Product Information as approved by the CHMP on 14 November 2019, pending endorsement by the European Commission

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
XELJANZ 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

XELJANZ 5 mg film-coated tablets

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

Excipient with known effect
Each film-coated tablet contains 59.44 mg of lactose.

XELJANZ 10 mg film-coated tablets

Each film-coated tablet contains tofacitinib citrate, equivalent to 10 mg tofacitinib.

Excipient with known effect
Each film-coated tablet contains 118.88 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Tofacitinib 5 mg film-coated tablets

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

Tofacitinib 10 mg film-coated tablets

Blue, round tablet of 9.5 mm diameter, debossed “Pfizer” on one side and “JKI 10” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Rheumatoid arthritis

Tofacitinib 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. Tofacitinib 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

Tofacitinib 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).

Ulcerative colitis

Tofacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent (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 tofacitinib is indicated.

Posology

Rheumatoid arthritis and psoriatic arthritis

The recommended dose is 5 mg administered twice daily, which should not be exceeded.

Rheumatoid arthritis

Switching between tofacitinib 5 mg film-coated tablets and tofacitinib 11 mg prolonged-release tablets
Patients treated with tofacitinib 5 mg film-coated tablets twice daily may be switched to tofacitinib 11 mg prolonged-release tablets once daily on the day following the last dose of tofacitinib 5 mg film-coated tablets.

Patients treated with tofacitinib 11 mg prolonged-release tablets once daily may be switched to tofacitinib 5 mg film-coated tablets twice daily on the day following the last dose of tofacitinib 11 mg prolonged-release tablets.

Dose adjustment

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

Ulcerative colitis

Induction treatment
The recommended dose is 10 mg given orally twice daily for induction for 8 weeks ~~and 5 mg given twice daily for maintenance~~.

For patients who do not achieve adequate therapeutic benefit by week 8, the induction dose of 10 mg twice daily can be extended for an additional 8 weeks (16 weeks total), followed by 5 mg twice daily for maintenance. Tofacitinib induction therapy should be discontinued in any patient who shows no evidence of therapeutic benefit by week 16.

~~For some patients, such as those who have failed prior tumour necrosis factor (TNF) antagonist therapy, consideration should be given to continuation of the 10 mg twice daily dose for maintenance in order to maintain therapeutic benefit (see section 5.1).~~

~~Patients who experience a decrease in response on tofacitinib 5 mg twice daily maintenance therapy may benefit from an increase to tofacitinib 10 mg administered twice daily.~~
Maintenance treatment
The recommended dose for maintenance treatment is tofacitinib 5 mg given orally twice daily.

Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known venous thromboembolism (VTE) risk factors, unless there is no suitable alternative treatment available (see section 4.4 and 4.8).

For patients with UC who are not at increased risk for VTE (see section 4.4), tofacitinib 10 mg orally twice daily may be considered if the patient experiences a decrease in response on tofacitinib 5 mg twice daily and failed to respond to alternative treatment options for ulcerative colitis such as tumour necrosis factor inhibitor (TNF inhibitor) treatment. Tofacitinib 10 mg twice daily for maintenance treatment should be used for the shortest duration possible. The lowest effective dose needed to maintain response should be used.

In patients who have responded to treatment with tofacitinib, corticosteroids may be reduced and/or discontinued in accordance with standard of care.

Retreatment in UC
If therapy is interrupted, restarting treatment with tofacitinib can be considered. If there has been a loss of response, reinduction with tofacitinib 10 mg twice daily may be considered. The treatment interruption period in clinical studies extended up to 1 year. Efficacy may be regained by 8 weeks of 10 mg twice daily therapy (see section 5.1).

Dose interruption and discontinuation

Tofacitinib 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/mm^3.

Table 1: Low absolute lymphocyte count

Low absolute lymphocyte count (ALC) (see section 4.4)	
Lab value (cells/mm^3)	**Recommendation**
ALC greater than or equal to 750	Dose should be maintained.
ALC 500-750	For persistent (2 sequential values in this range on routine testing) decrease in this range, dosing should be reduced or interrupted until ALC is greater than 750. For patients receiving tofacitinib 10 mg twice daily, dosing should be reduced to tofacitinib 5 mg twice daily. For patients receiving tofacitinib 5 mg twice daily, dosing should be interrupted. When ALC is greater than 750, treatment should be resumed as clinically appropriate.
ALC less than 500	If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in patients with an absolute neutrophil count (ANC) less than 1,000 cells/mm^3.

Table 2: Low absolute neutrophil count

Low absolute neutrophil count (ANC) (see section 4.4)	
Lab Value (cells/mm^3)	**Recommendation**
ANC greater than 1,000	Dose should be maintained.
ANC 500-1,000	For persistent (2 sequential values in this range on routine testing) decreases in this range, dosing should be reduced or interrupted until ANC is greater than 1,000. For patients receiving tofacitinib 10 mg twice daily, dosing should be reduced to tofacitinib 5 mg twice daily. For patients receiving tofacitinib 5 mg twice daily, dosing should be interrupted. When ANC is greater than 1,000, treatment should be resumed as clinically appropriate.
ANC less than 500	If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.

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

Table 3: Low haemoglobin value

Low haemoglobin value (Section 4.4)	
Lab value (g/dL)	**Recommendation**
Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Dose should be maintained.
Greater than 2 g/dL decrease or less than 8.0 g/dL (confirmed by repeat testing)	Dosing should be interrupted until haemoglobin values have normalised.

Drug-drug interactions
Tofacitinib total daily dose should be reduced by half in patients receiving potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) and in patients receiving 1 or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g., fluconazole) (see section 4.5) as follows:

- Tofacitinib dose should be reduced to 5 mg once daily in patients receiving 5 mg twice daily.
- Tofacitinib dose should be reduced to 5 mg twice daily in patients receiving 10 mg twice daily.

Special populations

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

Hepatic impairment

Table 4: Dose adjustment for hepatic impairment

Hepatic impairment category	**Classification**	**Dose adjustment in hepatic impairment for different strength tablets**
Mild	Child Pugh A	No dose adjustment required.
Moderate	Child Pugh B	Dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal hepatic function is 5 mg twice daily. Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal hepatic function is 10 mg twice daily (see section 5.2).
Severe	Child Pugh C	Tofacitinib should not be used in patients with severe hepatic impairment (see section 4.3).

Renal impairment

Table 5: Dose adjustment for renal impairment

Renal impairment category	**Creatinine clearance**	**Dose adjustment in renal impairment for different strength tablets**
Mild	50-80 mL/min	No dose adjustment required.
Moderate	30-49 mL/min	No dose adjustment required.
Severe (including patients undergoing haemodialysis)	< 30 mL/min	Dose should be reduced to 5 mg once daily when the indicated dose in the presence of normal renal function is 5 mg twice daily. Dose should be reduced to 5 mg twice daily when the indicated dose in the presence of normal renal function is 10 mg twice daily. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis (see section 5.2).

Paediatric population
The safety and efficacy of tofacitinib in children aged 0 to less than 18 years have not been established.

No data are available.

Method of administration

Oral use.

Tofacitinib is given orally with or without food.

For patients who have difficulties swallowing, tofacitinib 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

Tofacitinib has not been studied and its use should be avoided in combination with biologics such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, selective co-stimulation modulators and potent immunosuppressants such as azathioprine, 6-mercaptopurine, 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 tofacitinib with MTX versus tofacitinib as monotherapy in RA clinical studies.

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

Venous thromboembolism (VTE)

Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), have been observed in patients taking tofacitinib. A dose dependent increased risk for VTE was observed in a clinical study with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

Tofacitnib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage.

Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable alternative treatment available (see section 4.2).

VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (BMI ≥30), diabetes, hypertension, smoking status should also be considered. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.

Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.

Serious infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving tofacitinib. The risk of opportunistic infections is higher in Asian geographic regions (see section 4.8). Rheumatoid arthritis patients taking corticosteroids may be predisposed to infection.

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

The risks and benefits of treatment should be considered prior to initiating tofacitinib 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~~.~~,
- who are over 65 years of age

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tofacitinib. 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 tofacitinib 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). In patients over 65 years of age tofacitinib should only be considered if no suitable alternative treatment is available (see section 5.1).

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 tofacitinib 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 tofacitinib.

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

Antituberculosis therapy should also be considered prior to administration of tofacitinib 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 tofacitinib. In patients treated with tofacitinib, the incidence of herpes zoster appears to be increased in:

- Japanese or Korean patients.
- Patients with an ALC less than 1,000 cells/mm^3 (see section 4.2).
- Patients with long standing RA who have previously received two or more biological disease modifying antirheumatic drugs (DMARDs).
- Patients treated with 10 mg twice daily.

The impact of tofacitinib 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 tofacitinib.

Malignancy and lymphoproliferative disorder

The risks and benefits of tofacitinib 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 tofacitinib in patients who develop a malignancy. The possibility exists for tofacitinib to affect host defences against malignancies.

Lymphomas have been observed in patients treated with tofacitinib. 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 tofacitinib 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 tofacitinib on the development and course of malignancies is not known.

Non-melanoma skin cancer

NMSCs have been reported in patients treated with tofacitinib. The risk of NMSC may be higher in patients treated with tofacitinib 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer (see Table 6 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 tofacitinib 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. Tofacitinib 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 tofacitinib should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care.

Liver enzymes

Treatment with tofacitinib 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 tofacitinib 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 tofacitinib 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 tofacitinib 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 tofacitinib 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 tofacitinib was associated with an increased incidence of neutropenia (less than 2,000 cells/mm^3) compared to placebo. It is not recommended to initiate tofacitinib 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 tofacitinib has been associated with decreases in haemoglobin levels. It is not recommended to initiate tofacitinib 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 tofacitinib 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 tofacitinib therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia. Increases in total and LDL cholesterol associated with tofacitinib may be decreased to pretreatment levels with statin therapy.

Vaccinations

Prior to initiating tofacitinib, 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 tofacitinib. The decision to use live vaccines prior to tofacitinib 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 tofacitinib 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 tofacitinib.

Excipients with known effect

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

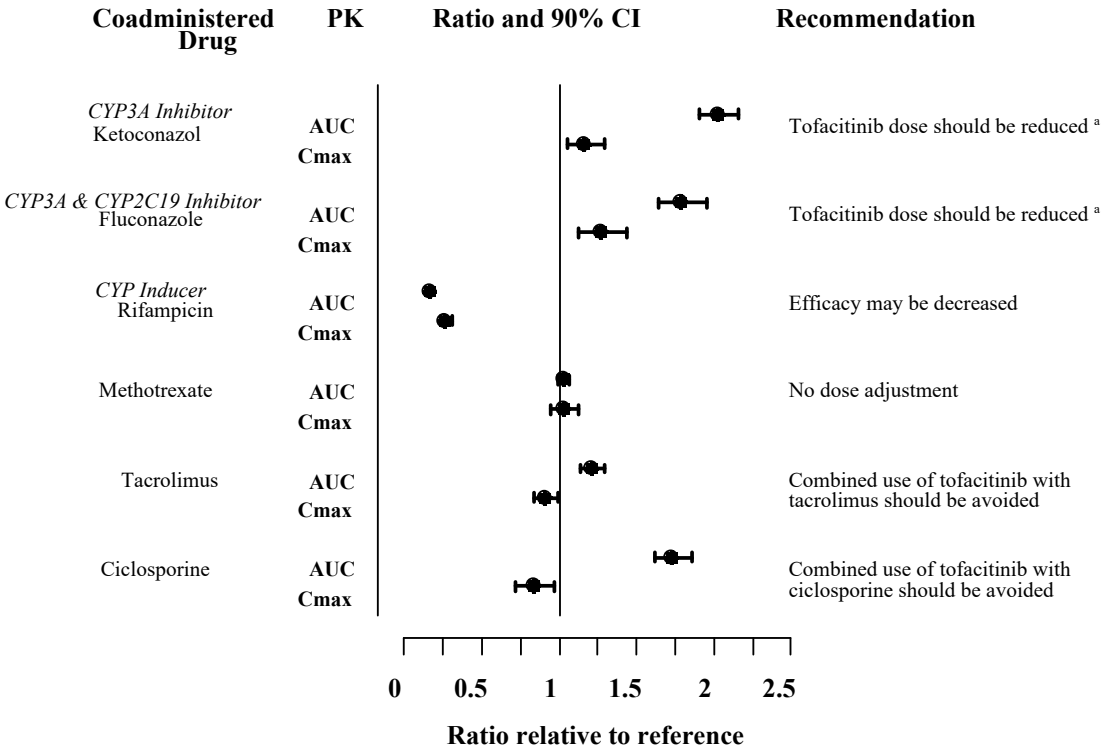
Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib

Since tofacitinib is metabolised by CYP3A4, interaction with medicinal products that inhibit or induce CYP3A4 is likely. Tofacitinib exposure is increased when coadministered with potent inhibitors of CYP3A4 (e.g., ketoconazole) or when administration of one or more concomitant medicinal products results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole) (see section 4.2).

Tofacitinib 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 tofacitinib.

Coadministration with ketoconazole (strong CYP3A4 inhibitor), fluconazole (moderate CYP3A4 and potent CYP2C19 inhibitor), tacrolimus (mild CYP3A4 inhibitor) and ciclosporine (moderate CYP3A4 inhibitor) increased tofacitinib AUC, while rifampicin (potent CYP inducer) decreased tofacitinib AUC. Coadministration of tofacitinib 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 tofacitinib is not recommended. Coadministration with ketoconazole and fluconazole increased tofacitinib C_{max}, while tacrolimus, ciclosporine and rifampicin decreased tofacitinib C_{max}. Concomitant administration with MTX 15-25 mg once weekly had no effect on the PK of tofacitinib in RA patients (see Figure 1).

Figure 1. Impact of other medicinal products on PK of tofacitinib



Note: Reference group is administration of tofacitinib alone.

[a] Tofacitinib dose should be reduced to 5 mg twice daily in patients receiving 10 mg twice daily. Tofacitinib dose should be reduced to 5 mg once daily in patients receiving 5 mg twice daily (see section 4.2).

Potential for tofacitinib to influence the PK of other medicinal products

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

In RA patients, coadministration of tofacitinib with MTX 15-25 mg once weekly decreased the AUC and C_{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.

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 tofacitinib 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 tofacitinib and for at least 4 weeks after the last dose.

Breast-feeding

It is not known whether tofacitinib 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 tofacitinib 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

Tofacitinib 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 most common serious adverse reactions were serious infections (see section 4.4). The most common serious infections reported with tofacitinib 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 tofacitinib. 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 6, 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 tofacitinib. The most common infections resulting in discontinuation of therapy were herpes zoster and pneumonia.

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

Ulcerative colitis
The most commonly reported adverse reactions in patients receiving tofacitinib 10 mg twice daily in the induction studies were headache, nasopharyngitis, nausea, and arthralgia.

In the induction and maintenance studies, across tofacitinib and placebo treatment groups, the most common categories of serious adverse reactions were gastrointestinal disorders and infections, and the most common serious adverse reaction was worsening of UC.

Overall, the safety profile observed in patients with UC treated with tofacitinib was consistent with the safety profile of tofacitinib in the RA indication.

Tabulated list of adverse reactions

The ADRs listed in the table below are from clinical studies in patients with RA, PsA, and UC 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 6: Adverse drug reactions

System organ class	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	Not known (cannot be estimated from the available data)
Infections and infestations	Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Nasopharyngitis Pharyngitis	Tuberculosis Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection	Sepsis Urosepsis Disseminated TB Necrotizing fasciitis Bacteraemia Staphylococcal bacteraemia *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal Pneumonia bacterial Encephalitis Atypical mycobacterial infection Cytomegalovirus infection Arthritis bacterial	Tuberculosis of central nervous system Meningitis cryptococcal *Mycobacterium avium* complex infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Non-melanoma skin cancers			
Blood and lymphatic system disorders	Anaemia	Leukopenia Lymphopenia Neutropenia			
Immune system disorders					Drug hypersensitivity* Angioedema* Urticaria*
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia Dehydration			
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache	Paraesthesia			
Vascular disorders	Hypertension	Venous thromboembolism**			
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea Sinus congestion			
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia				

System organ class	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	Not known (cannot be estimated from the available data)
Hepatobiliary disorders		Hepatic steatosis Hepatic enzyme increased Transaminases increased Liver function test abnormal Gamma glutamyl-transferase increased			
Skin and subcutaneous tissue disorders	Rash	Erythema Pruritus			
Musculoskeletal and connective tissue disorders	Arthralgia	Musculoskeletal pain Joint swelling Tendonitis			
General disorders and administration site conditions	Pyrexia Oedema peripheral Fatigue				
Investigations	Blood creatine phosphokinase increased	Blood creatinine increased Blood cholesterol increased Low density lipoprotein increased Weight increased			
Injury, poisoning and procedural complications		Ligament sprain Muscle strain			

*Spontaneous reporting data
**Venous thromboembolism includes PE and DVT

Description of selected adverse reactions

Venous thromboembolism

Rheumatoid arthritis
In a large, randomised post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors. The majority of these events were serious and some resulted in death. The incidence rates (95% CI) for PE for tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, and TNF inhibitors were 0.54 (0.32-0.87), 0.27 (0.12-0.52), and 0.09 (0.02-0.26) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for PE was 5.96 (1.75-20.33) and 2.99 (0.81-11.06) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily, respectively (see section 5.1).

In a subgroup analysis in patients with VTE risk factors in the above-mentioned study, the risk for PE was further increased. Compared with TNF inhibitors, the HR for PE was 9.14 (2.11-39.56) for tofacitinib 10 mg twice daily and 3.92 (0.83-18.48) for tofacitinib 5 mg twice daily.

Ulcerative colitis (UC)
In the UC ongoing extension trial, cases of PE and DVT have been observed in patients using tofacitinib 10 mg twice daily and with underlying VTE risk factor(s).

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) tofacitinib 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) tofacitinib 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 tofacitinib 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.

Ulcerative colitis
In the randomised 8-week Phase 2/3 induction studies, the proportions of patients with infections were 21.1% (198 patients) in the tofacitinib 10 mg twice daily group compared to 15.2% (43 patients) in the placebo group. In the randomised 52-week phase 3 maintenance study, the proportion of patients with infections were 35.9% (71 patients) in the 5 mg twice daily and 39.8% (78 patients) in the 10 mg twice daily tofacitinib groups, compared to 24.2% (48 patients) in the placebo group.

In the entire treatment experience with tofacitinib, the most commonly reported infection was nasopharyngitis, occurring in 18.2% of patients (211 patients).

In the entire treatment experience with tofacitinib, the overall incidence rate of infections was 60.3 events per 100 patient-years (involving 49.4% of patients; total 572 patients).

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 tofacitinib monotherapy group was 1.7 patients with events per 100 patient-years. In the 10 mg twice daily tofacitinib 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 tofacitinib 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 tofacitinib 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).

Ulcerative colitis
The incidence rates and types of serious infections in the UC clinical studies were generally similar to those reported in RA clinical studies with tofacitinib monotherapy treatment groups.

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 tofacitinib-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 tofacitinib 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/mm^3, or patients treated with 10 mg twice daily 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/mm^3 occurred in 0.3% of patients and for ALC between 500 and 750 cells/mm^3 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/mm^3 occurred in 1.3% of patients and for ALC between 500 and 750 cells/mm^3 in 8.4% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

Confirmed ALC less than 750 cells/mm^3 were associated with an increased incidence of serious infections (see section 4.4).

In the clinical studies in UC, changes in ALC observed with tofacitinib treatment were similar to the changes observed in clinical studies in RA.

Neutrophils
In the controlled RA clinical studies, confirmed decreases in ANC below 1,000 cells/mm^3 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/mm^3 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).

In the clinical studies in UC, changes in ANC observed with tofacitinib treatment were similar to the changes observed in clinical studies in RA.

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 tofacitinib, or reduction in tofacitinib 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, tofacitinib 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, tofacitinib 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, tofacitinib 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, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the controlled portion of the RA phase 3 studies on background DMARDs (0-3 months) (studies 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, tofacitinib 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, tofacitinib 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 tofacitinib 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 tofacitinib 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 clinical studies in UC, changes in liver enzyme tests observed with tofacitinib treatment were similar to the changes observed in clinical studies in RA.

Lipids
Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were first assessed at 1 month following initiation of tofacitinib 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 tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at month 12, and increased by 16% in the tofacitinib 5 mg twice daily arm and 19% in the tofacitinib 10 mg twice daily arm at month 24.
- Mean HDL cholesterol increased by 17% in the tofacitinib 5 mg twice daily arm and 18% in the tofacitinib 10 mg twice daily arm at month 12, and increased by 19% in the tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at month 24.

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

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

In an 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.

In the clinical studies in UC, changes in lipids observed with tofacitinib treatment were similar to the changes observed in clinical studies in RA.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 tofacitinib. 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 groups: Immunosuppressants, 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 tofacitinib 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 tofacitinib was associated with dose-dependent increases in B cell counts. Changes in circulating T-lymphocyte counts and T-lymphocyte subsets (CD3+, CD4+ and CD8+) were small and inconsistent.

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

Vaccine studies

In a controlled clinical trial of patients with RA initiating tofacitinib 10 mg twice daily or placebo, the number of responders to influenza vaccine was similar in both groups: tofacitinib (57%) and placebo (62%). For pneumococcal polysaccharide vaccine the number of responders was as follows: 32% in patients receiving both tofacitinib and MTX; 62% for tofacitinib 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 tofacitinib 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 tofacitinib 5 mg twice daily or placebo. Evidence of humoral and cell-mediated responses to VZV was observed in both tofacitinib 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. Tofacitinib 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 tofacitinib 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 7 provides information regarding the pertinent study design and population characteristics.

Table 7: Phase 3 clinical trials of tofacitinib 5 mg and 10 mg twice daily doses in patients with RA

Studies	Study I (ORAL Solo)	Study II (ORAL Sync)	Study III (ORAL Standard)	Study IV (ORAL Scan)	Study V (ORAL Step)	Study VI (ORAL Start)	Study VII (ORAL Strategy)
Population	DMARD-IR	DMARD-IR	MTX-IR	MTX-IR	TNFi-IR	MTX-naïve[a]	MTX-IR
Control	Placebo	Placebo	Placebo	Placebo	Placebo	MTX	MTX, ADA
Background treatment	None[b]	csDMARDs	MTX	MTX	MTX	None[b]	3 Parallel arms: • Tofacitinib monotherapy • Tofacitinib+MTX • ADA+MTX
Key features	Monotherapy	Various csDMARDs	Active control (ADA)	X-Ray	TNFi-IR	Monotherapy, Active comparator (MTX), X-Ray	Tofacitinib with and without MTX in comparison to ADA with MTX

Studies	Study I (ORAL Solo)	Study II (ORAL Sync)	Study III (ORAL Standard)	Study IV (ORAL Scan)	Study V (ORAL Step)	Study VI (ORAL Start)	Study VII (ORAL Strategy)
Number of patients treated	610	792	717	797	399	956	1,146
Total study duration	6 months	1 year	1 year	2 years	6 months	2 years	1 year
Co-primary efficacy endpoints[c]	Month 3: ACR20 HAQ-DI DAS28-4(ESR)<2.6	Month 6: ACR20 DAS28-4(ESR)<2.6 Month 3: HAQ-DI	Month 6: ACR20 DAS28-4(ESR)<2.6 Month 3: HAQ-DI	Month 6: ACR20 mTSS DAS28-4(ESR)<2.6 Month 3: HAQ-DI	Month 3: ACR20 HAQ-DI DAS28-4(ESR)<2.6	Month 6: mTSS ACR70	Month 6: ACR50
Time of mandatory placebo rescue to tofacitinib 5 or 10 mg twice daily	Month 3	Month 6 (placebo subjects with < 20% improvement in swollen and tender joint counts advanced to tofacitinib at month 3)			Month 3	NA	NA

[a.] ≤3 weekly doses (MTX-naïve).
[b.] Antimalarials were allowed.
[c.] Co-primary endpoints as follows: mean change from baseline in mTSS; percent of subjects achieving ACR20 or ACR70 responses; mean change from baseline in HAQ-DI; percent of subjects achieving a DAS28-4(ESR) <2.6 (remission).
mTSS=modified Total Sharp Score, ACR20(70)=American College of Rheumatology ≥20% (≥70%) improvement, DAS28=Disease Activity Score 28 joints, ESR=Erythrocyte Sedimentation Rate, HAQ-DI=Health Assessment Questionnaire Disability Index, DMARD=disease-modifying antirheumatic drug, IR=inadequate responder, csDMARD=conventional synthetic DMARD, TNFi=tumour necrosis factor inhibitor, NA=not applicable, ADA=adalimumab, MTX=methotrexate.

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, ORAL Start, and ORAL Strategy are shown in Table 8. In all studies, patients treated with either 5 mg 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.

Over the course of ORAL Strategy, responses with tofacitinib 5 mg twice daily + MTX were numerically similar compared to adalimumab 40 mg + MTX and both were numerically higher than tofacitinib 5 mg twice daily.

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 8: Proportion (%) of patients with an ACR response

ORAL Solo: DMARD inadequate responders				
Endpoint	**Time**	**Placebo N=122**	**Tofacitinib 5 mg twice daily monotherapy N=241**	**Tofacitinib 10 mg twice daily monotherapy N=243**
ACR20	Month 3	26	60***	65***
	Month 6	NA	69	71
ACR50	Month 3	12	31***	37***

	Month 6	NA	42	47
ACR70	Month 3	6	15*	20***
	Month 6	NA	22	29
ORAL Sync: DMARD inadequate responders				
Endpoint	**Time**	**Placebo + DMARD(s) N=158**	**Tofacitinib 5 mg twice daily + DMARD(s) N=312**	**Tofacitinib 10 mg twice daily + DMARD(s) N=315**
ACR20	Month 3	27	56***	63***
	Month 6	31	53***	57***
	Month 12	NA	51	56
ACR50	Month 3	9	27***	33***
	Month 6	13	34***	36***
	Month 12	NA	33	42
ACR70	Month 3	2	8**	14***
	Month 6	3	13***	16***
	Month 12	NA	19	25
ORAL Standard: MTX inadequate responders				
Endpoint	**Time**	**Placebo**	**Tofacitinib twice daily + MTX**	**Adalimumab 40 mg QOW + MTX**
		N=105	**5 mg N=198** / **10 mg N=197**	**N=199**
ACR20	Month 3	26	59***	57***	56***
	Month 6	28	51***	51***	46**
	Month 12	NA	48	49	48
ACR50	Month 3	7	33***	27***	24***
	Month 6	12	36***	34***	27**
	Month 12	NA	36	36	33
ACR70	Month 3	2	12**	15***	9*
	Month 6	2	19***	21***	9*
	Month 12	NA	22	23	17
ORAL Scan: MTX inadequate responders				
Endpoint	**Time**	**Placebo + MTX N=156**	**Tofacitinib 5 mg twice daily + MTX N=316**	**Tofacitinib 10 mg twice daily + MTX N=309**
ACR20	Month 3	27	55***	66***
	Month 6	25	50***	62***
	Month 12	NA	47	55
	Month 24	NA	40	50
ACR50	Month 3	8	28***	36***
	Month 6	8	32***	44***
	Month 12	NA	32	39
	Month 24	NA	28	40
ACR70	Month 3	3	10**	17***
	Month 6	1	14***	22***
	Month 12	NA	18	27
	Month 24	NA	17	26
ORAL Step: TNF Inhibitor inadequate responders				
Endpoint	**Time**	**Placebo + MTX N=132**	**Tofacitinib 5 mg twice daily + MTX N=133**	**Tofacitinib 10 mg twice daily + MTX N=134**
ACR20	Month 3	24	41*	48***

	Month 6	NA	51	54
ACR50	Month 3	8	26***	28***
	Month 6	NA	37	30
ACR70	Month 3	2	14***	10*
	Month 6	NA	16	16
ORAL Start: MTX-naïve				
Endpoint	**Time**	**MTX N=184**	**Tofacitinib 5 mg twice daily monotherapy N=370**	**Tofacitinib 10 mg twice daily monotherapy N=394**
ACR20	Month 3	52	69***	77***
	Month 6	51	71***	75***
	Month 12	51	67**	71***
	Month 24	42	63***	64***
ACR50	Month 3	20	40***	49***
	Month 6	27	46***	56***
	Month 12	33	49**	55***
	Month 24	28	48***	49***
ACR70	Month 3	5	20***	26***
	Month 6	12	25***	37***
	Month 12	15	28**	38***
	Month 24	15	34***	37***
ORAL Strategy: MTX inadequate responders				
Endpoint	**Time**	**Tofacitinib 5 mg twice daily N=384**	**Tofacitinib 5 mg twice daily + MTX N=376**	**Adalimumab + MTX N=386**
ACR20	Month 3	62.50	70.48ǂ	69.17
	Month 6	62.84	73.14ǂ	70.98
	Month 12	61.72	70.21ǂ	67.62
ACR50	Month 3	31.51	40.96ǂ	37.31
	Month 6	38.28	46.01ǂ	43.78
	Month 12	39.31	47.61ǂ	45.85
ACR70	Month 3	13.54	19.41ǂ	14.51
	Month 6	18.23	25.00ǂ	20.73
	Month 12	21.09	28.99ǂ	25.91

*p<0.05
**p<0.001
***p<0.0001 verses placebo (versus MTX for ORAL Start)
ǂp<0.05 – tofacitinib 5 mg + MTX versus tofacitinib 5 mg for ORAL Strategy (normal p-values without multiple comparison adjustment)
QOW=every other week, N=number of subjects analysed, ACR20/50/70=American College of Rheumatology ≥20, 50, 70% improvement, NA=not applicable, MTX=methotrexate.

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 9.

Table 9: Number (%) of subjects achieving DAS28-4(ESR) < 2.6 remission at months 3 and 6

	Time Point	N	%
ORAL Step: TNF Inhibitor inadequate responders			
Tofacitinib 5 mg twice daily + MTX	Month 3	133	6
Tofacitinib 10 mg twice daily + MTX	Month 3	134	8*
Placebo + MTX	Month 3	132	2
ORAL Sync: DMARD inadequate responders			
Tofacitinib 5 mg twice daily	Month 6	312	8*
Tofacitinib 10 mg twice daily	Month 6	315	11***
Placebo	Month 6	158	3
ORAL Standard: MTX inadequate responders			
Tofacitinib 5 mg twice daily + MTX	Month 6	198	6*
Tofacitinib 10 mg twice daily + MTX	Month 6	197	11***
Adalimumab 40 mg SC QOW + MTX	Month 6	199	6*
Placebo + MTX	Month 6	105	1

*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 10, 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 10: Radiographic changes at months 6 and 12

	ORAL Scan: MTX inadequate responders				
	Placebo + MTX N=139 Mean (SD)[a]	**Tofacitinib 5 mg twice daily + MTX N=277 Mean (SD)[a]**	**Tofacitinib 5 mg twice daily + MTX Mean difference from placebo[b] (CI)**	**Tofacitinib 10 mg twice daily + MTX N=290 Mean (SD)[a]**	**Tofacitinib 10 mg twice daily + MTX Mean difference from placebo[b] (CI)**
mTSS[c]					
Baseline	33 (42)	31 (48)	-	37 (54)	-
Month 6	0.5 (2.0)	0.1 (1.7)	-0.3 (-0.7, 0.0)	0.1 (2.0)	-0.4 (-0.8, 0.0)
Month 12	1.0 (3.9)	0.3 (3.0)	-0.6 (-1.3, 0.0)	0.1 (2.9)	-0.9 (-1.5, -0.2)
	ORAL Start: MTX-naïve				
	MTX N=168 Mean (SD)[a]	**Tofacitinib 5 mg twice daily N=344 Mean (SD)[a]**	**Tofacitinib 5 mg twice daily Mean difference from MTX[d] (CI)**	**Tofacitinib 10 mg twice daily N=368 Mean (SD)[a]**	**Tofacitinib 10 mg twice daily Mean difference from MTX[d] (CI)**
mTSS[c]					
Baseline	16 (29)	20 (41)	-	19 (39)	-
Month 6	0.9 (2.7)	0.2 (2.3)	-0.7 (-1.0, -0.3)	0.0 (1.2)	-0.8 (-1.2, -0.4)
Month 12	1.3 (3.7)	0.4 (3.0)	-0.9 (-1.4, -0.4)	0.0 (1.5)	-1.3 (-1.8, -0.8)

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

Physical function response and health-related outcomes

Tofacitinib, 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 11.

Table 11: LS mean change from baseline in HAQ-DI at month 3

	Placebo + MTX	**Tofacitinib 5 mg twice daily + MTX**	**Tofacitinib 10 mg twice daily + MTX**	**Adalimumab 40 mg QOW + MTX**
ORAL Standard: MTX inadequate responders				
N=96		**N=185**	**N=183**	**N=188**
-0.24		-0.54***	-0.61***	-0.50***
ORAL Step: TNF inhibitor inadequate responders				
N=118		**N=117**	**N=125**	NA
-0.18		-0.43***	-0.46***	NA
Placebo + DMARD(s)		**Tofacitinib 5 mg twice daily + DMARD(s)**	**Tofacitinib 10 mg twice daily + DMARD(s)**	
ORAL Sync: DMARD inadequate responders				
N=147		**N=292**	**N=292**	NA
-0.21		-0.46***	-0.56***	NA

*** p<0.0001, tofacitinib versus placebo + MTX, LS = least squares, N = number of patients, QOW = every other week, NA = not applicable, HAQ-DI = Health Assessment Questionnaire Disability Index

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.

Long-term controlled safety data

Study ORAL Surveillance (A3921133) is a large (N=4362), ongoing, randomised active-controlled post-authorisation safety surveillance study of rheumatoid arthritis patients who were at least 50 years of age and older and had at least one cardiovascular risk factor (CV risk factors defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g. nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations).

Patients were randomised to open-label tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, or a TNF inhibitor (TNF inhibitor was either etanercept 50 mg once weekly or adalimumab 40 mg every other week) in a 1:1:1 ratio. The co-primary endpoints are adjudicated malignancy (excluding NMSC) and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessment of endpoints are blinded. The study is an event-powered study that also requires at least 1500 patients to be followed for 3 years. The study treatment of tofacitinib 10 mg twice daily has been stopped and patients were switched to 5 mg twice daily because of a dose-dependent signal of venous thromboembolic events (VTE).

Venous thromboembolism (VTE)
In an interim analysis of study A3921133, an increased and dose-dependent incidence of VTE was observed in patients treated with tofacitinib compared to TNF inhibitors (see section 4.8). The majority of these events were serious and some cases of PE resulted in death. The incidence rates (95% CI) for PE for tofacitinib 10 mg twice daily, 5 mg twice daily, and TNF inhibitors were 0.54 (0.32-0.87), 0.27 (0.12-0.52), and 0.09 (0.02-0.26) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the HR for PE with tofacitinib 10 mg twice daily was 5.96 (1.75-20.33), and for 5 mg twice daily the HR was 2.99 (0.81-11.06). The incidence rates (95% CI) for DVT for tofacitinib 10 mg twice daily, 5 mg twice daily, and TNF inhibitors were 0.38

(0.20-0.67), 0.30 (0.14-0.55), and 0.18 (0.07-0.39) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the HR for DVT with tofacitinib 10 mg twice daily was 2.13 (0.80-5.69), and for 5 mg twice daily the HR was 1.66 (0.60-4.57).

Mortality
In an interim analysis of study A3921133, increased mortality within 28 days of last treatment was observed in patients treated with tofacitinib compared to TNF inhibitors. The incidence rates (95% CI) were 0.89 (0.59-1.29) for tofacitinib 10 mg twice daily, 0.57 (0.34-0.89) for tofacitinib 5 mg twice daily, and 0.27 (0.12-0.51) for TNF-inhibitors; with a HR (95% CI) of 3.28 (1.55-6.95) for tofacitinib 10 mg twice daily and of 2.11 (0.96-4.67) for tofacitinib 5 mg twice daily, versus TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies.

For cardiovascular mortality within 28 days of last treatment, the incidence rates (95% CI) per 100 patients-years were 0.45 (0.24-0.75) for tofacitinib 10 mg twice daily, 0.24 (0.10-0.47) for tofacitinib 5 mg twice daily, and 0.21 (0.08-0.43) for TNF inhibitors; with an incident rate ratio (IRR) (95% CI) of 2.12 (0.80-6.20) for tofacitinib 10 mg twice daily and of 1.14 (0.36-3.70) for tofacitinib 5 mg twice daily, versus TNF inhibitors.

For fatal infections within 28 days of last treatment, the incidence rates per 100 patient-years (95% CI) were 0.22 (0.09-0.46), 0.18 (0.07-0.39), and 0.06 (0.01-0.22) for tofacitinib 10 mg twice daily and 5 mg twice daily, and TNF inhibitors, respectively; with an IRR (95% CI) of 3.70 (0.71-36.5) for 10 mg twice daily and of 3.00 (0.54-30.4) for tofacitinib 5 mg twice daily, versus TNF inhibitors.

Serious infections
For non-fatal serious infections, the incidence rates (95% CI) per 100 patient-years were 3.51 (2.93-4.16), 3.35 (2.78-4.01), and 2.79 (2.28-3.39), for tofacitinib 10 mg and 5 mg twice daily and TNF inhibitors, respectively. The risk of serious (fatal and non-fatal) infections was further increased in patients over 65 years of age, as compared to younger patients in study A3921133.

Psoriatic arthritis
The efficacy and safety of tofacitinib 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 sulfasalazine, 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 tofacitinib received 5 mg twice daily or tofacitinib 10 mg twice daily for 12 months. Patients randomised to placebo were advanced in a blinded manner at month 3 to either tofacitinib 5 mg twice daily or tofacitinib 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 sulfasalazine, 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 tofacitinib received 5 mg twice daily or tofacitinib 10 mg twice daily for 6 months. Patients randomised to

placebo were advanced in a blinded manner at month 3 to either tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily and received treatment until month 6.

Signs and symptoms
Treatment with tofacitinib 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 12.

Table 12: Proportion (%) of PsA patients who achieved clinical response and mean change from baseline in OPAL BROADEN and OPAL BEYOND studies

	Conventional synthetic DMARD inadequate responders[a] (TNFi-Naïve)			**TNFi inadequate responders[b]**	
	OPAL BROADEN			**OPAL BEYOND[c]**	
Treatment group	**Placebo**	**Tofacitinib 5 mg twice daily**	**Adalimumab 40 mg SC q2W**	**Placebo**	**Tofacitinib 5 mg twice daily**
N	105	107	106	131	131
ACR20					
Month 3	33%	50%[d,*]	52%[*]	24%	50%[d,***]
Month 6	NA	59%	64%	NA	60%
Month 12	NA	68%	60%	-	-
ACR50					
Month 3	10%	28%[e,**]	33%[***]	15%	30%[e,*]
Month 6	NA	38%	42%	NA	38%
Month 12	NA	45%	41%	-	-
ACR70					
Month 3	5%	17%[e,*]	19%[*]	10%	17%
Month 6	NA	18%	30%	NA	21%
Month 12	NA	23%	29%	-	-
ΔLEI[f]					
Month 3	-0.4	-0.8	-1.1[*]	-0.5	-1.3[*]
Month 6	NA	-1.3	-1.3	NA	-1.5
Month 12	NA	-1.7	-1.6	-	-
ΔDSS[f]					
Month 3	-2.0	-3.5	-4.0	-1.9	-5.2[*]
Month 6	NA	-5.2	-5.4	NA	-6.0
Month 12	NA	-7.4	-6.1	-	-
PASI75[g]					
Month 3	15%	43%[d,***]	39%[**]	14%	21%
Month 6	NA	46%	55%	NA	34%
Month 12	NA	56%	56%	-	-

[*] Nominal p≤0.05; [**] Nominal p<0.001; [***] Nominal p<0.0001 for active treatment versus placebo at month 3.
Abbreviations: BSA=body surface area; ΔLEI=change from baseline in Leeds Enthesitis Index; ΔDSS=change from baseline in Dactylitis Severity Score; ACR20/50/70=American College of Rheumatology ≥ 20%, 50%, 70% improvement; csDMARD=conventional synthetic disease-modifying antirheumatic drug; N=number of randomised and treated patients; NA=Not applicable, as data for placebo treatment is not available beyond month 3 due to placebo advanced to tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily; SC q2w=subcutaneously once every 2 weeks; TNFi=tumour necrosis factor inhibitor; PASI=Psoriasis Area and Severity index; PASI75=≥ 75% improvement in PASI.

[a] Inadequate response to at least 1 csDMARD due to lack of efficacy and/or intolerability.
[b] Inadequate response to a least 1 TNFi due to lack of efficacy and/or intolerability.
[c] OPAL BEYOND had a duration of 6 months.
[d] Achieved statistical significance globally at p≤ 0.05 per the pre-specified step-down testing procedure.
[e] Achieved statistical significance within the ACR family (ACR50 and ACR70) at p≤ 0.05 per the pre-specified step-down testing procedure.
[f] For patients with Baseline score > 0.
[g] For patients with Baseline BSA ≥ 3% and PASI > 0.

Both TNF inhibitor naïve and TNF inhibitor inadequate responder tofacitinib 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 tofacitinib. 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 tofacitinib 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 tofacitinib 5 mg BID, adalimumab and placebo treated patients, respectively (tofacitinib 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 tofacitinib 5 mg BID and placebo treated patients, respectively, however tofacitinib 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 tofacitinib 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 tofacitinib 5 mg twice daily demonstrated greater improvement ($p \leq 0.05$) from baseline in physical functioning compared to placebo at month 3 (see Table 13).

Table 13: Change from baseline in HAQ-DI in PsA studies OPAL BROADEN and OPAL BEYOND

	Least squares mean change from baseline in HAQ-DI				
	Conventional synthetic DMARD inadequate responders[a] (TNFi-naïve)			**TNFi inadequate responders[b]**	
	OPAL BROADEN			**OPAL BEYOND**	
Treatment group	**Placebo**	**Tofacitinib 5 mg twice daily**	**Adalimumab 40 mg SC q2W**	**Placebo**	**Tofacitinib 5 mg twice daily**
N	104	107	106	131	129
Month 3	-0.18	-0.35[c,*]	-0.38[*]	-0.14	-0.39[c,***]
Month 6	NA	-0.45	-0.43	NA	-0.44
Month 12	NA	-0.54	-0.45	NA	NA

[*] Nominal $p \leq 0.05$; [***] Nominal $p < 0.0001$ for active treatment versus placebo at month 3.
Abbreviations: DMARD=disease-modifying antirheumatic drug; HAQ-DI=Health Assessment Questionnaire Disability Index; N=total number of patients in the statistical analysis; SC q2w=subcutaneously once every 2 weeks; TNFi=tumour necrosis factor inhibitor.
[a] Inadequate response to at least one conventional synthetic DMARD (csDMARD) due to lack of efficacy and/or intolerability.
[b] Inadequate response to a least one TNF inhibitor (TNFi) due to lack of efficacy and/or intolerability.
[c] Achieved statistical significance globally at $p \leq 0.05$ 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 tofacitinib 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 tofacitinib 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 $p \leq 0.05$). 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 tofacitinib 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 $p \leq 0.05$).

Ulcerative colitis
The efficacy and safety of tofacitinib for the treatment of adult patients with moderately to severely active UC (Mayo score 6 to 12 with endoscopy subscore ≥ 2 and rectal bleeding subscore ≥ 1) were assessed in 3 multicentre, double-blind, randomised, placebo-controlled studies: 2 identical induction studies (OCTAVE Induction 1 and OCTAVE Induction 2) followed by 1 maintenance study (OCTAVE Sustain). Enrolled patients had failed at least 1 conventional therapy, including corticosteroids, immunomodulators, and/or a TNF inhibitor. Concomitant stable doses of oral aminosalicylates and corticosteroids (prednisone or equivalent daily dose up to 25 mg) were permitted with taper of corticosteroids to discontinuation mandated within 15 weeks of entering the maintenance study. Tofacitinib was administered as monotherapy (i.e., without concomitant use of biologics and immunosuppressants) for UC.

Table 14 provides additional information regarding pertinent study design and population characteristics.

Table 14: Phase 3 clinical studies of tofacitinib 5 mg and 10 mg twice daily doses in patients with UC

	OCTAVE Induction 1	**OCTAVE Induction 2**	**OCTAVE Sustain**
Treatment groups (randomisation ratio)	**Tofacitinib 10 mg twice daily placebo (4:1)**	**Tofacitinib 10 mg twice daily placebo (4:1)**	**Tofacitinib 5 mg twice daily Tofacitinib 10 mg twice daily placebo (1:1:1)**
Number of patients enrolled	598	541	593
Study duration	8 weeks	8 weeks	52 weeks
Primary efficacy endpoint	Remission	Remission	Remission
Key secondary efficacy endpoints	Improvement of endoscopic appearance of the mucosa	Improvement of endoscopic appearance of the mucosa	Improvement of endoscopic appearance of the mucosa Sustained corticosteroid-free remission among patients in remission at baseline
Prior TNFi failure	51.3%	52.1%	44.7%
Prior corticosteroid failure	74.9%	71.3%	75.0%
Prior immunosuppressant failure	74.1%	69.5%	69.6%
Baseline corticosteroid use	45.5%	46.8%	50.3%

Abbreviations: TNFi=tumour necrosis factor inhibitor; UC=ulcerative colitis.

In addition, safety and efficacy of tofacitinib were assessed in an open-label long-term extension study (OCTAVE Open). Patients who completed 1 of the induction studies (OCTAVE Induction 1 or OCTAVE Induction 2) but did not achieve clinical response or patients who completed or withdrew early due to treatment failure in the maintenance study (OCTAVE Sustain) were eligible for OCTAVE Open. Patients from OCTAVE Induction 1 or OCTAVE Induction 2 who did not achieve clinical response after 8 weeks in OCTAVE Open were to be discontinued from OCTAVE Open. Corticosteroid tapering was also required upon entrance into OCTAVE Open.

Induction efficacy data (OCTAVE Induction 1 and OCTAVE Induction 2)
The primary endpoint of OCTAVE Induction 1 and OCTAVE Induction 2 was the proportion of patients in remission at week 8, and the key secondary endpoint was the proportion of patients with improvement of endoscopic appearance of the mucosa at week 8. Remission was defined as clinical remission (a total Mayo score ≤ 2 with no individual subscore > 1) and rectal bleeding subscore of 0. Improvement of endoscopic appearance of the mucosa was defined as endoscopy subscore of 0 or 1.

A significantly greater proportion of patients treated with tofacitinib 10 mg twice daily achieved remission, improvement of endoscopic appearance of the mucosa, and clinical response at week 8 compared to placebo in both studies, as shown in Table 15.

The efficacy results based on the endoscopic readings at the study sites were consistent with the results based on the central endoscopy readings.

Table 15: Proportion of patients meeting efficacy endpoints at week 8 (OCTAVE induction study 1 and OCTAVE induction study 2)

	OCTAVE induction study 1			
	Central endoscopy read		**Local endoscopy read**	
Endpoint	**Placebo**	**Tofacitinib 10 mg twice daily**	**Placebo**	**Tofacitinib 10 mg twice daily**
	N=122	**N=476**	**N=122**	**N=476**
Remission[a]	8.2%	18.5%‡	11.5%	24.8%‡
Improvement of endoscopic appearance of the mucosa[b]	15.6%	31.3%†	23.0%	42.4%*
Normalisation of endoscopic appearance of the mucosa[c]	1.6%	6.7%‡	2.5%	10.9%‡
Clinical response[d]	32.8%	59.9%*	34.4%	60.7%*
	OCTAVE induction study 2			
	Central endoscopy read		**Local endoscopy read**	
Endpoint	**Placebo**	**Tofacitinib 10 mg twice daily**	**Placebo**	**Tofacitinib 10 mg twice daily**
	N=112	**N=429**	**N=112**	**N=429**
Remission[a]	3.6%	16.6%†	5.4%	20.7%†
Improvement of endoscopic appearance of the mucosa[b]	11.6%	28.4%†	15.2%	36.4%*
Normalisation of endoscopic appearance of the mucosa[c]	1.8%	7.0%‡	0.0%	9.1%‡
Clinical response[d]	28.6%	55.0%*	29.5%	58.0%*

* p<0.0001; † p<0.001; ‡ p<0.05.
N=number of patients in the analysis set.

a. Primary endpoint: Remission was defined as clinical remission (a Mayo score ≤ 2 with no individual subscore > 1) and rectal bleeding subscore of 0.
b. Key secondary endpoint: Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).
c. Normalisation of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0.
d. Clinical response was defined as a decrease from baseline in Mayo score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the subscore for rectal bleeding of ≥ 1 point or absolute subscore for rectal bleeding of 0 or 1.

In both subgroups of patients with or without prior TNF inhibitor failure, a greater proportion of patients treated with tofacitinib 10 mg twice daily achieved remission and improvement of endoscopic appearance of the mucosa at week 8 as compared to placebo. This treatment difference was consistent between the 2 subgroups (Table 16).

Table 16. Proportion of patients meeting primary and key secondary efficacy endpoints at week 8 by TNF inhibitor therapy subgroups (OCTAVE induction study 1 and OCTAVE induction study 2, central endoscopy read)

OCTAVE induction study 1		
Endpoint	**Placebo N=122**	**Tofacitinib 10 mg twice daily N=476**
Remission[a]		
With prior TNF inhibitor failure	1.6% (1/64)	11.1% (27/243)
Without prior TNF inhibitor failure[b]	15.5% (9/58)	26.2% (61/233)
Improvement of endoscopic appearance of the mucosa[c]		
With prior TNF inhibitor failure	6.3% (4/64)	22.6% (55/243)
Without prior TNF inhibitor failure[b]	25.9% (15/58)	40.3% (94/233)
OCTAVE induction study 2		
Endpoint	**Placebo N=112**	**Tofacitinib 10 mg twice daily N=429**
Remission[a]		
With prior TNF inhibitor failure	0.0% (0/60)	11.7% (26/222)
Without prior TNF inhibitor failure[b]	7.7% (4/52)	21.7% (45/207)
Improvement of endoscopic appearance of the mucosa[c]		
With prior TNF inhibitor failure	6.7% (4/60)	21.6% (48/222)
Without prior TNF inhibitor failure[b]	17.3% (9/52)	35.7% (74/207)

TNF=tumour necrosis factor; N=number of patients in the analysis set.

a. Remission was defined as clinical remission (a Mayo score ≤ 2 with no individual subscore > 1) and rectal bleeding subscore of 0.

b. Included TNF Inhibitor naïve patients

c. Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).

As early as week 2, the earliest scheduled study visit, and at each visit thereafter, significant differences were observed between tofacitinib 10 mg twice daily and placebo in the change from baseline in rectal bleeding and stool frequency, and partial Mayo score.

Maintenance (OCTAVE Sustain)

Patients who completed 8 weeks in 1 of the induction studies and achieved clinical response were re-randomised into OCTAVE Sustain; 179 out of 593 (30.2%) patients were in remission at baseline of OCTAVE Sustain.

The primary endpoint in OCTAVE Sustain was the proportion of patients in remission at week 52. The 2 key secondary endpoints were the proportion of patients with improvement of endoscopic appearance at week 52, and the proportion of patients with sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline of OCTAVE Sustain.

A significantly greater proportion of patients in both the tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily treatment groups achieved the following endpoints at week 52 as compared to placebo: remission, improvement of endoscopic appearance of the mucosa, normalisation of endoscopic appearance of the mucosa, maintenance of clinical response, remission among patients in remission at baseline, and sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline, as shown in Table 17.

Table 17: Proportion of patients meeting efficacy endpoints at week 52 (OCTAVE sustain)

	Central endoscopy read			Local endoscopy read		
Endpoint	**Placebo N=198**	**Tofacitinib 5 mg twice daily N=198**	**Tofacitinib 10 mg twice daily N=197**	**Placebo N=198**	**Tofacitinib 5 mg twice daily N=198**	**Tofacitinib 10 mg twice daily N=197**
Remission[a]	11.1%	34.3%*	40.6%*	13.1%	39.4%*	47.7%*
Improvement of endoscopic appearance of the mucosa[b]	13.1%	37.4%*	45.7%*	15.7%	44.9%*	53.8%*
Normalisation of endoscopic appearance of the mucosa[c]	4.0%	14.6%**	16.8%*	5.6%	22.2%*	29.4%*
Maintenance of clinical response[d]	20.2%	51.5%*	61.9%*	20.7%	51.0%*	61.4%*
Remission among patients in remission at baseline[a,f]	10.2%	46.2%*	56.4%*	11.9%	50.8%*	65.5%*
Sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline[e,f]	5.1%	35.4%*	47.3%*	11.9%	47.7%*	58.2%*
Corticosteroid-free remission among patients taking corticosteroids at baseline[a,g]	10.9%	27.7%†	27.6%†	13.9%	32.7%†	31.0%†

* p<0.0001; **p<0.001; †p<0.05 for tofacitinib versus placebo.
N=number of patients in the analysis set.

a. Remission was defined as clinical remission (a Mayo score ≤ 2 with no individual subscore > 1) and rectal bleeding subscore of 0.
b. Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).
c. Normalisation of endoscopic appearance of the mucosa was defined as a Mayo endoscopic subscore of 0.
d. Maintenance of clinical response was defined by a decrease from the induction study (OCTAVE Induction 1, OCTAVE Induction 2) baseline Mayo score of ≥ 3 points and ≥ 30%, with an accompanying decrease in the rectal bleeding subscore of ≥ 1 point or rectal bleeding subscore of 0 or 1. Patients were to be in clinical response at baseline of the maintenance study OCTAVE Sustain.
e. Sustained corticosteroid-free remission was defined as being in remission and not taking corticosteroids for at least 4 weeks prior to the visit at both week 24 and week 52.
f. N=59 for placebo, N=65 for tofacitinib 5 mg twice daily, N=55 for tofacitinib 10 mg twice daily.
g. N=101 for placebo, N=101 for tofacitinib 5 mg twice daily, N=87 for tofacitinib 10 mg twice daily.

In both subgroups of patients with or without prior TNF inhibitor failure, a greater proportion of patients treated with either tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily achieved the following endpoints at week 52 of OCTAVE Sustain as compared to placebo: remission, improvement

of endoscopic appearance of the mucosa, or sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline (Table 18). This treatment difference from placebo was similar between tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily in the subgroup of patients without prior TNF inhibitor failure. In the subgroup of patients with prior TNF inhibitor failure, the observed treatment difference from placebo was numerically greater for tofacitinib 10 mg twice daily than tofacitinib 5 mg twice daily by 9.7 to 16.7 percentage points across the primary and key secondary endpoints.

Table 18: Proportion of patients meeting primary and key secondary efficacy endpoints at week 52 by TNF inhibitor therapy subgroup (OCTAVE sustain, central endoscopy read)

Endpoint	**Placebo N=198**	**Tofacitinib 5 mg twice daily N=198**	**Tofacitinib 10 mg twice daily N=197**
Remission[a]			
With prior TNF inhibitor failure	10/89 (11.2%)	20/83 (24.1%)	34/93 (36.6%)
Without prior TNF inhibitor failure[b]	12/109 (11.0%)	48/115 (41.7%)	46/104 (44.2%)
Improvement of endoscopic appearance of the mucosa[c]			
With prior TNF inhibitor failure	11/89 (12.4%)	25/83 (30.1%)	37/93 (39.8%)
Without prior TNF inhibitor failure[b]	15/109 (13.8%)	49/115 (42.6%)	53/104 (51.0%)
Sustained corticosteroid-free remission at both week 24 and week 52 among patients in remission at baseline[d]			
With prior TNF inhibitor failure	1/21 (4.8%)	4/18 (22.2%)	7/18 (38.9%)
Without prior TNF inhibitor failure[b]	2/38 (5.3%)	19/47 (40.4%)	19/37 (51.4%)

TNF=tumour necrosis factor; N=number of patients in the analysis set.

a. Remission was defined as clinical remission (a Mayo score ≤ 2 with no individual subscore > 1) and rectal bleeding subscore of 0.

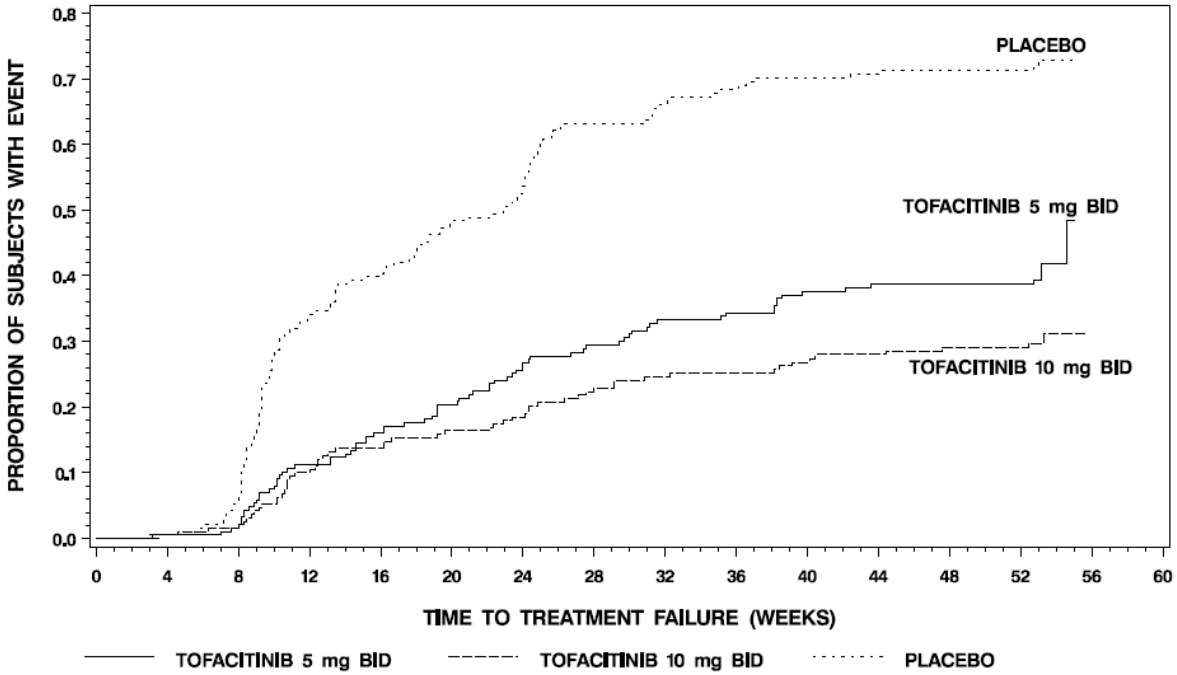
b. Included TNF Inhibitor naïve patients.

c. Improvement of endoscopic appearance of the mucosa was defined as Mayo endoscopy subscore of 0 (normal or inactive disease) or 1 (erythema, decreased vascular pattern).

d. Sustained corticosteroid-free remission was defined as being in remission and not taking corticosteroids for at least 4 weeks prior to the visit at both week 24 and week 52.

The proportion of patients in both tofacitinib groups who had treatment failure was lower compared to placebo at each time point as early as week 8, the first time point where treatment failure was assessed, as shown in Figure 2.

Figure 2. Time to treatment failure in maintenance study OCTAVE sustain (Kaplan-Meier Curves)



p<0.0001 for tofacitinib 5 mg twice daily versus placebo.
p<0.0001 for tofacitinib 10 mg twice daily versus placebo.
BID=twice daily.
Treatment failure was defined as an increase in Mayo score of ≥ 3 points from maintenance study baseline, accompanied by an increase in rectal bleeding subscore by ≥ 1 point, and an increase of endoscopic subscore of ≥ 1 point yielding an absolute endoscopic subscore of ≥ 2 after a minimum treatment of 8 weeks in the study.

Health-related and quality of life outcomes

Tofacitinib 10 mg twice daily demonstrated greater improvement from baseline compared to placebo in physical component summary (PCS) and mental component summary (MCS) scores, and in all 8 domains of the SF-36 in the induction studies (OCTAVE Induction 1, OCTAVE Induction 2). In the maintenance study (OCTAVE Sustain), tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily demonstrated greater maintenance of improvement compared to placebo in PCS and MCS scores, and in all 8 domains of the SF-36 at week 24 and week 52.

Tofacitinib 10 mg twice daily demonstrated greater improvement from baseline compared to placebo at week 8 in the total and all 4 domain scores of the Inflammatory Bowel Disease Questionnaire (IBDQ) (bowel symptoms, systemic function, emotional function, and social function) in the induction studies (OCTAVE Induction 1, OCTAVE Induction 2). In the maintenance study (OCTAVE Sustain), tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily demonstrated greater maintenance of improvement compared to placebo in the total and all 4 domain scores of the IBDQ at week 24 and week 52.

Improvements were also observed in the EuroQoL 5-Dimension (EQ-5D) and various domains of the Work Productivity and Activity Impairment (WPAI-UC) questionnaire in both induction and maintenance studies compared to placebo.

Open-label extension study (OCTAVE Open)

Patients who did not achieve clinical response in one of the induction studies (OCTAVE Induction 1 or OCTAVE Induction 2) after 8 weeks of tofacitinib 10 mg twice daily were allowed to enter an open-label extension study (OCTAVE Open). After an additional 8 weeks of tofacitinib 10 mg twice daily in OCTAVE Open, 53% (154/293) patients achieved clinical response and 14% (42/293) patients achieved remission.

Patients who achieved clinical response in 1 of the induction studies (OCTAVE Induction 1 or OCTAVE Induction 2) with tofacitinib 10 mg twice daily but experienced treatment failure after their dose was reduced to tofacitinib 5 mg twice daily or following treatment interruption in OCTAVE Sustain (i.e., were randomised to placebo), had their dose increased to tofacitinib 10 mg twice daily in OCTAVE Open. After 8 weeks on tofacitinib 10 mg twice daily in OCTAVE Open, remission was achieved in 35% (20/58) patients who received tofacitinib 5 mg twice daily in OCTAVE Sustain and 40% (40/99) patients with dose interruption in OCTAVE Sustain. At month 12 in OCTAVE Open, 52% (25/48) and 45% (37/83) of these patients achieved remission, respectively.

Furthermore, at month 12 of study OCTAVE Open, 74% (48/65) of patients who achieved remission at the end of study OCTAVE Sustain on either tofacitinib 5 mg twice daily or tofacitinib 10 mg twice daily remained in remission while receiving tofacitinib 5 mg twice daily.

Paediatric population

The European Medicines Agency has deferred the obligation to submit results of studies with tofacitinib in one or more subsets of the paediatric population in juvenile idiopathic arthritis and in ulcerative colitis (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_{max} was reduced by 32%. In clinical trials, tofacitinib was administered without regard to meal.

After intravenous administration, the volume of distribution is 87 L. 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.

Biotransformation 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 radiolabelled 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.

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 tofacitinib does not vary with time, indicating that treatment with tofacitinib 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 or moderate to severe UC 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, tofacitinib 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, tofacitinib 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.

Drug interactions

Tofacitinib is not an inhibitor or inducer of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) and is not an inhibitor of UGTs (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7). Tofacitinib is not an inhibitor of MDR1, OATP1B1/1B3, OCT2, OAT1/3, or MRP at clinically meaningful concentrations.

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 or 3 times the clinical tofacitinib exposure level (unbound AUC in humans at a dose of 5 mg or 10 mg twice daily), and 0 of 14 juvenile monkeys at 5 or 2.5 times the clinical exposure level of 5 mg or 10 mg twice daily. Exposure in monkeys at the no observed adverse effect level (NOAEL) for the lymphomas was approximately 1 or 0.5 times the clinical exposure level of 5 mg or 10 mg twice daily. 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 or 19 times the clinical exposure level at 5 mg or 10 mg twice daily. 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 or 41 times the

clinical exposure level at 5 mg or 10 mg twice daily. Benign thymomas were observed in female rats at 187 or 94 times the clinical exposure level at 5 mg or 10 mg twice daily.

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)
FD&C Blue #2/Indigo Carmine Aluminum Lake (E132) (10 mg strength only)
FD&C Blue #1/Brilliant Blue FCF Aluminum Lake (E133) (10 mg strength only)

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 package in order to protect from moisture.

6.5 Nature and contents of container

XELJANZ 5 mg film-coated tablets

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

Aluminium foil/PVC backed aluminium foil blisters containing 14 film-coated tablets. Each pack contains 56, 112, or 182 film-coated tablets.

XELJANZ 10 mg film-coated tablets

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

Aluminium foil/PVC backed aluminium foil blisters containing 14 film-coated tablets. Each pack contains 56, 112, or 182 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

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
EU/1/17/1178/005
EU/1/17/1178/006
EU/1/17/1178/007
EU/1/17/1178/008
EU/1/17/1178/009
EU/1/17/1178/014

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.

▼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 11 mg prolonged-release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each prolonged-release tablet contains tofacitinib citrate, equivalent to 11 mg tofacitinib.

Excipient with known effect

Each prolonged-release tablet contains 152.23 mg of sorbitol.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablets

Pink, oval tablet of approximate average dimension of 10.8 mm × 5.5 mm × 4.4 mm (length by width by thickness) with a drilled hole at one end of the tablet band and "JKI 11" printed on one side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Tofacitinib 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. Tofacitinib 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).

4.2 Posology and method of administration

Treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis.

Posology

The recommended dose is one 11 mg prolonged-release tablet administered once daily, which should not be exceeded.

Switching between tofacitinib 11 mg prolonged-release tablets and tofacitinib 5mg film-coated tablets
Patients treated with tofacitinib 5 mg film-coated tablets twice daily may be switched to tofacitinib 11 mg prolonged-release tablets once daily on the day following the last dose of tofacitinib 5 mg film-coated tablets.

Patients treated with tofacitinib 11 mg prolonged-release tablets once daily may be switched to tofacitinib 5 mg film-coated tablets twice daily on the day following the last dose of tofacitinib 11 mg prolonged-release tablets.

Tofacitinib 11 mg prolonged-release tablets once daily has demonstrated pharmacokinetic equivalence (AUC and C_{max}) to tofacitinib 5 mg film-coated tablets twice daily.

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

Dose interruption and discontinuation

Tofacitinib 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/mm^3.

Table 1: Low absolute lymphocyte count

Low absolute lymphocyte count (ALC) (see section 4.4)	
Lab value (cells/mm^3)	**Recommendation**
ALC greater than or equal to 750	Dose should be maintained.
ALC 500-750	For persistent (2 sequential values in this range on routine testing) decrease in this range, tofacitinib 11 mg prolonged-release dosing should be interrupted until ALC is greater than 750. When ALC is greater than 750, treatment should be resumed as clinically appropriate.
ALC less than 500	If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in patients with an absolute neutrophil count (ANC) less than 1,000 cells/mm^3.

Table 2: Low absolute neutrophil count

Low absolute neutrophil count (ANC) (see section 4.4)	
Lab Value (cells/mm^3)	**Recommendation**
ANC greater than 1,000	Dose should be maintained.
ANC 500-1,000	For persistent (2 sequential values in this range on routine testing) decreases in this range, tofacitinib 11 mg prolonged-release dosing should be interrupted until ANC is greater than 1,000. When ANC is greater than 1,000, treatment should be resumed as clinically appropriate.
ANC less than 500	If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.

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

Table 3: Low haemoglobin value

Low haemoglobin value (Section 4.4)	
Lab Value (g/dL)	**Recommendation**
Less than or equal to 2 g/dL decrease and greater than or equal to 9.0 g/dL	Dose should be maintained.
Greater than 2 g/dL decrease or less than 8.0 g/dL (confirmed by repeat testing)	Dosing should be interrupted until haemoglobin values have normalised.

Drug-drug interactions
Tofacitinib total daily dose should be reduced by half in patients receiving potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) and in patients receiving 1 or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g., fluconazole) (see section 4.5).

Tofacitinib dose should be reduced to 5 mg film-coated tablet once daily in patients receiving 11 mg prolonged-release tablet once daily.

Special populations

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

Hepatic impairment

Table 4: Dose adjustment for hepatic impairment

Hepatic impairment category	**Classification**	**Dose adjustment in hepatic impairment for different strength tablets**
Mild	Child Pugh A	No dose adjustment required.
Moderate	Child Pugh B	Dose should be reduced to 5 mg film-coated tablets once daily when the indicated dose in the presence of normal hepatic function is 11 mg prolonged-release tablet once daily (see section 5.2).
Severe	Child Pugh C	Tofacitinib should not be used in patients with severe hepatic impairment (see section 4.3).

Renal impairment

Table 5: Dose adjustment for renal impairment

Renal impairment category	**Creatinine clearance**	**Dose adjustment in renal impairment for different strength tablets**
Mild	50-80 mL/min	No dose adjustment required.
Moderate	30-49 mL/min	No dose adjustment required.
Severe (including patients undergoing haemodialysis)	< 30 mL/min	Dose should be reduced to 5 mg film-coated tablet once daily when the indicated dose in the presence of normal renal function is 11 mg prolonged-release tablet once daily (see section 5.2). Patients with severe renal impairment should remain on a reduced dose even after haemodialysis (see section 5.2).

Paediatric population
The safety and efficacy of tofacitinib in children aged 0 to less than 18 years have not been established.

No data are available.

Method of administration

Oral use.

Tofacitinib is given orally with or without food.

Tofacitinib 11 mg prolonged-release tablets must be taken whole in order to ensure the entire dose is delivered correctly. They must not be crushed, split or chewed.

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

Tofacitinib has not been studied and its use should be avoided in combination with biologics such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, selective co-stimulation modulators and potent immunosuppressants such as azathioprine, 6-mercaptopurine, 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 tofacitinib with MTX versus tofacitinib as monotherapy in RA clinical studies.

Venous thromboembolism (VTE)

Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), have been observed in patients taking tofacitinib. A dose dependent increased risk

for VTE was observed in a clinical study with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

Tofacitnib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage.

VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (BMI ≥30), diabetes, hypertension, smoking status should also be considered. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.

Promptly evaluate patients with signs and symptoms of VTE and discontinue tofacitinib in patients with suspected VTE, regardless of dose or indication.

Serious infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving tofacitinib. The risk of opportunistic infections is higher in Asian geographic regions (see section 4.8). Rheumatoid arthritis patients taking corticosteroids may be predisposed to infection.

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

The risks and benefits of treatment should be considered prior to initiating tofacitinib 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,
- who are over 65 years of age

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with tofacitinib. 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 tofacitinib 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). In patients over 65 years of age tofacitinib should only be considered if no suitable alternative treatment is available (see section 5.1).

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 tofacitinib 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 tofacitinib.

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

Antituberculosis therapy should also be considered prior to administration of tofacitinib 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 tofacitinib. In patients treated with tofacitinib, the incidence of herpes zoster appears to be increased in:

- Japanese or Korean patients.
- Patients with an ALC less than 1,000 cells/mm^3 (see section 4.2).
- Patients with long standing RA who have previously received two or more biological disease modifying antirheumatic drugs (DMARDs).
- Patients treated with 10 mg twice daily.

The impact of tofacitinib 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 tofacitinib.

Malignancy and lymphoproliferative disorder

The risks and benefits of tofacitinib 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 tofacitinib in patients who develop a malignancy. The possibility exists for tofacitinib to affect host defences against malignancies.

Lymphomas have been observed in patients treated with tofacitinib. 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 tofacitinib 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 tofacitinib on the development and course of malignancies is not known.

Non-melanoma skin cancer

NMSCs have been reported in patients treated with tofacitinib. The risk of NMSC may be higher in patients treated with tofacitinib 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer (see Table 6 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 tofacitinib 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. Tofacitinib 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 patients have an increased risk for cardiovascular disorders. Patients treated with tofacitinib should have risk factors (e.g., hypertension, hyperlipidaemia) managed as part of usual standard of care.

Liver enzymes

Treatment with tofacitinib 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 tofacitinib 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 tofacitinib 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 tofacitinib 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 tofacitinib 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 tofacitinib was associated with an increased incidence of neutropenia (less than 2,000 cells/mm^3) compared to placebo. It is not recommended to initiate tofacitinib 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 tofacitinib has been associated with decreases in haemoglobin levels. It is not recommended to initiate tofacitinib 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 tofacitinib 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 tofacitinib therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia. Increases in total and LDL cholesterol associated with tofacitinib may be decreased to pretreatment levels with statin therapy.

Vaccinations

Prior to initiating tofacitinib, 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 tofacitinib. The decision to use live vaccines prior to tofacitinib 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 tofacitinib 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 tofacitinib.

Gastrointestinal obstruction with a non-deformable prolonged-release formulation

Caution should be used when administering tofacitinib 11 mg prolonged-release tablets to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of other medicinal products utilising a non-deformable prolonged-release formulation.

Excipients with known effect

Tofacitinib 11 mg prolonged-release tablets contains sorbitol. The additive effect of concomitantly administered products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

4.5 Interaction with other medicinal products and other forms of interaction

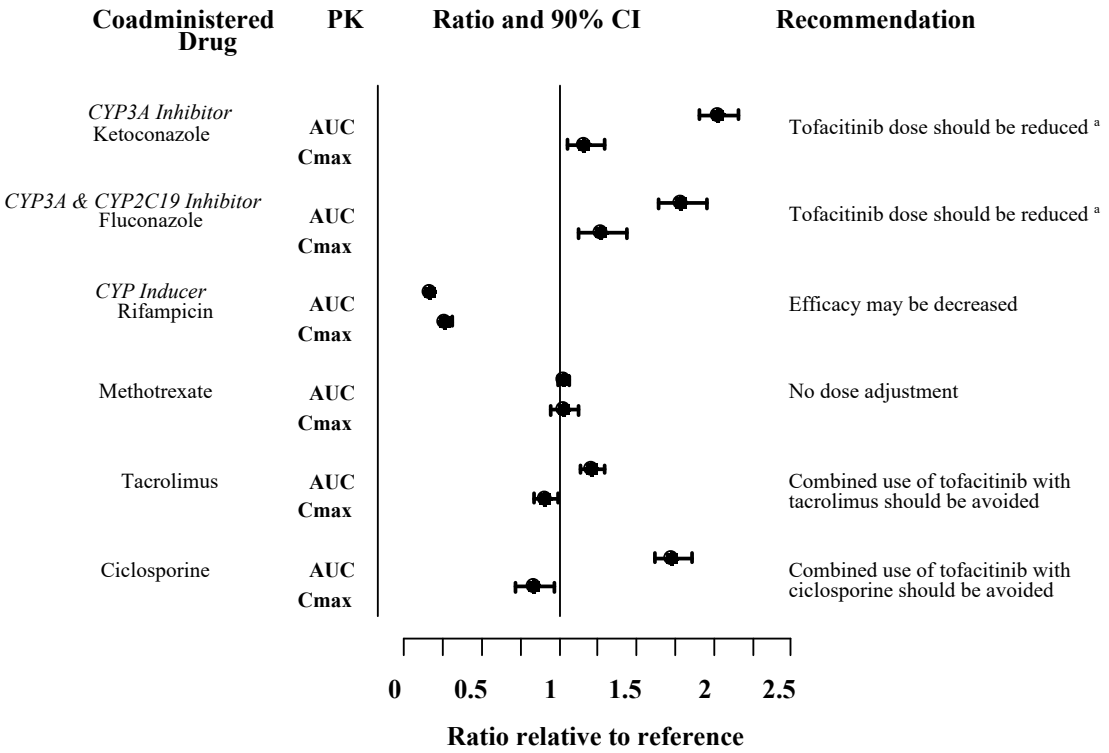
Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib

Since tofacitinib is metabolised by CYP3A4, interaction with medicinal products that inhibit or induce CYP3A4 is likely. Tofacitinib exposure is increased when coadministered with potent inhibitors of CYP3A4 (e.g., ketoconazole) or when administration of one or more concomitant medicinal products results in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19 (e.g., fluconazole) (see section 4.2).

Tofacitinib 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 tofacitinib.

Coadministration with ketoconazole (strong CYP3A4 inhibitor), fluconazole (moderate CYP3A4 and potent CYP2C19 inhibitor), tacrolimus (mild CYP3A4 inhibitor) and ciclosporine (moderate CYP3A4 inhibitor) increased tofacitinib AUC, while rifampicin (potent CYP inducer) decreased tofacitinib AUC. Coadministration of tofacitinib 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 tofacitinib is not recommended. Coadministration with ketoconazole and fluconazole increased tofacitinib C_{max}, while tacrolimus, ciclosporine and rifampicin decreased tofacitinib C_{max}. Concomitant administration with MTX 15-25 mg once weekly had no effect on the PK of tofacitinib in RA patients (see Figure 1).

Figure 1. Impact of other medicinal products on PK of tofacitinib



Note: Reference group is administration of tofacitinib alone.

[a] Tofacitinib dose should be reduced to 5 mg (as film-coated tablet) once daily in patients receiving 11 mg (as prolonged-release tablet) once daily (see section 4.2).

Potential for tofacitinib to influence the PK of other medicinal products

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

In RA patients, coadministration of tofacitinib with MTX 15-25 mg once weekly decreased the AUC and C_{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.

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 tofacitinib 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 tofacitinib and for at least 4 weeks after the last dose.

Breast-feeding

It is not known whether tofacitinib 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 tofacitinib 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

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

4.8 Undesirable effects

Summary of the safety profile

The most common serious adverse reactions were serious infections (see section 4.4). The most common serious infections reported with tofacitinib 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 tofacitinib. 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 6, 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 tofacitinib. The most common infections resulting in discontinuation of therapy were herpes zoster and pneumonia.

Tabulated list of adverse reactions

The ADRs listed in the table below are from clinical studies in patients with RA, PsA, and UC 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 6: Adverse drug reactions

System organ class	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	Not known (cannot be estimated from the available data)
Infections and infestations	Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Nasopharyngitis Pharyngitis	Tuberculosis Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection	Sepsis Urosepsis Disseminated TB Necrotizing fasciitis Bacteraemia Staphylococcal bacteraemia *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal Pneumonia bacterial Encephalitis Atypical mycobacterial infection Cytomegalovirus infection Arthritis bacterial	Tuberculosis of central nervous system Meningitis cryptococcal *Mycobacterium avium* complex infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Non-melanoma skin cancers			
Blood and lymphatic system disorders	Anaemia	Leukopenia Lymphopenia Neutropenia			
Immune system disorders					Drug hypersensitivity* Angioedema* Urticaria*
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia Dehydration			
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache	Paraesthesia			
Vascular disorders	Hypertension	Venous thromboembolism**			
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea Sinus congestion			
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia				

System organ class	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	Not known (cannot be estimated from the available data)
Hepatobiliary disorders		Hepatic steatosis Hepatic enzyme increased Transaminases increased Liver function test abnormal Gamma glutamyl-transferase increased			
Skin and subcutaneous tissue disorders	Rash	Erythema Pruritus			
Musculoskeletal and connective tissue disorders	Arthralgia	Musculoskeletal pain Joint swelling Tendonitis			
General disorders and administration site conditions	Pyrexia Oedema peripheral Fatigue				
Investigations	Blood creatine phosphokinase increased	Blood creatinine increased Blood cholesterol increased Low density lipoprotein increased Weight increased			
Injury, poisoning and procedural complications		Ligament sprain Muscle strain			

*Spontaneous reporting data
**Venous thromboembolism includes PE and DVT

Description of selected adverse reactions

Venous thromboembolism

In a large, randomised post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors. The majority of these events were serious and some resulted in death. The incidence rates (95% CI) for PE for tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, and TNF inhibitors were 0.54 (0.32-0.87), 0.27 (0.12-0.52), and 0.09 (0.02-0.26) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for PE was 5.96 (1.75-20.33) and 2.99 (0.81-11.06) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily, respectively (see section 5.1).

In a subgroup analysis in patients with VTE risk factors in the above-mentioned study, the risk for PE was further increased. Compared with TNF inhibitors, the HR for PE was 9.14 (2.11-39.56) for tofacitinib 10 mg twice daily and 3.92 (0.83-18.48) for tofacitinib 5 mg twice daily.

Overall infections

In controlled phase 3 clinical studies, the rates of infections over 0-3 months in the 5 mg film-coated tablets twice daily (total 616 patients) and 10 mg twice daily (total 642 patients) tofacitinib 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) tofacitinib 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 tofacitinib 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

In the 6-month and 24-month, controlled clinical studies, the rate of serious infections in the 5 mg twice daily tofacitinib monotherapy group was 1.7 patients with events per 100 patient-years. In the 10 mg twice daily tofacitinib 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 tofacitinib 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 tofacitinib 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).

Viral reactivation

Patients treated with tofacitinib 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/mm^3, or patients treated with 10 mg twice daily 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/mm^3 occurred in 0.3% of patients and for ALC between 500 and 750 cells/mm^3 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/mm^3 occurred in 1.3% of patients and for ALC between 500 and 750 cells/mm^3 in 8.4% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

Confirmed ALC less than 750 cells/mm^3 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/mm^3 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/mm^3 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 tofacitinib, or reduction in tofacitinib 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, tofacitinib 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, tofacitinib 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, tofacitinib 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, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the controlled portion of the RA phase 3 studies on background DMARDs (0-3 months) (studies 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, tofacitinib 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, tofacitinib 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 tofacitinib 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 tofacitinib 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.

Lipids
Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were first assessed at 1 month following initiation of tofacitinib 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 tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at month 12, and increased by 16% in the tofacitinib 5 mg twice daily arm and 19% in the tofacitinib 10 mg twice daily arm at month 24.
- Mean HDL cholesterol increased by 17% in the tofacitinib 5 mg twice daily arm and 18% in the tofacitinib 10 mg twice daily arm at month 12, and increased by 19% in the tofacitinib 5 mg twice daily arm and 20% in the tofacitinib 10 mg twice daily arm at month 24.

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

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

In an 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 tofacitinib. 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 groups: Immunosuppressants, 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 tofacitinib 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 tofacitinib was associated with dose-dependent increases in B cell counts. Changes in circulating T-lymphocyte counts and T-lymphocyte subsets (CD3+, CD4+ and CD8+) were small and inconsistent.

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

Vaccine studies

In a controlled clinical trial of patients with RA initiating tofacitinib 10 mg twice daily or placebo, the number of responders to influenza vaccine was similar in both groups: tofacitinib (57%) and placebo (62%). For pneumococcal polysaccharide vaccine the number of responders was as follows: 32% in patients receiving both tofacitinib and MTX; 62% for tofacitinib 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 tofacitinib 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 tofacitinib 5 mg twice daily or placebo. Evidence of humoral and cell-mediated responses to VZV was observed in both tofacitinib 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. Tofacitinib 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

The efficacy and safety of tofacitinib 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 7 provides information regarding the pertinent study design and population characteristics.

Table 7: Phase 3 clinical trials of tofacitinib 5 mg and 10 mg twice daily doses in patients with RA

Studies	Study I (ORAL Solo)	Study II (ORAL Sync)	Study III (ORAL Standard)	Study IV (ORAL Scan)	Study V (ORAL Step)	Study VI (ORAL Start)	Study VII (ORAL Strategy)
Population	DMARD-IR	DMARD-IR	MTX-IR	MTX-IR	TNFi-IR	MTX-naïve[a]	MTX-IR
Control	Placebo	Placebo	Placebo	Placebo	Placebo	MTX	MTX, ADA
Background treatment	None[b]	csDMARDs	MTX	MTX	MTX	None[b]	3 Parallel arms: • Tofacitinib monotherapy • Tofacitinib+MTX • ADA+MTX

Studies	Study I (ORAL Solo)	Study II (ORAL Sync)	Study III (ORAL Standard)	Study IV (ORAL Scan)	Study V (ORAL Step)	Study VI (ORAL Start)	Study VII (ORAL Strategy)
Key features	Monotherapy	Various csDMARDs	Active control (ADA)	X-Ray	TNFi-IR	Monotherapy, Active comparator (MTX), X-Ray	Tofacitinib with and without MTX in comparison to ADA with MTX
Number of patients treated	610	792	717	797	399	956	1,146
Total study duration	6 months	1 year	1 year	2 years	6 months	2 years	1 year
Co-primary efficacy endpoints[c]	Month 3: ACR20 HAQ-DI DAS28-4(ESR)<2.6	Month 6: ACR20 DAS28-4(ESR)<2.6 Month 3: HAQ-DI	Month 6: ACR20 DAS28-4(ESR)<2.6 Month 3: HAQ-DI	Month 6: ACR20 mTSS DAS28-4(ESR)<2.6 Month 3: HAQ-DI	Month 3: ACR20 HAQ-DI DAS28-4(ESR)<2.6	Month 6: mTSS ACR70	Month 6: ACR50
Time of mandatory placebo rescue to tofacitinib 5 mg or 10 mg twice daily	Month 3	Month 6 (placebo subjects with < 20% improvement in swollen and tender joint counts advanced to tofacitinib at month 3)			Month 3	NA	NA

[a.] ≤3 weekly doses (MTX-naïve).
[b.] Antimalarials were allowed.
[c.] Co-primary endpoints as follows: mean change from baseline in mTSS; percent of subjects achieving ACR20 or ACR70 responses; mean change from baseline in HAQ-DI; percent of subjects achieving a DAS28-4(ESR) <2.6 (remission).
mTSS=modified Total Sharp Score, ACR20(70)=American College of Rheumatology ≥20% (≥70%) improvement, DAS28=Disease Activity Score 28 joints, ESR=Erythrocyte Sedimentation Rate, HAQ-DI=Health Assessment Questionnaire Disability Index, DMARD=disease-modifying antirheumatic drug, IR=inadequate responder, csDMARD=conventional synthetic DMARD, TNFi=tumour necrosis factor inhibitor, NA=not applicable, ADA=adalimumab, MTX=methotrexate.

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, ORAL Start, and ORAL Strategy are shown in Table 8. In all studies, patients treated with either 5 mg 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.

Over the course of ORAL Strategy, responses with tofacitinib 5 mg twice daily + MTX were numerically similar compared to adalimumab 40 mg + MTX and both were numerically higher than tofacitinib 5 mg twice daily.

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 8: Proportion (%) of patients with an ACR response

ORAL Solo: DMARD inadequate responders				
Endpoint	**Time**	**Placebo N=122**	**Tofacitinib 5 mg twice daily monotherapy N=241**	**Tofacitinib 10 mg twice daily monotherapy N=243**
ACR20	Month 3	26	60***	65***
	Month 6	NA	69	71
ACR50	Month 3	12	31***	37***
	Month 6	NA	42	47
ACR70	Month 3	6	15*	20***
	Month 6	NA	22	29

ORAL Sync: DMARD inadequate responders				
Endpoint	**Time**	**Placebo + DMARD(s) N=158**	**Tofacitinib 5 mg twice daily + DMARD(s) N=312**	**Tofacitinib 10 mg twice daily + DMARD(s) N=315**
ACR20	Month 3	27	56***	63***
	Month 6	31	53***	57***
	Month 12	NA	51	56
ACR50	Month 3	9	27***	33***
	Month 6	13	34***	36***
	Month 12	NA	33	42
ACR70	Month 3	2	8**	14***
	Month 6	3	13***	16***
	Month 12	NA	19	25

ORAL Standard: MTX inadequate responders					
Endpoint	**Time**	**Placebo**	**Tofacitinib twice daily + MTX**		**Adalimumab 40 mg QOW + MTX**
		N=105	**5 mg N=198**	**10 mg N=197**	**N=199**
ACR20	Month 3	26	59***	57***	56***
	Month 6	28	51***	51***	46**
	Month 12	NA	48	49	48
ACR50	Month 3	7	33***	27***	24***
	Month 6	12	36***	34***	27**
	Month 12	NA	36	36	33
ACR70	Month 3	2	12**	15***	9*
	Month 6	2	19***	21***	9*
	Month 12	NA	22	23	17

ORAL Scan: MTX inadequate responders				
Endpoint	**Time**	**Placebo + MTX N=156**	**Tofacitinib 5 mg twice daily + MTX N=316**	**Tofacitinib 10 mg twice daily + MTX N=309**
ACR20	Month 3	27	55***	66***
	Month 6	25	50***	62***
	Month 12	NA	47	55
	Month 24	NA	40	50
ACR50	Month 3	8	28***	36***
	Month 6	8	32***	44***
	Month 12	NA	32	39
	Month 24	NA	28	40
ACR70	Month 3	3	10**	17***

	Month 6	1	14***	22***
	Month 12	NA	18	27
	Month 24	NA	17	26
ORAL Step: TNF inhibitor inadequate responders				
Endpoint	**Time**	**Placebo + MTX N=132**	**Tofacitinib 5 mg twice daily + MTX N=133**	**Tofacitinib 10 mg twice daily + MTX N=134**
ACR20	Month 3	24	41*	48***
	Month 6	NA	51	54
ACR50	Month 3	8	26***	28***
	Month 6	NA	37	30
ACR70	Month 3	2	14***	10*
	Month 6	NA	16	16
ORAL Start: MTX-naïve				
Endpoint	**Time**	**MTX N=184**	**Tofacitinib 5 mg twice daily monotherapy N=370**	**Tofacitinib 10 mg twice daily monotherapy N=394**
ACR20	Month 3	52	69***	77***
	Month 6	51	71***	75***
	Month 12	51	67**	71***
	Month 24	42	63***	64***
ACR50	Month 3	20	40***	49***
	Month 6	27	46***	56***
	Month 12	33	49**	55***
	Month 24	28	48***	49***
ACR70	Month 3	5	20***	26***
	Month 6	12	25***	37***
	Month 12	15	28**	38***
	Month 24	15	34***	37***
ORAL Strategy: MTX inadequate responders				
Endpoint	**Time**	**Tofacitinib 5 mg twice daily N=384**	**Tofacitinib 5 mg twice daily + MTX N=376**	**Adalimumab + MTX N=386**
ACR20	Month 3	62.50	70.48ǂ	69.17
	Month 6	62.84	73.14ǂ	70.98
	Month 12	61.72	70.21ǂ	67.62
ACR50	Month 3	31.51	40.96ǂ	37.31
	Month 6	38.28	46.01ǂ	43.78
	Month 12	39.31	47.61ǂ	45.85
ACR70	Month 3	13.54	19.41ǂ	14.51
	Month 6	18.23	25.00ǂ	20.73
	Month 12	21.09	28.99ǂ	25.91

*p<0.05
**p<0.001
***p<0.0001 verses placebo (versus MTX for ORAL Start)
ǂp<0.05 – tofacitinib 5 mg + MTX versus tofacitinib 5 mg for ORAL Strategy (normal p-values without multiple comparison adjustment)
QOW=every other week, N=number of subjects analysed, ACR20/50/70=American College of Rheumatology ≥20, 50, 70% improvement, NA=not applicable, MTX=methotrexate.

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 9.

Table 9: Number (%) of subjects achieving DAS28-4(ESR) < 2.6 remission at months 3 and 6

	Time point	N	%
ORAL Step: TNF inhibitor inadequate responders			
Tofacitinib 5 mg twice daily + MTX	Month 3	133	6
Tofacitinib 10 mg twice daily + MTX	Month 3	134	8*
Placebo + MTX	Month 3	132	2
ORAL Sync: DMARD inadequate responders			
Tofacitinib 5 mg twice daily	Month 6	312	8*
Tofacitinib 10 mg twice daily	Month 6	315	11***
Placebo	Month 6	158	3
ORAL Standard: MTX inadequate responders			
Tofacitinib 5 mg twice daily + MTX	Month 6	198	6*
Tofacitinib 10 mg twice daily + MTX	Month 6	197	11***
Adalimumab 40 mg SC QOW + MTX	Month 6	199	6*
Placebo + MTX	Month 6	105	1

*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 mg 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 10, 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 mg or 10 mg twice daily respectively, both significant versus MTX.

Table 10: Radiographic changes at months 6 and 12

	ORAL Scan: MTX inadequate responders				
	Placebo + MTX N=139 Mean (SD)[a]	**Tofacitinib 5 mg twice daily + MTX N=277 Mean (SD)[a]**	**Tofacitinib 5 mg twice daily + MTX Mean difference from placebo[b] (CI)**	**Tofacitinib 10 mg twice daily + MTX N=290 Mean (SD)[a]**	**Tofacitinib 10 mg twice daily + MTX Mean difference from placebo[b] (CI)**
mTSS[c]					
Baseline	33 (42)	31 (48)	-	37 (54)	-
Month 6	0.5 (2.0)	0.1 (1.7)	-0.3 (-0.7, 0.0)	0.1 (2.0)	-0.4 (-0.8, 0.0)
Month 12	1.0 (3.9)	0.3 (3.0)	-0.6 (-1.3, 0.0)	0.1 (2.9)	-0.9 (-1.5, -0.2)
	ORAL Start: MTX-naïve				
	MTX N=168 Mean (SD)[a]	**Tofacitinib 5 mg twice daily N=344 Mean (SD)[a]**	**Tofacitinib 5 mg twice daily Mean difference from MTX[d] (CI)**	**Tofacitinib 10mg twice daily N=368 Mean (SD)[a]**	**Tofacitinib 10 mg twice daily Mean difference from MTX[d] (CI)**
mTSS[c]					
Baseline	16 (29)	20 (41)	-	19 (39)	-
Month 6	0.9 (2.7)	0.2 (2.3)	-0.7 (-1.0, -0.3)	0.0 (1.2)	-0.8 (-1.2, -0.4)
Month 12	1.3 (3.7)	0.4 (3.0)	-0.9 (-1.4, -0.4)	0.0 (1.5)	-1.3 (-1.8, -0.8)

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

Physical function response and health-related outcomes

Tofacitinib, alone or in combination with MTX, has shown improvements in physical function, as measured by the HAQ-DI. Patients receiving tofacitinib 5 mg 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 mg 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 11.

Table 11: LS Mean change from baseline in HAQ-DI at month 3

	Placebo + MTX	**Tofacitinib 5 mg twice daily + MTX**	**Tofacitinib 10 mg twice daily + MTX**	**Adalimumab 40 mg QOW + MTX**
ORAL Standard: MTX inadequate responders				
N=96		**N=185**	**N=183**	**N=188**
-0.24		-0.54***	-0.61***	-0.50***
ORAL Step: TNF inhibitor inadequate responders				
N=118		**N=117**	**N=125**	NA
-0.18		-0.43***	-0.46***	NA
Placebo + DMARD(s)		**Tofacitinib 5 mg twice daily + DMARD(s)**	**Tofacitinib 10 mg twice daily + DMARD(s)**	
ORAL Sync: DMARD inadequate responders				
N=147		**N=292**	**N=292**	NA
-0.21		-0.46***	-0.56***	NA

*** p<0.0001, tofacitinib versus placebo + MTX, LS = least squares, N = number of patients, QOW = every other week, NA = not applicable, HAQ-DI = Health Assessment Questionnaire Disability Index

Health-related quality of life was assessed by the Short Form Health Survey (SF-36). Patients receiving either 5 mg 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 mg 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 mg 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.

Long-term controlled safety data

Study ORAL Surveillance (A3921133) is a large (N=4362), ongoing, randomised active-controlled post-authorisation safety surveillance study of rheumatoid arthritis patients who were at least 50 years of age and older and had at least one cardiovascular risk factor (CV risk factors defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g. nodules, Sjögren's syndrome, anemia of chronic disease, pulmonary manifestations).

Patients were randomised to open-label tofacitinib 10 mg twice daily, tofacitinib 5 mg twice daily, or a TNF inhibitor (TNF inhibitor was either etanercept 50 mg once weekly or adalimumab 40 mg every other week) in a 1:1:1 ratio. The co-primary endpoints are adjudicated malignancy (excluding NMSC) and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessment of endpoints are blinded. The study is an event-powered study that also requires at least 1500 patients to be followed for 3 years. The study treatment of tofacitinib 10 mg twice daily has been stopped and patients were switched to 5 mg twice daily because of a dose-dependent signal of venous thromboembolic events (VTE).

Venous thromboembolism (VTE)
In an interim analysis of study A3921133, an increased and dose-dependent incidence of VTE was observed in patients treated with tofacitinib compared to TNF inhibitors (see section 4.8). The majority of these events were serious and some cases of PE resulted in death. The incidence rates (95% CI) for PE for tofacitinib 10 mg twice daily, 5 mg twice daily, and TNF inhibitors were 0.54 (0.32-0.87), 0.27 (0.12-0.52), and 0.09 (0.02-0.26) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the HR for PE with tofacitinib 10 mg twice daily was 5.96 (1.75-20.33), and for 5 mg twice daily the HR was 2.99 (0.81-11.06). The incidence rates (95% CI) for DVT for tofacitinib 10 mg twice daily, 5 mg twice daily, and TNF inhibitors were 0.38

(0.20-0.67), 0.30 (0.14-0.55), and 0.18 (0.07-0.39) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the HR for DVT with tofacitinib 10 mg twice daily was 2.13 (0.80-5.69), and for 5 mg twice daily the HR was 1.66 (0.60-4.57).

Mortality
In an interim analysis of study A3921133, increased mortality within 28 days of last treatment was observed in patients treated with tofacitinib compared to TNF inhibitors. The incidence rates (95% CI) were 0.89 (0.59-1.29) for tofacitinib 10 mg twice daily, 0.57 (0.34-0.89) for tofacitinib 5 mg twice daily, and 0.27 (0.12-0.51) for TNF-inhibitors; with a HR (95% CI) of 3.28 (1.55-6.95) for tofacitinib 10 mg twice daily and of 2.11 (0.96-4.67) for tofacitinib 5 mg twice daily, versus TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies.

For cardiovascular mortality within 28 days of last treatment, the incidence rates (95% CI) per 100 patients-years were 0.45 (0.24-0.75) for tofacitinib 10 mg twice daily, 0.24 (0.10-0.47) for tofacitinib 5 mg twice daily, and 0.21 (0.08-0.43) for TNF inhibitors; with an incident rate ratio (IRR) (95% CI) of 2.12 (0.80-6.20) for tofacitinib 10 mg twice daily and of 1.14 (0.36-3.70) for tofacitinib 5 mg twice daily, versus TNF inhibitors.

For fatal infections within 28 days of last treatment, the incidence rates per 100 patient-years (95% CI) were 0.22 (0.09-0.46), 0.18 (0.07-0.39), and 0.06 (0.01-0.22) for tofacitinib 10 mg twice daily and 5 mg twice daily, and TNF inhibitors, respectively; with an IRR (95% CI) of 3.70 (0.71-36.5) for 10 mg twice daily and of 3.00 (0.54-30.4) for tofacitinib 5 mg twice daily, versus TNF inhibitors.

Serious infections
For non-fatal serious infections, the incidence rates (95% CI) per 100 patient-years were 3.51 (2.93-4.16), 3.35 (2.78-4.01), and 2.79 (2.28-3.39), for tofacitinib 10 mg and 5 mg twice daily and TNF inhibitors, respectively. The risk of serious (fatal and non-fatal) infections was further increased in patients over 65 years of age, as compared to younger patients in study A3921133.

Paediatric population

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

5.2 Pharmacokinetic properties

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

Absorption and distribution

Coadministration of tofacitinib 11 mg prolonged-release tablet with a high-fat meal resulted in no changes in AUC while C_{max} was increased by 27%.

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.

Biotransformation 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 radiolabelled 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.

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 tofacitinib does not vary with time, indicating that treatment with tofacitinib 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%.

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, tofacitinib 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, tofacitinib 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.

Drug interactions

Tofacitinib is not an inhibitor or inducer of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) and is not an inhibitor of UGTs (UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7). Tofacitinib is not an inhibitor of MDR1, OATP1B1/1B3, OCT2, OAT1/3, or MRP at clinically meaningful concentrations.

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 or 3 times the clinical tofacitinib exposure level (unbound AUC in humans at a dose of 5 mg or 10 mg twice daily), and 0 of 14 juvenile monkeys at 5 or 2.5 times the clinical exposure level of 5 mg or 10 mg twice daily. Exposure in monkeys at the no observed adverse effect level (NOAEL) for the lymphomas was approximately 1 or 0.5 times the clinical exposure level of 5 mg or 10 mg twice daily. 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 or 19 times the clinical exposure level at 5 mg or 10 mg twice daily. 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 or 41 times the clinical exposure level at 5 mg or 10 mg twice daily. Benign thymomas were observed in female rats at 187 or 94 times the clinical exposure level at 5 mg or 10 mg twice daily.

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

sorbitol (E420)
hydroxyethyl cellulose
copovidone
magnesium stearate

Film coat

cellulose acetate
hydroxypropyl cellulose (E463)
hypromellose (E464)
titamium dioxide (E171)
triacetin (E1518)
red iron oxide (E172)

Printing ink

shellac (E904)
ammomium hydroxide (E527)
propylene glycol (E1520)
black iron oxide (E172)

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 package in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottles with 2 silica gel desiccants and child-resistant, polypropylene closure containing 30 or 90 prolonged-release tablets.

Aluminium foil/PVC backed aluminium foil blisters containing 7 prolonged-release tablets. Each pack contains 28 or 91 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1178/010
EU/1/17/1178/011
EU/1/17/1178/012
EU/1/17/1178/013

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 (PSURs)**

The requirements for submission of PSURs 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.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (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 MAH shall ensure that in each EU Member State where XELJANZ is marketed, healthcare professionals who intend to prescribe XELJANZ have been provided with an educational package.

The main objective of the programme is to increase awareness about the risks of the product, specifically in regards to serious infections, venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), 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)
    - The above key element needs to be updated with details on the VTE risk including the VTE risk factors as well as with details on the risk of serious infections in patients >65 years old.
  - 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)
    - The above key element should be updated with details on the VTE risk should be minimised in clinical practice, i.e., that tofacitinib should be used with caution in patients with known VTE risk factors and that 10 mg twice daily is not recommended for maintenance treatment in UC patients with known VTE risk factors unless there is no suitable alternative treatment available. In addition, details on how to minimize the risk of serious infections in patients >65 years old should be provided as well.
  - Key message to convey in patients counselling
  - Instructions on how to handle possible adverse events
  - Information about the BSRBR, ARTIS, RABBIT and BIODABASER and UC registries 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 and maintenance of the patient
  - Vaccination course to be completed before treatment
  - A specific reference to the fact that the patient has been informed and understands that tofacitinib is contraindicated during pregnancy and breast-feeding and women of childbearing potential should use effective contraception during treatment with tofacitinib and for at least 4 weeks after the last dose
  - That the benefit risk of tofacitinib should be discussed with the patient, and the patient alert card should be given to and discussed with the patient
  - 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, venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), 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/or when to seek attention from a HCP: infections, venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), 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 biologics and immunosuppressants including B lymphocyte depleting agents, increased risk of adverse events when XELJANZ is administered in combination with MTX, increased exposure to XELJANZ when co-administered with CYP3A4 and CYP2C19 inhibitors, effects on pregnancy and foetus, use in breast-feeding, effect on vaccination efficacy and the use of live/attenuated vaccines.
    - Contact details of the prescriber

- **The website repository** 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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 5 MG BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 5 mg film-coated tablets
tofacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 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

56 film-coated tablets
112 film-coated tablets
182 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1178/003 56 film-coated tablets
EU/1/17/1178/004 182 film-coated tablets
EU/1/17/1178/014 112 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

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

BLISTER FOR 5 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 5 mg tablets
tofacitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon., Tue., Wed., Thu., Fri., Sat., Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LABEL FOR 5 MG BOTTLE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 5 mg film-coated tablets
tofacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 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

Read the package leaflet before use.
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

Do not swallow the dessicant.

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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 10 MG BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 10 mg film-coated tablets
tofacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 mg of tofacitinib (as tofacitinib citrate).

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

56 film-coated tablets
112 film-coated tablets
182 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1178/007 56 film-coated tablets
EU/1/17/1178/008 112 film-coated tablets
EU/1/17/1178/009 182 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XELJANZ 10 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

BLISTER FOR 10 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 10 mg tablets
tofacitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon., Tue., Wed., Thu., Fri., Sat., Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LABEL FOR 10 MG BOTTLE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 10 mg film-coated tablets
tofacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 10 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

Read the package leaflet before use.
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

Do not swallow the desiccant.

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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1178/005 60 film-coated tablets
EU/1/17/1178/006 180 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XELJANZ 10 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 11 MG BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 11 mg prolonged-release tablets
tofacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 11 mg of tofacitinib (as tofacitinib citrate).

3. LIST OF EXCIPIENTS

Contains sorbitol (E420). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

28 prolonged-release tablets
91 prolonged-release tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.
Do not crush, split or chew.

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

Once daily

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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1178/012 28 prolonged-release tablets
EU/1/17/1178/013 91 prolonged-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XELJANZ 11 mg

17. UNIQUE IDENTIFIER - 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTER OR STRIPS

BLISTER FOR 11 MG TABLETS

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 11 mg prolonged-release tablets
tofacitinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA holder logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Mon., Tue., Wed., Thu., Fri., Sat., Sun.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

LABEL FOR 11 MG BOTTLE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 11 mg prolonged-release tablets
tofacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each prolonged-release tablet contains 11 mg of tofacitinib (as tofacitinib citrate).

3. LIST OF EXCIPIENTS

Contains sorbitol (E420). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

30 prolonged-release tablets
90 prolonged-release tablets
2 silica gel desiccants

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For oral use.
Do not crush, split or chew

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

Once daily
Do not swallow the desiccant.

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 Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1178/010 30 prolonged-release tablets
EU/1/17/1178/011 90 prolonged-release tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XELJANZ 11 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
XELJANZ 10 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

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
- ulcerative colitis

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.

Ulcerative colitis
Ulcerative colitis is an inflammatory disease of the large bowel. XELJANZ is used to reduce the signs and symptoms of ulcerative colitis when you did not respond well enough or were intolerant to previous ulcerative colitis treatment.

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 had 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 have heart problems, high blood pressure, or high cholesterol

There have been reports of patients treated with XELJANZ who have developed blood clots in the lungs or veins. Your doctor will evaluate your risk to develop blood clots in the lungs or veins and determine if XELJANZ is appropriate for you. If you have already had problems on developing blood clots in lungs and veins or have an increased risk for developing this (for example: if you are seriously overweight, if you have cancer, heart problems, diabetes, experienced a heart attack (within previous 3 months), recent major surgery, if you use hormonal contraceptives\hormonal replacement therapy, if a coagulation defect is identified in you or your close relatives), if you are of older age, or if you smoke, your doctor may decide that XELJANZ is not suitable for you.

Talk to your doctor straight away if you develop sudden shortness of breath or difficulty breathing, chest pain or pain in upper back, swelling of the leg or arm, leg pain or tenderness, or redness or discoloration in the leg or arm while taking XELJANZ, as these may be signs of a clot in the lungs or veins.

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.

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 rifampicin, used to treat bacterial infections
- fluconazole, ketoconazole, 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, anti-integrins, and strong chemical immunosuppressants

including azathioprine, mercaptopurine, ciclosporine, and tacrolimus. Taking XELJANZ with these medicines may increase your risk of side effects including infection.

Serious infections may happen more often in people who also take corticosteroids (e.g., prednisone).

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 must 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 must 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
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 condition.

Always take this medicine exactly as your doctor has told you, the recommended dose should not be exceeded. 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.

Ulcerative colitis
- The recommended dose is 10 mg twice a day for 8 weeks, followed by 5 mg twice a day.
- Your doctor may decide to extend the initial 10 mg twice a day treatment by an additional 8 weeks (16 weeks in total), followed by 5 mg twice a day.
- Your doctor may decide to stop XELJANZ if XELJANZ does not work for you within 16 weeks.
- For patients, who have previously taken biologic medicines to treat ulcerative colitis (such as those that block the activity of tumour necrosis factor in the body) and these medicines did not work, the doctor may decide to ~~continue giving~~increase your dose of XELJANZ to 10 mg twice a day if you do not respond sufficiently to 5 mg twice a day. Your doctor will consider the potential risks, including that of developing blood clots in the lungs or veins, and potential benefits to you. Your doctor will tell you if this applies to you.
- ~~If maintaining XELJANZ 5 mg twice a day did not work for you, your doctor may decide to increase the dose to 10 mg twice a day.~~
- If your treatment is interrupted, your doctor may decide to restart your treatment.

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

Tofacitinib tablets may be crushed and taken with water.

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 ulcers or holes in your stomach (uncommon) 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).

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

Signs of blood clots in lungs or veins (uncommon: venous thromboembolism) include

- sudden shortness of breath or difficulty breathing
- chest pain or pain in upper back
- swelling of the leg or arm
- leg pain or tenderness
- redness or discoloration in the leg or arm

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, low red blood cell count (anaemia), fever, fatigue (tiredness), 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 (including increased LDL), weight gain, dehydration, muscle strain, pain in the muscles and joints, tendonitis, joint swelling, joint sprain, abnormal sensations, poor sleep, sinus congestion, shortness of breath or difficulty breathing, skin redness, itching, fatty liver, 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), disseminated tuberculosis involving bones and other organs, other unusual infections, joint infections.

Very rare (may affect up to 1 in 10,000 people): tuberculosis involving the brain and spinal cord, meningitis.

In general, fewer side effects were seen when XELJANZ was used alone than in combination with methotrexate in rheumatoid arthritis.

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

XELJANZ 5 mg film-coated tablet
- The active substance is tofacitinib.
- Each 5 mg 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 (E464), titanium dioxide (E171), macrogol, and triacetin (E1518).

XELJANZ 10 mg film-coated tablet
- The active substance is tofacitinib.
- Each 10 mg film-coated tablet contains 10 mg of tofacitinib (as tofacitinib citrate).
- The other ingredients are microcrystalline cellulose, lactose monohydrate (see section 2), croscarmellose sodium, magnesium stearate, hypromellose (E464), titanium dioxide (E171), macrogol, triacetin (E1518), FD&C Blue #2/Indigo Carmine Aluminum Lake (E132), and FD&C Blue #1/Brilliant Blue FCF Aluminum Lake (E133).

What XELJANZ looks like and contents of the pack

XELJANZ 5 mg film-coated tablets
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, 112, or 182 tablets and each bottle contains 60 or 180 tablets.

XELJANZ 10 mg film-coated tablets
XELJANZ 10 mg film-coated tablet is blue and round in appearance.

The tablets are provided in blisters containing 14 tablets. Each pack contains 56, 112, or 182 tablets and each bottle contains 60 or 180 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België /Belgique / Belgien
Pfizer S.A./N.V.
Tél/Tel: +32 (0)2 554 62 11

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Česká republika
Pfizer PFE, spol. s r.o.
Tel: +420 283 004 111

Danmark
Pfizer ApS
Tlf: +45 44 20 11 00

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)30 550055-51000

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
PFIZER ΕΛΛΑΣ Α.Ε.
Τηλ: +30 210 67 85 800

España
Pfizer S.L.
Tel: +34 91 490 99 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Hrvatska
Pfizer Croatia d.o.o.
Tel: +385 1 3908 777

Ireland
Pfizer Healthcare Ireland
Tel: 1800 633 363 (toll free)
+44 (0)1304 616161

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Pfizer S.r.l.
Tel: +39 06 33 18 21

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel. +3705 2514000

Luxembourg/Luxemburg
Pfizer S.A.
Tél/Tel: +32 (0)2 554 62 11

Magyarország
Pfizer Kft.
Tel.: +36 1 488 37 00

Malta
Vivian Corporation Ltd.
Tel: +35621 344610

Nederland
Pfizer bv
Tel: +31 (0)10 406 43 01

Norge
Pfizer Norge AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.,
Tel.: +48 22 335 61 00

Portugal
Pfizer Biofarmacêutica, Sociedade Unipessoal, Lda.
Tel: +351 21 423 5500

România
Pfizer Romania S.R.L.
Tel: +40 21 207 28 00

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: +386 (0) 1 52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: +421-2-3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358 (0)9 430 040

Κύπρος
PFIZER ΕΛΛΑΣ A.E. (CYPRUS BRANCH)
Τηλ: +357 22 817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel: +371 670 35 775

Sverige
Pfizer Innovations AB
Tel: +46 (0)8 550 520 00

United Kingdom
Pfizer Limited
Tel: +44 (0)1304 616161

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the patient
XELJANZ 11 mg prolonged-release 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

XELJANZ is a medicine that contains the active substance tofacitinib.

XELJANZ11 mg prolonged-release tablets are 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 11 mg prolonged-release tablets are used together with methotrexate when previous rheumatoid arthritis treatment was not sufficient or was not well tolerated. XELJANZ 11 mg prolonged-release tablets can also be taken on its own in those cases where methotrexate treatment is not tolerated or treatment with methotrexate is not advised.

XELJANZ 11 mg prolonged-release tablets have 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.

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 had 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 have heart problems, high blood pressure, or high cholesterol
- if you have narrowing of the digestive tract tell your doctor as there have been rare reports of blockage in the digestive tract in patients taking other medicines using similar prolonged-release tablets
- when you take XELJANZ 11 mg prolonged-release tablets, you may see something in your stool that looks like a tablet. This is the empty shell from the prolonged-release tablet after the medicine has been absorbed by your body. This is to be expected and you should not be concerned

There have been reports of patients treated with XELJANZ who have developed blood clots in the lungs or veins. Your doctor will evaluate your risk to develop blood clots in the lungs or veins and determine if XELJANZ is appropriate for you. If you have already had problems on developing blood clots in lungs and veins or have an increased risk for developing this (for example: if you are seriously overweight, if you have cancer, heart problems, diabetes, experienced a heart attack (within previous 3 months), recent major surgery, if you use hormonal contraceptives\hormonal replacement therapy, if a coagulation defect is identified in you or your close relatives), if you are of older age, or if you smoke, your doctor may decide that XELJANZ is not suitable for you.

Talk to your doctor straight away if you develop sudden shortness of breath or difficulty breathing, chest pain or pain in upper back, swelling of the leg or arm, leg pain or tenderness, or redness or

discoloration in the leg or arm while taking XELJANZ, as these may be signs of a clot in the lungs or veins.

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.

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 rifampicin, used to treat bacterial infections
- fluconazole, ketoconazole, 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 and strong chemical immunosuppressants including azathioprine, mercaptopurine, ciclosporine, and tacrolimus. Taking XELJANZ with these medicines may increase your risk of side effects including infection.

Serious infections may happen more often in people who also take corticosteroids (e.g., prednisone).

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 must 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 must 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 11 mg prolonged-release tablet contains sorbitol
This medicine contains approximately 152 mg sorbitol in each prolonged-release tablet.

3. How to take XELJANZ

Always take this medicine exactly as your doctor has told you, the recommended dose should not be exceeded. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 11 mg prolonged-release tablet administered once daily.

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.

If you suffer from rheumatoid arthritis, your doctor may switch your tablets from XELJANZ 5 mg film-coated tablets twice daily to XELJANZ 11 mg prolonged-release tablets once daily. You can start the Xeljanz 11 mg prolonged-release tablets once daily the day following the last dose of XELJANZ 5 mg film-coated tablets. You should not switch between the XELJANZ 5 mg film-coated tablet and the XELJANZ 11 mg prolonged-release tablet unless instructed by your doctor.

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

Try to take your tablet (one 11 mg prolonged-release tablet) at the same time each day, e.g., morning or evening.

Swallow XELJANZ 11 mg prolonged-release tablets whole in order to ensure the entire dose is delivered correctly. Do not crush, split, or chew.

If you take more XELJANZ than you should
If you take more 11 mg prolonged-release 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 11 mg prolonged-release tablet. Take your next 11 mg prolonged-release 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 ulcers or holes in your stomach (uncommon) 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).

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

Signs of blood clots in lungs or veins (uncommon: venous thromboembolism) include
- sudden shortness of breath or difficulty breathing
- chest pain or pain in upper back
- swelling of the leg or arm
- leg pain or tenderness
- redness or discoloration in the leg or arm

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, low red blood cell count (anaemia), fever, fatigue (tiredness), 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 (including increased LDL), weight gain, dehydration, muscle strain, pain in the muscles and joints, tendonitis, joint swelling, joint sprain, abnormal sensations, poor sleep, sinus congestion, shortness of breath or difficulty breathing, skin redness, itching, fatty liver, 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), disseminated tuberculosis involving bones and other organs, other unusual infections, joint infections.

Very rare (may affect up to 1 in 10,000 people): tuberculosis involving the brain and spinal cord, meningitis.

In general, fewer side effects were seen when XELJANZ was used alone than in combination with methotrexate in rheumatoid arthritis.

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 11 mg prolonged-release tablet contains 11 mg of tofacitinib (as tofacitinib citrate).
- The other ingredients are sorbitol (E420) (see section 2), hydroxyethyl cellulose, copovidone, magnesium stearate, cellulose acetate, hydroxypropyl cellulose (E463), hypromellose (E464), titanium dioxide (E171), triacetin (E1518), red iron oxide (E172), shellac (E904), ammonium hydroxide (E527), propylene glycol (E1520) and black iron oxide (E172).

What XELJANZ looks like and contents of the pack

- XELJANZ 11 mg prolonged-release tablet is pink and oval in appearance.
- The 11 mg prolonged-release tablets are provided in blisters containing 7 prolonged-release tablets. Each pack contains 28 or 91 prolonged-release tablets.
- The prolonged-release tablets are also available in bottles with silica gel desiccant containing 30 or 90 prolonged-release tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Pfizer Europe MA EEIG
Boulevard de la Plaine 17

1050 Bruxelles
Belgium

Manufacturer

Pfizer Manufacturing Deutschland GmbH
Betriebsstätte Freiburg
Mooswaldallee 1
79090 Freiburg
Germany

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België /Belgique / Belgien
Pfizer S.A./N.V.
Tél/Tel: +32 (0)2 554 62 11

България
Пфайзер Люксембург САРЛ, Клон България
Тел.: +359 2 970 4333

Česká republika
Pfizer PFE, spol. s r.o.
Tel: +420 283 004 111

Danmark
Pfizer ApS
Tlf: +45 44 20 11 00

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)30 550055-51000

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Ελλάδα
PFIZER ΕΛΛΑΣ A.E.
Τηλ: +30 210 67 85 800

España
Pfizer S.L.
Tel: +34 91 490 99 00

France
Pfizer
Tél: +33 (0)1 58 07 34 40

Hrvatska
Pfizer Croatia d.o.o.
Tel: +385 1 3908 777

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel. +3705 2514000

Luxembourg/Luxemburg
Pfizer S.A.
Tél/Tel: +32 (0)2 554 62 11

Magyarország
Pfizer Kft.
Tel.: +36 1 488 37 00

Malta
Vivian Corporation Ltd.
Tel : +35621 344610

Nederland
Pfizer bv
Tel: +31 (0)10 406 43 01

Norge
Pfizer Norge AS
Tlf: +47 67 52 61 00

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel: +43 (0)1 521 15-0

Polska
Pfizer Polska Sp. z o.o.,
Tel.: +48 22 335 61 00

Portugal
Pfizer Biofarmacêutica, Sociedade Unipessoal, Lda.
Tel: +351 21 423 5500

România
Pfizer Romania S.R.L.
Tel: +40 21 207 28 00

Ireland
Pfizer Healthcare Ireland
Tel: 1800 633 363 (toll free)
+44 (0)1304 616161

Ísland
Icepharma hf.
Sími: +354 540 8000

Italia
Pfizer S.r.l.
Tel: +39 06 33 18 21

Κύπρος
PFIZER ΕΛΛΑΣ A.E. (CYPRUS BRANCH)
Τηλ: +357 22 817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel: +371 670 35 775

Slovenija
Pfizer Luxembourg SARL
Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: +386 (0) 1 52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: +421-2-3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: +358 (0)9 430 040

Sverige
Pfizer Innovations AB
Tel: +46 (0)8 550 520 00

United Kingdom
Pfizer Limited
Tel: +44 (0)1304 616161

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.