal disease (ESRD), contribution of dialysis to the total clearance of tofacitinib was relatively small. Following a single dose of 10 mg, mean AUC in subjects with ESRD based on concentrations measured on a non-dialysis day was approximately 40% (90% confidence intervals: 1.5-95%) higher compared to subjects with normal renal function. In clinical trials, XELJANZ was not evaluated in patients with baseline creatinine clearance values (estimated by Cockroft-Gault equation) less than 40 mL/min (see section 4.2).

Hepatic impairment
Subjects with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment had 3%, and 65% higher AUC, respectively, compared to subjects with normal hepatic function. In clinical trials, XELJANZ was not evaluated in subjects with severe (Child Pugh C) hepatic impairment (see sections 4.2 and 4.4), or in patients screened positive for hepatitis B or C.

5.3 Preclinical safety data
In non-clinical studies, effects were observed on the immune and haematopoietic systems that were attributed to the pharmacological properties (JAK inhibition) of tofacitinib. Secondary effects from
immunosuppression, such as bacterial and viral infections and lymphoma were observed at clinically relevant doses. Lymphoma was observed in 3 of 8 adult monkeys at 6 times the clinical tofacitinib exposure level (unbound AUC in humans at a dose of 5 mg twice daily), and 0 of 14 juvenile monkeys at 5 times the clinical exposure level. Exposure in monkeys at the no observed adverse effect level (NOAEL) for the lymphomas was approximately equal to the clinical exposure level. Other findings at doses exceeding human exposures included effects on the hepatic and gastrointestinal systems.

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

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 at exposures up to 38 times the clinical exposure level. Benign testicular interstitial (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 exposures greater than or equal to 83 times the clinical exposure level. Benign thymomas were observed in female rats at 187 times the clinical exposure level.

Tofacitinib was shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility (decreased pregnancy rate; decreases in the numbers of corpora lutea, implantation sites, and viable foetuses; and an increase in early resorptions), parturition, and peri/postnatal development. Tofacitinib had no effects on male fertility, sperm motility or sperm concentration. Tofacitinib was secreted in milk of lactating rats at concentrations approximately 2-fold those in serum from 1 to 8 hours postdose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
- microcrystalline cellulose
- lactose monohydrate
- croscarmellose sodium
- magnesium stearate

Film coat
- hypromellose 6cP (E464)
- titanium dioxide (E171)
- lactose monohydrate
- macrogol 3350
- triacetin (E1518)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original, bottle and/or blister, in order to protect from moisture.
6.5  Nature and contents of container

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

Aluminium foil/PVC backed aluminium foil blisters containing 14 film-coated tablets. Each pack contains 56 or 182 film-coated tablets.

Not all pack sizes may be marketed.

6.6  Special precautions for disposal

No special requirements for disposal.

7.  MARKETING AUTHORISATION HOLDER

Pfizer Limited, Ramsgate Road, Sandwich, Kent CT13 9NJ, United Kingdom

8.  MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1178/001  
EU/1/17/1178/002  
EU/1/17/1178/003  
EU/1/17/1178/004

9.  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2017

10.  DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- Additional risk minimisation measures

Prior to launch of XELJANZ in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The main objective of the programme is to increase awareness about the risks of the product, specifically in regards to serious infections, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy, gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities.
The MAH shall ensure that in each Member State where XELJANZ is marketed, all healthcare professionals and patients/carers who are expected to prescribe or use XELJANZ have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

- **The physician educational material** should contain:
  - The Summary of Product Characteristics
  - Guide for healthcare professionals
  - Prescriber checklist
  - Patient alert card
  - A reference to the website with the educational material and patient alert card

- **The Guide for healthcare professionals** shall contain the following key elements:
  - Relevant information of the safety concerns addressed by the aRMM (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable)
  - Details of the population at higher risk for the safety concern addressed by the aRMM (i.e. contraindications, risk factors, increased risk by interactions with certain medicine)
  - Details on how to minimise the safety concern addressed by the aRMM through appropriate monitoring and management (i.e. what to do, what not do, and who is most likely be impacted according to different scenarios, like when to limit or stop prescribing/ingestion, how to administer the medicine, when to increase/decrease the dosage according to laboratory measurements, signs and symptoms)
  - Key message to convey in patients counselling
  - Instructions on how to handle possible adverse events
  - Information about the BSRBR, ARTIS, RABBIT and BIODABASER registries in RA and the importance of contributing to these

- **The Prescriber checklist** shall contain the following key messages:
  - Lists of tests to be conducted during the initial screening of the patient
  - Vaccination course to be completed before treatment
  - Relevant comorbidities for which caution is advised when XELJANZ is administered and conditions in which XELJANZ should not be administered
  - List of concomitant medications which are not compatible with treatment with XELJANZ
  - The need to discuss with the patients the risks associated with the use of XELJANZ, specifically in regards to infections, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy, gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities
  - The need to monitor for any signs and symptoms and laboratory abnormalities for early identification of the abovementioned risks.

- **The patient alert card** shall contain the following key messages:
  - A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using XELJANZ
  - That treatment with XELJANZ may increase the risk of infections and non melanoma skin cancer
  - That patients should inform health professionals if they are planning to receive any vaccine or become pregnant
Signs or symptoms of the following safety concern and when to seek attention from a HCP: infections, herpes zoster reactivation, non-melanoma skin cancer, transaminase elevation and potential for drug induced liver injury, gastrointestinal perforation, interstitial lung disease, increased immunosuppression when used in combination with biologic DMARDs and immunosuppressants including B lymphocyte depleting agents, increased risk of adverse events when tofacitinib is administered in combination with MTX, increased exposure to tofacitinib when co-administered with CYP3A4 and CYP2C19 inhibitors, effects on pregnancy and foetus, use in breastfeeding, effect on vaccination efficacy and the use of live/attenuated vaccines.

Contact details of the prescriber

- **The centralised website** shall contain:
  - The educational material in digital format
  - The patient alert card in digital format

- **The patient information pack** should contain:
  - Patient information leaflet
  - The patient alert card
A. LABELLING
## PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON FOR BLISTER PACK

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
<th></th>
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<tbody>
<tr>
<td>XELJANZ 5 mg film-coated tablets</td>
<td>tofacitinib</td>
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</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Each film-coated tablet contains 5 mg of tofacitinib (as tofacitinib citrate).</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Contains lactose. See leaflet for further information.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>56 film-coated tablets</td>
<td></td>
</tr>
<tr>
<td>182 film-coated tablets</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>For oral use.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
<th></th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Store in the original package in order to protect from moisture.</td>
<td></td>
</tr>
</tbody>
</table>
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORIZATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORIZATION NUMBER(S)

EU/1/17/1178/003 56 film-coated tablets
EU/1/17/1178/004 182 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XELJANZ 5 mg

17. UNIQUE IDENTIFIER-2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER-HUMAN READABLE DATA

PC:
SN:
NN:
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BLISTER STRIPS</strong></td>
</tr>
</tbody>
</table>

| 1. NAME OF THE MEDICINAL PRODUCT                  |
| XELJANZ 5 mg tablets                              |
| tofacitinib                                      |

| 2. NAME OF THE MARKETING AUTHORISATION HOLDER     |
| Pfizer Ltd                                       |

| 3. EXPIRY DATE                                   |
| EXP                                              |

| 4. BATCH NUMBER                                  |
| Lot                                              |

| 5. OTHER                                         |
PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LABEL FOR BOTTLE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 5 mg tablets
tofacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 5 mg of tofacitinib (as tofacitinib citrate).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

60 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in the original package in order to protect from moisture.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich
Kent CT13 9NJ
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1178/001 60 film-coated tablets
EU/1/17/1178/002 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XELJANZ 5 mg

17. UNIQUE IDENTIFIER-2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER-HUMAN READABLE DATA

PC:
SN:
NN:
B. PACKAGE LEAFLET
Package leaflet: Information for the patient
XELJANZ 5 mg film-coated tablets
tofacitinib

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

In addition to this leaflet, your doctor will also give you a Patient Alert Card, which contains important safety information that you need to be aware of before you are given XELJANZ and during treatment with XELJANZ. Keep this Patient Alert Card with you.

What is in this leaflet
1. What XELJANZ is and what it is used for
2. What you need to know before you take XELJANZ
3. How to take XELJANZ
4. Possible side effects
5. How to store XELJANZ
6. Contents of the pack and other information

1. What XELJANZ is and what it is used for

XELJANZ is a medicine that contains the active substance tofacitinib.

XELJANZ is used for the treatment of the following inflammatory diseases:
- rheumatoid arthritis
- psoriatic arthritis

Rheumatoid arthritis
XELJANZ is used to treat adult patients with moderate to severe active rheumatoid arthritis, a long-term disease that mainly causes pain and swelling of your joints.

XELJANZ is used together with methotrexate when previous rheumatoid arthritis treatment was not sufficient or was not well tolerated. XELJANZ can also be taken on its own in those cases where methotrexate treatment is not tolerated or treatment with methotrexate is not advised.

XELJANZ has been shown to reduce pain and swelling of the joints and improve the ability to perform daily activities when given on its own, or together with methotrexate.

Psoriatic arthritis
XELJANZ is used to treat a condition called psoriatic arthritis. This condition is an inflammatory disease of the joints, often accompanied by psoriasis. If you have active psoriatic arthritis you will be first given another medicine to treat your psoriatic arthritis. If you do not respond well enough or the medicine is not tolerated, you may be given XELJANZ to reduce the sign and symptoms of active psoriatic arthritis and improve the ability to perform daily activities.

XELJANZ is used together with methotrexate to treat adult patients with active psoriatic arthritis.
2. **What you need to know before you take XELJANZ**

**Do not take XELJANZ:**
- if you are allergic to tofacitinib or any of the other ingredients of this medicine (listed in section 6)
- if you have a severe infection such as bloodstream infection or active tuberculosis
- if you have been informed that you have severe liver problems, including cirrhosis (scarring of the liver)
- if you are pregnant or breast-feeding

If you are not sure regarding any of the information provided above, please contact your doctor.

**Warnings and precautions**

Talk to your doctor or pharmacist before taking XELJANZ:
- if you think you have an infection or have symptoms of an infection such as fever, sweating, chills, muscle aches, cough, shortness of breath, new phlegm or change in phlegm, weight loss, warm or red or painful skin or sores on your body, difficulty or pain when swallowing, diarrhoea or stomach pain, burning when you urinate or urinating more often than normal, feeling very tired
- if you have any condition that increases your chance of infection (e.g., diabetes, HIV/AIDS, or a weak immune system)
- if you have any kind of infection, are being treated for any infection, or if you have infections that keep coming back. Tell your doctor immediately if you feel unwell. XELJANZ can reduce your body’s ability to respond to infections and may make an existing infection worse or increase the chance of getting a new infection
- if you have or have a history of tuberculosis or have been in close contact with someone with tuberculosis. Your doctor will test you for tuberculosis before starting XELJANZ and may retest during treatment
- if you have any chronic lung disease
- if you have liver problems
- if you have or have a history of hepatitis B or hepatitis C (viruses that affect the liver). The virus may become active while you are taking XELJANZ. Your doctor may do blood tests for hepatitis before you start treatment with XELJANZ and while you are taking XELJANZ
- if you have ever had any type of cancer. XELJANZ may increase your risk of certain cancers. Lymphoma and other cancers (such as lung, breast, melanoma, prostate and pancreatic) have been reported in patients treated with XELJANZ. If you develop cancer while taking XELJANZ your doctor will review whether to stop XELJANZ treatment.
- if you are at high risk of developing skin cancer, your doctor may recommend that you have regular skin examinations while taking XELJANZ.
- if you have had diverticulitis (a type of inflammation of the large intestine) or ulcers in stomach or intestines (see section 4)
- if you have kidney problems
- if you are planning to get vaccinated, tell your doctor. Certain types of vaccines should not be given when taking XELJANZ. Before you start XELJANZ, you should be up to date with all recommended vaccinations. Your doctor will decide whether you need to have herpes zoster vaccination.
- if you are planning to have surgery or a medical procedure. Your doctor will decide if you can be given XELJANZ if you plan to have surgery or a medical procedure
- if you have heart problems, high blood pressure, or high cholesterol

**Additional monitoring tests**

Your doctor should perform blood tests before you start taking XELJANZ, and after 4 to 8 weeks of treatment and then every 3 months, to determine if you have a low white blood cell (neutrophil or lymphocyte) count, or a low red blood cell count (anaemia).
You should not receive XELJANZ if your white blood cell (neutrophil or lymphocyte) count or red blood cell count is too low. If needed, your doctor may interrupt your XELJANZ treatment to reduce the risk of infection (white blood cell counts) or anaemia (red blood cell counts).

Your doctor may also perform other tests, for example to check your blood cholesterol levels or monitor the health of your liver. Your doctor should test your cholesterol levels 8 weeks after you start receiving XELJANZ. Your doctor should perform liver tests periodically.

Elderly
There is a higher rate of infections in patients aged 65 years and older. Tell your doctor as soon as you notice any signs or symptoms of infections.

Asian patients
There is a higher rate of shingles in Japanese and Korean patients. Tell your doctor if you notice any painful blisters on your skin.

You may also be at higher risk of certain lung problems. Tell your doctor if you notice any breathing difficulties.

Children and adolescents
XELJANZ is not recommended for use in children or adolescents under 18 years of age. The safety and benefits of XELJANZ in children or adolescents have not yet been established.

Other medicines and XELJANZ
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

XELJANZ may be used in combination with methotrexate or sometimes alone when used to treat rheumatoid arthritis. In general, fewer side effects were seen when XELJANZ was used alone in rheumatoid arthritis.

Some medicines should not be taken with XELJANZ. If taken with XELJANZ, they could alter the level of XELJANZ in your body, and the dose of XELJANZ may require adjustment. You should tell your doctor if you are using medicines (taken by mouth) that contain any of the following active substances:

- antibiotics such as clarithromycin and rifampicin, used to treat bacterial infections
- fluconazole, ketoconazole, clotrimazole,itraconazole, and voriconazole, used to treat fungal infections

XELJANZ is not recommended for use with medicines that depress the immune system, including so-called targeted biologic (antibody) therapies, such as those that inhibit tumour necrosis factor, interleukin-17, interleukin-12/interleukin-23 and strong chemical immunosuppressants including azathioprine, tacrolimus and ciclosporine. Taking XELJANZ with these medicines may increase your risk of side effects including infection.

Pregnancy and breast-feeding
If you are a woman of childbearing age, you should use effective birth control during treatment with XELJANZ and for at least 4 weeks after the last dose.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. XELJANZ should not be used during pregnancy.

Tell your doctor right away if you become pregnant while taking XELJANZ.

If you are taking XELJANZ and breast-feeding, you should stop breast-feeding until you talk to your doctor about stopping treatment with XELJANZ.
Driving and using machines
XELJANZ has no or limited effect on your ability to drive or use machines.

XELJANZ contains lactose
This medicine contains approximately 59 mg lactose in each tablet. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to Take XELJANZ
This medicine is provided to you and supervised by a specialised doctor who knows how to treat your arthritis condition.

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Rheumatoid arthritis
• The recommended dose is 5 mg twice a day.

Psoriatic arthritis
• The recommended dose is 5 mg twice a day.

Try to take your tablet at the same time every day (one tablet in the morning and one tablet in the evening).

Your doctor may reduce the dose if you have liver or kidney problems or if you are prescribed certain other medicines. Your doctor may also stop treatment temporarily or permanently if blood tests show low white blood cell or red blood cell counts.

XELJANZ is for oral use. You can take XELJANZ with or without food.

If you take more XELJANZ than you should
If you take more tablets than you should, immediately tell your doctor or pharmacist.

If you forget to take XELJANZ
Do not take a double dose to make up for a forgotten tablet. Take your next tablet at the usual time and continue as before.

If you stop taking XELJANZ
You should not stop taking XELJANZ without discussing this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some may be serious and need medical attention.

Possible serious side effects
In rare cases, infection may be life-threatening
If you notice any of the following serious side effects you need to tell a doctor straight away.

**Signs of serious infections (common) include**
- fever and chills
- cough
- skin blisters
- stomach ache
- persistent headaches

**Signs of allergic reactions (rare) include**
- chest tightness
- wheezing
- severe dizziness or light-headedness
- swelling of the lips, tongue or throat
- hives (itching or skin rash)

**Signs of stomach problems (uncommon: ulcers or holes in your stomach or intestines) include**
- fever
- stomach or abdominal pain
- blood in the stool
- unexplained changes in bowel habits

Holes in stomach or intestines happen most often in people who also take nonsteroidal anti-inflammatory drugs or corticosteroids (e.g., prednisone).

**Other side effects** which have been observed with XELJANZ are listed below.

**Common** (may affect up to 1 in 10 people): lung infection (pneumonia and bronchitis), shingles (herpes zoster), infections of nose, throat or the windpipe (nasopharyngitis), influenza, sinusitis, urinary bladder infection (cystitis), sore throat (pharyngitis), increased muscle enzymes in the blood (sign of muscle problems), stomach (belly) pain (which may be from inflammation of the stomach lining), vomiting, diarrhoea, feeling sick (nausea), indigestion, joint sprain, low red blood cell count (anaemia), swelling of the feet and hands, headache, high blood pressure (hypertension), cough, rash.

**Uncommon** (may affect up to 1 in 100 people): tuberculosis, kidney infection, skin infection, herpes simplex or cold sores (oral herpes), low white blood cell counts, increased liver enzymes in the blood (sign of liver problems), blood creatinine increased (a possible sign of kidney problems), increased cholesterol, weight gain, dehydration, muscle strain, pain in the muscles and joints, tendonitis, joint swelling, abnormal sensations, poor sleep, sinus congestion, shortness of breath or difficulty breathing, skin redness, itching, fatty liver, fever, fatigue (tiredness), painful inflammation of small pockets in the lining of your intestine (diverticulitis), viral infections, viral infections affecting the gut, some types of skin cancers (non-melanoma-types).

**Rare** (may affect up to 1 in 1,000 people): blood infection (sepsis), tuberculosis involving the brain and spinal cord, bones and other organs, and other unusual infections, joint infections.

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.
5. **How to store XELJANZ**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

Store in the original package in order to protect from moisture.

Do not use this medicine if you notice the tablets show visible signs of deterioration (for example, are broken or discoloured).

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. **Contents of the pack and other information**

**What XELJANZ contains**
- The active substance is tofacitinib.
- Each film-coated tablet contains 5 mg of tofacitinib (as tofacitinib citrate).
- The other ingredients are microcrystalline cellulose, lactose monohydrate (see section 2), croscarmellose sodium, magnesium stearate, hypromellose 6cP, titanium dioxide, macrogol 3350, and triacetin.

**What XELJANZ looks like and contents of the pack**
XELJANZ 5 mg film-coated tablet is white and round in appearance.

The tablets are provided in blisters containing 14 tablets. Each pack contains 56 or 182 tablets and each bottle contains 60 or 180 tablets.

Not all pack sizes may be marketed.

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