ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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)

XELJANZ 5 mg film-coated tablets

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

XELJANZ 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 (DMARDs) (see section 5.1). 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).

Ankylosing spondylitis

Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

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).

Juvenile idiopathic arthritis (JIA)

Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs.

Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

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 film-coated tablets administered twice daily, which should not be exceeded.

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

For information on switching between tofacitinib film-coated tablets and tofacitinib prolonged-release tablets see Table 1.

Table 1: Switching between tofacitinib film-coated tablets and tofacitinib prolonged-release tablets

Switching between tofacitinib 5 mg film-coated tablets and tofacitinib 11 mg prolonged-release tablet[a]	Treatment with tofacitinib 5 mg film-coated tablets twice daily and tofacitinib 11 mg prolonged-release tablet once daily may be switched between each other on the day following the last dose of either tablet.

[a] See section 5.2 for comparison of pharmacokinetics of prolonged-release and film-coated formulations.

Ankylosing spondylitis

The recommended dose of tofacitinib is 5 mg administered twice daily.

Ulcerative colitis

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

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.

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), major adverse cardiovascular events (MACE) and malignancy 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, MACE and malignancy (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).

Polyarticular JIA and juvenile PsA (children between 2 and 18 years of age)

Tofacitinib may be used as monotherapy or in combination with MTX.

The recommended dose in patients 2 years of age and older is based upon the following weight categories:

Table 2: Tofacitinib dose for patients with polyarticular juvenile idiopathic arthritis and juvenile PsA two years of age and older

Body weight (kg)	Dose regimen
10 - < 20	3.2 mg (3.2 mL of oral solution) twice daily
20 - < 40	4 mg (4 mL of oral solution) twice daily
≥ 40	5 mg (5 mL of oral solution or 5 mg film-coated tablet) twice daily

Patients ≥ 40 kg treated with tofacitinib 5 mL oral solution twice daily may be switched to tofacitinib 5 mg film-coated tablets twice daily. Patients < 40 kg cannot be switched from tofacitinib oral solution.

Dose interruption and discontinuation in adults and paediatric patients

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 3, 4 and 5 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 3: Low absolute lymphocyte count

Low absolute lymphocyte count (ALC) (see section 4.4)	
Laboratory 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. 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 laboratory value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in adult patients with an absolute neutrophil count (ANC) less than 1,000 cells/mm^3. It is recommended not to initiate dosing in paediatric patients with an absolute neutrophil count (ANC) less than 1,200 cells/mm^3.

Table 4: Low absolute neutrophil count

Low absolute neutrophil count (ANC) (see section 4.4)	
Laboratory 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. 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 laboratory value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in adult patients with haemoglobin less than 9 g/dL. It is recommended not to initiate dosing in paediatric patients with haemoglobin less than 10 g/dL.

Table 5: Low haemoglobin value

Low haemoglobin value (see section 4.4)	
Laboratory 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.

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 (adult and paediatric patients).
- Tofacitinib dose should be reduced to 5 mg twice daily in patients receiving 10 mg twice daily (adult patients).

Only in paediatric patients: available data suggest that clinical improvement is observed within 18 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

Dose discontinuation in AS

Available data suggest that clinical improvement in AS is observed within 16 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

Special populations

Elderly

No dose adjustment is required in patients 65 years of age and older. There are limited data in patients aged 75 years and older. See section 4.4 for Use in patients 65 years of age and older.

Hepatic impairment

Table 6: 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 7: 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 less than 2 years of age with polyarticular JIA and juvenile PsA has not been established. No data are available.

The safety and efficacy of tofacitinib in children less than 18 years of age with other indications (e.g., ulcerative colitis) has 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

Tofacitinib should only be used if no suitable treatment alternatives are available in patients: -65 years of age and older; -patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers); -patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Use in patients 65 years of age and older

Considering the increased risk of serious infections, myocardial infarction, malignancies and all cause mortality with tofacitinib in patients 65 years of age and older, tofacitinib should only be used in these patients if no suitable treatment alternatives are available (see further details below in section 4.4 and section 5.1).

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, ciclosporin 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. In a randomised post-authorisation safety study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, a dose dependent increased risk for VTE was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

In a post hoc exploratory analysis within this study, in patients with known VTE risk factors, occurrences of subsequent VTEs were observed more frequently in tofacitinib-treated patients that, at 12 months treatment, had D-dimer level ≥2× ULN versus those with D-dimer level <2× ULN; this was not evident in TNF inhibitor-treated patients. Interpretation is limited by the low number of VTE events and restricted D-dimer test availability (only assessed at Baseline, Month 12, and at the end of the study). In patients who did not have a VTE during the study, mean D-dimer levels were significantly reduced at Month 12 relative to Baseline across all treatment arms. However, D-dimer levels ≥2× ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D-Dimer testing in this study.

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

In patients with cardiovascular or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events (MACE)” and “Malignancy”) tofacitinib should only be used if no suitable treatment alternatives are available.

In patients with VTE risk factors other than MACE or malignancy risk factors, tofacitinib should be used with caution. VTE risk factors other than MACE or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.

For patients with RA with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is ≥ 2× ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib.

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

Retinal venous thrombosis

Retinal venous thrombosis (RVT) has been reported in patients treated with tofacitinib (see section 4.8). The patients should be advised to promptly seek medical care in case they experience symptoms suggestive of RVT.

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 (see section 4.8). 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.

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 65 years of age and older, tofacitinib should only be used if no suitable treatment alternatives are 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) have been observed in patients receiving tofacitinib (see section 4.8).

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 studies. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with tofacitinib.

Major adverse cardiovascular events (including myocardial infarction)

Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib.

In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1). In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1).

Malignancies and lymphoproliferative disorder

Tofacitinib may affect host defences against malignancies.

In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies, particularly NMSC, lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

NMSC lung cancers and lymphoma in patients treated with tofacitinib have also been observed in other clinical studies and in the post marketing setting.

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

In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1). Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer (see Table 8 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 studies 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 studies 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.

Fractures

Fractures have been observed in patients treated with tofacitinib.

Tofacitinib should be used with caution in patients with known risk factors for fractures such as elderly patients, female patients and patients with corticosteroid use, regardless of indication and dosage.

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 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 adult patients with an ANC less than 1,000 cells/mm^3 and in paediatric patients with an ANC less than 1,200 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 adult patients with a haemoglobin value less than 9 g/dL and in paediatric patients with a haemoglobin value less than 10 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.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of tofacitinib in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycaemia occurs.

Vaccinations

Prior to initiating tofacitinib, it is recommended that all patients, particularly pJIA and jPsA 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 contents

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.

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

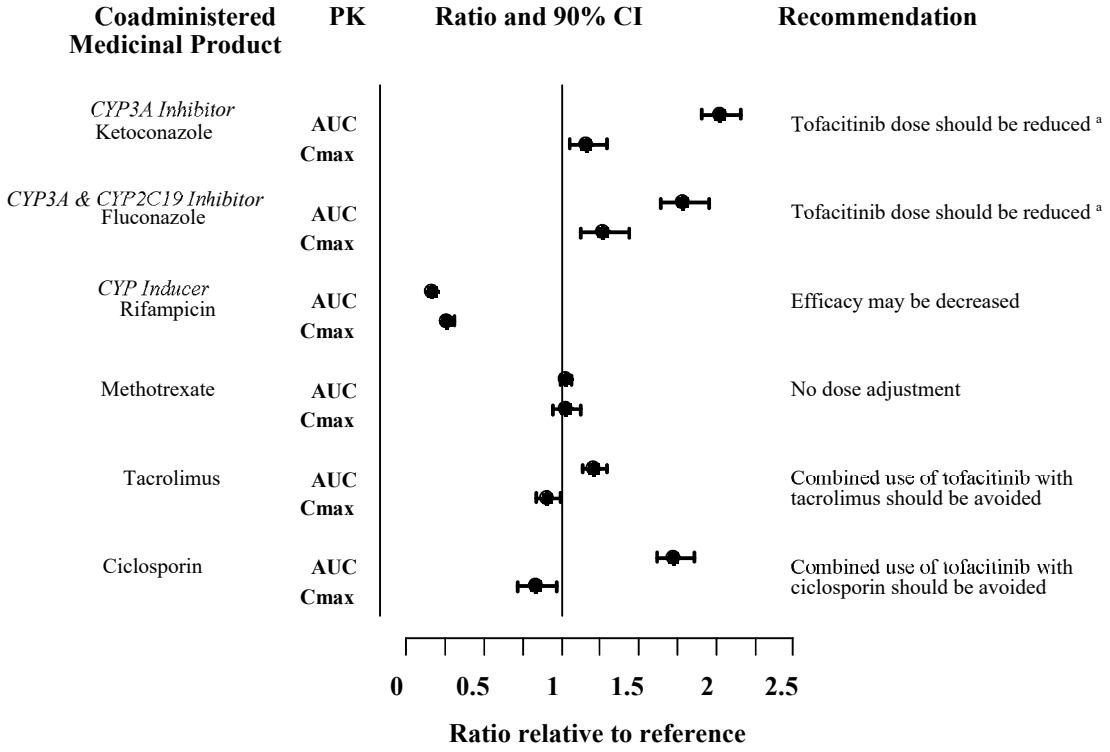
Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib

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 ciclosporin (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, ciclosporin 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.

Paediatric population

Interaction studies have only been performed in adults.

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). In the long-term safety all exposure population, the most common serious infections reported with tofacitinib were pneumonia (1.7%), herpes zoster (0.6%), urinary tract infection (0.4%), cellulitis (0.4%), diverticulitis (0.3%), and appendicitis (0.2%). Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus infection, 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 of the double-blind, placebo or MTX controlled clinical studies were headache (3.9%), upper respiratory tract infections (3.8%), viral upper respiratory tract infection (3.3%), diarrhoea (2.9%), nausea (2.7%), and hypertension (2.2%).

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 during the first 3 months in controlled clinical studies were herpes zoster (0.19%) and pneumonia (0.15%).

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.

Ankylosing spondylitis
Overall, the safety profile observed in patients with active AS 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 adverse reactions listed in the table below are from clinical studies in patients with RA, PsA, AS, 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, adverse reactions are presented in the order of decreasing seriousness.

Table 8: Adverse 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 Bacteraemia *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal Pneumonia bacterial Cytomegalovirus infection Arthritis bacterial	Tuberculosis of central nervous system Meningitis cryptococcal Necrotizing fasciitis Encephalitis Staphylococcal bacteraemia *Mycobacterium avium* complex infection Atypical mycobacterial infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Lung cancer Non-melanoma skin cancers	Lymphoma		
Blood and lymphatic system disorders	Lymphopenia Anaemia	Leukopenia Neutropenia			
Immune system disorders					Hypersensitivity * Angioedema* Urticaria*
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia Dehydration			
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache	Paraesthesia			
Cardiac disorders		Myocardial infarction			
Vascular disorders	Hypertension	Venous thromboembolism**			

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)
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea Sinus congestion			
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia				
Hepatobiliary disorders		Hepatic steatosis Hepatic enzyme increased Transaminases increased Gamma glutamyl-transferase increased	Liver function test abnormal		
Skin and subcutaneous tissue disorders	Rash	Erythema Pruritus			
Musculoskeletal and connective tissue disorders	Arthralgia	Joint swelling Tendonitis	Musculoskeletal pain		
General disorders and administration site conditions	Oedema peripheral	Pyrexia 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, DVT, and Retinal Venous Thrombosis

Description of selected adverse reactions

Venous thromboembolism

Rheumatoid arthritis
In a large (N=4,362), randomised post-authorisation safety study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors (see section 5.1). The majority of these events were serious and some resulted in death. The incidence rates (95% CI) for PE for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.17 (0.08-0.33), 0.50 (0.32-0.74), and 0.06 (0.01-0.17) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for PE was 2.93 (0.79-10.83) and 8.26 (2.49, 27.43) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, respectively (see section 5.1). In tofacitinib-treated patients where PE was observed, the majority (97%) had VTE risk factors.

Ankylosing spondylitis

In the combined Phase 2 and Phase 3 randomised controlled clinical studies, there were no VTE events in 420 patients (233 patient-years of observation) receiving tofacitinib up to 48 weeks.

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.

Ankylosing spondylitis
In the combined Phase 2 and Phase 3 clinical studies, during the placebo-controlled period of up to 16 weeks, the frequency of infections in the tofacitinib 5 mg twice daily group (185 patients) was 27.6% and the frequency in the placebo group (187 patients) was 23.0%. In the combined Phase 2 and Phase 3 clinical studies, among the 316 patients treated with tofacitinib 5 mg twice daily for up to 48 weeks, the frequency of infections was 35.1%.

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).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, a dose-dependent increase in serious infections was observed with tofacitinib compared to TNF inhibitors (see section 4.4).

The incidence rates (95% CI) for serious infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 2.86 (2.41, 3.37), 3.64 (3.11, 4.23), and 2.44 (2.02, 2.92) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for serious infections was 1.17 (0.92, 1.50) and 1.48 (1.17, 1.87) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily, respectively.

Ankylosing spondylitis
In the combined Phase 2 and Phase 3 clinical studies, among the 316 patients treated with tofacitinib 5 mg twice daily for up to 48 weeks, there was one serious infection (aseptic meningitis) yielding a rate of 0.43 patients with events per 100 patient-years.

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).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, an increase in serious infections was observed in patients 65 years of age and older for tofacitinib 10 mg twice daily compared to TNF inhibitors and to tofacitinib 5 mg twice daily (see section 4.4). The incidence rates (95% CI) for serious infections in patients ≥65 years were 4.03 (3.02, 5.27), 5.85 (4.64, 7.30), and 3.73 (2.81, 4.85) patients with events per 100 patient-years for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors, respectively.

Compared with TNF inhibitors, the hazard ratio (HR) for serious infections in patients ≥65 years of age was 1.08 (0.74, 1.58) and 1.55 (1.10, 2.19) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, respectively.

Serious infections from non-interventional post approval safety study
Data from a non-interventional post approval safety study that evaluated tofacitinib in RA patients from a registry (US Corrona) showed that a numerically higher incidence rate of serious infection was observed for the 11 mg prolonged-release tablet administered once daily than the 5 mg film-coated tablet

administered twice daily. Crude incidence rates (95% CI) (i.e., not adjusted for age or sex) from availability of each formulation at 12 months following initiation of treatment were 3.45 (1.93, 5.69) and 2.78 (1.74, 4.21) and at 36 months were 4.71 (3.08, 6.91) and 2.79 (2.01, 3.77) patients with events per 100 patient-years in the 11 mg prolonged-release tablet once daily and 5 mg film-coated tablet twice daily groups, respectively. The unadjusted hazard ratio was 1.30 (95% CI: 0.67, 2.50) at 12 months and 1.93 (95% CI: 1.15, 3.24) at 36 months for the 11 mg prolonged-release once daily dose compared to the 5 mg film-coated twice daily dose. Data is based on a small number of patients with events observed with relatively large confidence intervals and limited follow up time.

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).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, an increase in herpes zoster events was observed in patients treated with tofacitinib compared to TNF inhibitors. The incidence rates (95% CI) for herpes zoster for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 3.75 (3.22, 4.34), 3.94 (3.38, 4.57), and 1.18 (0.90, 1.52) patients with events per 100 patient-years, respectively.

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.

Platelets
Patients in the Phase 3 controlled clinical studies (RA, PsA, AS, UC) were required to have a platelet count ≥ 100,000 cells/mm^3 to be eligible for enrolment, therefore, there is no information available for patients with a platelet count < 100,000 cells/mm^3 before starting treatment with tofacitinib.

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 a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, ALT elevations greater than or equal to 3x ULN were observed in 6.01%, 6.54% and 3.77% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors respectively. AST elevations greater than or equal to 3x ULN were observed in 3.21%, 4.57% and 2.38% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors respectively.

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 studies 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 study, 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 a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, changes in lipid parameters from baseline through 24 months are summarised below:

- Mean LDL cholesterol increased by 13.80%, 17.04%, and 5.50% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor, respectively, at month 12. At month 24, the increase was 12.71%, 18.14%, and 3.64%, respectively,
- Mean HDL cholesterol increased by 11.71%, 13.63%, and 2.82% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor, respectively, at month 12. At month 24, the increase was 11.58%, 13.54%, and 1.42%, respectively.

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

Myocardial infarction

Rheumatoid arthritis
In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for non-fatal myocardial infarction for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), and 0.16 (0.07, 0.31) patients with events per 100 patient-years, respectively. Few fatal myocardial infarctions were reported with rates similar in patients treated with tofacitinib compared to TNF inhibitors (see sections 4.4 and 5.1). The study required at least 1500 patients to be followed for 3 years.

Malignancies excluding NMSC

Rheumatoid arthritis
In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for lung cancer for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.23 (0.12, 0.40), 0.32 (0.18, 0.51), and 0.13 (0.05, 0.26) patients with events per 100 patient-years, respectively (see sections 4.4 and 5.1). The study required at least 1500 patients to be followed for 3 years.

The incidence rates (95% CI) for lymphoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), and 0.02 (0.00, 0.10) patients with events per 100 patient-years, respectively (see sections 4.4 and 5.1).

Paediatric population

Polyarticular juvenile idiopathic arthritis and juvenile PsA
The adverse reactions in JIA patients in the clinical development program were consistent in type and frequency with those seen in adult RA patients, with the exception of some infections (influenza, pharyngitis, sinusitis, viral infection) and gastrointestinal or general disorders (abdominal pain, nausea, vomiting, pyrexia, headache, cough), which were more common in JIA paediatric population. MTX was the most frequent concomitant csDMARD used (on Day 1, 156 of 157 patients on csDMARDs took MTX). There are insufficient data regarding the safety profile of tofacitinib used concomitantly with any other csDMARDs.

Infections
In the double-blind portion of the pivotal Phase 3 trial (Study JIA-I), infection was the most commonly reported adverse reaction (44.3%). The infections were generally mild to moderate in severity.

In the integrated safety population, 7 patients had serious infections during treatment with tofacitinib within the reporting period (up to 28 days after the last dose of study medication), representing an incidence rate of 1.92 patients with events per 100 patient-years: pneumonia, epidural empyema (with sinusitis and subperiosteal abscess), pilonidal cyst, appendicitis, escherichia pyelonephritis, abscess limb, and UTI.

In the integrated safety population, 3 patients had non-serious events of herpes zoster within the reporting window representing an incidence rate of 0.82 patients with events per 100 patient-years. One (1) additional patient had an event of serious HZ outside the reporting window.

Hepatic events

Patients in the JIA pivotal study were required to have AST and ALT levels less than 1.5 times the upper limit of normal to be eligible for enrolment. In the integrated safety population, there were 2 patients with ALT elevations ≥ 3 times the ULN at 2 consecutive visits. Neither event met Hy's Law criteria. Both patients were on background MTX therapy and each event resolved after discontinuation of MTX and permanent discontinuation of tofacitinib.

Laboratory tests

Changes in laboratory tests in JIA patients in the clinical development program were consistent with those seen in adult RA patients. Patients in the JIA pivotal study were required to have a platelet count ≥ 100,000 cells/mm^3 to be eligible for enrolment, therefore, there is no information available for JIA patients with a platelet count <100,000 cells/mm^3 before starting treatment with tofacitinib.

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 study 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 herpes virus vaccine 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 medicinal product. 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 film-coated tablets 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 9 provides information regarding the pertinent study design and population characteristics.

Table 9: Phase 3 clinical studies 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
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

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)

[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 10. 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 10: 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 11.

Table 11: 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 12, 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 12: 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 13.

Table 13: 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 5 years is also provided from data in a randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, as well as in completed open-label, long-term follow-up studies up to 8 years.

Long-term controlled safety data

Study ORAL Surveillance (A3921133) was a large (N=4362), randomised active-controlled post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional 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, anaemia of chronic disease, pulmonary manifestations). The majority (more than 90%) of tofacitinib patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively. Patients were required to be on a stable dose of methotrexate at study entry; dose adjustment was permitted during the study.

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 were adjudicated malignancies excluding NMSC and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessment of endpoints were blinded. The study was an event-powered study that also required at least 1500 patients to be followed for 3 years. The study treatment of tofacitinib 10 mg twice daily was stopped and patients were switched to 5 mg twice daily because of a dose-dependent signal of venous thromboembolic events (VTE). For patients in the tofacitinib 10 mg twice daily treatment arm, the data collected before and after the dose switch were analysed in their originally randomised treatment group.

The study did not meet the non-inferiority criterion for the primary comparison of the combined tofacitinib doses to TNF inhibitor since the upper limit of the 95% CI for HR exceeded the pre-specified non-inferiority criterion of 1.8 for adjudicated MACE and adjudicated malignancies excluding NMSC.

The results for adjudicated MACE, adjudicated malignancies excluding NMSC, and selected other events are provided below.

MACE (including myocardial infarction) and venous thromboembolism (VTE)
An increase in non-fatal myocardial infarction was observed in patients treated with tofacitinib compared to TNF inhibitor. A dose-dependent increase in VTE events was observed in patients treated with tofacitinib compared to TNF inhibitor (see sections 4.4 and 4.8).

Table 14: Incidence rate and hazard ratio for MACE, myocardial infarction and venous thromboembolism

	Tofacitinib 5 mg twice daily	**Tofacitinib 10 mg twice daily[a]**	**All Tofacitinib[b]**	**TNF inhibitor (TNFi)**
MACE[c]				
IR (95% CI) per 100 PY	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.98 (0.79, 1.19)	0.73 (0.52, 1.01)
HR (95% CI) vs TNFi	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)	
Fatal MI[c]				
IR (95% CI) per 100 PY	0.00 (0.00, 0.07)	0.06 (0.01, 0.18)	0.03 (0.01, 0.09)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	0.00 (0.00, Inf)	1.03 (0.21, 5.11)	0.50 (0.10, 2.49)	
Non-fatal MI[c]				
IR (95% CI) per 100 PY	0.37 (0.22, 0.57)	0.33 (0.19, 0.53)	0.35 (0.24, 0.48)	0.16 (0.07, 0.31)
HR (95% CI) vs TNFi	2.32 (1.02, 5.30)	2.08 (0.89, 4.86)	2.20 (1.02, 4.75)	
VTE[d]				
IR (95% CI) per 100 PY	0.33 (0.19, 0.53)	0.70 (0.49, 0.99)	0.51 (0.38, 0.67)	0.20 (0.10, 0.37)
HR (95% CI) vs TNFi	1.66 (0.76, 3.63)	3.52 (1.74, 7.12)	2.56 (1.30, 5.05)	
PE[d]				
IR (95% CI) per 100 PY	0.17 (0.08, 0.33)	0.50 (0.32, 0.74)	0.33 (0.23, 0.46)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	2.93 (0.79, 10.83)	8.26 (2.49, 27.43)	5.53 (1.70, 18.02)	

DVT[d]				
IR (95% CI) per 100 PY	0.21 (0.11, 0.38)	0.31 (0.17, 0.51)	0.26 (0.17, 0.38)	0.14 (0.06, 0.29)
HR (95% CI) vs TNFi	1.54 (0.60, 3.97)	2.21 (0.90, 5.43)	1.87 (0.81, 4.30)	

[a] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.
[b] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
[c] Based on events occurring on treatment or within 60 days of treatment discontinuation.
[d] Based on events occurring on treatment or within 28 days of treatment discontinuation.
Abbreviations: MACE = major adverse cardiovascular events, MI = myocardial infarction, VTE = venous thromboembolism, PE = pulmonary embolism, DVT = deep vein thrombosis, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, Inf = infinity

The following predictive factors for development of MI (fatal and non-fatal) were identified using a multivariate Cox model with backward selection: age ≥65 years, male, current or past smoking, history of diabetes, and history of coronary artery disease (which includes myocardial infarction, coronary heart disease, stable angina pectoris, or coronary artery procedures) (see sections 4.4 and 4.8).

Malignancies

An increase in malignancies excluding NMSC, particularly lung cancer, lymphoma and an increase in NMSC was observed in patients treated with tofacitinib compared to TNF inhibitor.

Table 15: Incidence rate and hazard ratio for malignancies[a]

	Tofacitinib 5 mg twice daily	**Tofacitinib 10 mg twice daily[b]**	**All Tofacitinib[c]**	**TNF inhibitor (TNFi)**
Malignancies excluding NMSC				
IR (95% CI) per 100 PY	1.13 (0.87, 1.45)	1.13 (0.86, 1.45)	1.13 (0.94, 1.35)	0.77 (0.55, 1.04)
HR (95% CI) vs TNFi	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)	
Lung cancer				
IR (95% CI) per 100 PY	0.23 (0.12, 0.40)	0.32 (0.18, 0.51)	0.28 (0.19, 0.39)	0.13 (0.05, 0.26)
HR (95% CI) vs TNFi	1.84 (0.74, 4.62)	2.50 (1.04, 6.02)	2.17 (0.95, 4.93)	
Lymphoma				
IR (95% CI) per 100 PY	0.07 (0.02, 0.18)	0.11 (0.04, 0.24)	0.09 (0.04, 0.17)	0.02 (0.00, 0.10)
HR (95% CI) vs TNFi	3.99 (0.45, 35.70)	6.24 (0.75, 51.86)	5.09 (0.65, 39.78)	
NMSC				
IR (95% CI) per 100 PY	0.61 (0.41, 0.86)	0.69 (0.47, 0.96)	0.64 (0.50, 0.82)	0.32 (0.18, 0.52)
HR (95% CI) vs TNFi	1.90 (1.04, 3.47)	2.16 (1.19, 3.92)	2.02 (1.17, 3.50)	

[a] For malignancies excluding NMSC, lung cancer, and lymphoma, based on events occurring on treatment or after treatment discontinuation up to the end of the study. For NMSC based on events occurring on treatment or within 28 days of treatment discontinuation.
[b] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.
[c] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
Abbreviations: NMSC = non melanoma skin cancer, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years

The following predictive factors for development of malignancies excluding NMSC were identified using a Multivariate Cox model with backward selection: age ≥65 years and current or past smoking (see sections 4.4 and 4.8).

Mortality

Increased mortality was observed in patients treated with tofacitinib compared to TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies.

Table 16: Incidence rate and hazard ratio for mortality[a]

	Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily[b]	All Tofacitinib[c]	TNF inhibitor (TNFi)
Mortality (all cause)				
IR (95% CI) per 100 PY	0.50 (0.33, 0.74)	0.80 (0.57, 1.09)	0.65 (0.50, 0.82)	0.34 (0.20, 0.54)
HR (95% CI) vs TNFi	1.49 (0.81, 2.74)	2.37 (1.34, 4.18)	1.91 (1.12, 3.27)	
Fatal infections				
IR (95% CI) per 100 PY	0.08 (0.02, 0.20)	0.18 (0.08, 0.35)	0.13 (0.07, 0.22)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	1.30 (0.29, 5.79)	3.10 (0.84, 11.45)	2.17 (0.62, 7.62)	
Fatal CV events				
IR (95% CI) per 100 PY	0.25 (0.13, 0.43)	0.41 (0.25, 0.63)	0.33 (0.23, 0.46)	0.20 (0.10, 0.36)
HR (95% CI) vs TNFi	1.26 (0.55, 2.88)	2.05 (0.96, 4.39)	1.65 (0.81, 3.34)	
Fatal Malignancies				
IR (95% CI) per 100 PY	0.10 (0.03, 0.23)	0.00 (0.00, 0.08)	0.05 (0.02, 0.12)	0.02 (0.00, 0.11)
HR (95% CI) vs TNFi	4.88 (0.57, 41.74)	0 (0.00, Inf)	2.53 (0.30, 21.64)	

[a] Based on events occurring on treatment or within 28 days of treatment discontinuation.
[b] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.
[c] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
Abbreviations: TNF = tumor necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, CV = cardiovascular, Inf = infinity

Psoriatic arthritis
The efficacy and safety of tofacitinib film-coated tablets 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 17.

Table 17: 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 twice daily -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 twice daily 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 twice daily, adalimumab and placebo treated patients, respectively (tofacitinib 5 mg twice daily 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 twice daily and placebo treated patients, respectively, however tofacitinib 5 mg twice daily 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 18).

Table 18: 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 $p \leq 0.05$).

Ankylosing spondylitis

The tofacitinib clinical development program to assess the efficacy and safety included one placebo-controlled confirmatory trial (Study AS-I). Study AS-I was a randomised, double-blind, placebo-controlled, 48-week treatment clinical study in 269 adult patients who had an inadequate response (inadequate clinical response or intolerance) to at least 2 NSAIDs. Patients were randomised and treated with tofacitinib 5 mg twice daily or placebo for 16 weeks of blinded treatment and then all were advanced to tofacitinib 5 mg twice daily for an additional 32 weeks. Patients had active disease as defined by both Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and back pain score (BASDAI question 2) of greater or equal to 4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or DMARD therapy.

Approximately 7% and 21% of patients used concomitant methotrexate or sulfasalazine, respectively, from baseline to Week 16. Patients were allowed to receive a stable low dose of oral corticosteroids (8.6% received) and/or NSAIDs (81.8% received) from baseline to Week 48. Twenty-two percent of patients had an inadequate response to 1 or 2 TNF blockers. The primary endpoint was to evaluate the proportion of patients who achieved an ASAS20 response at Week 16.

Clinical response

Patients treated with tofacitinib 5 mg twice daily achieved greater improvements in ASAS20 and ASAS40 responses compared to placebo at Week 16 (Table 19). The responses were maintained from Week 16 through to Week 48 in patients receiving tofacitinib 5 mg twice daily.

Table 19: ASAS20 and ASAS40 Responses at Week 16, Study AS-I

	Placebo (N=136)	**Tofacitinib 5 mg Twice Daily (N=133)**	**Difference from Placebo (95% CI)**
ASAS20 response*, %	29	56	27 (16, 38)**
ASAS40 response*, %	13	41	28 (18, 38)**

* type I error-controlled.
** $p < 0.0001$.

The efficacy of tofacitinib was demonstrated in bDMARD naïve and TNF-inadequate responders (IR)/bDMARD experienced (non-IR) patients (Table 20).

Table 20. ASAS20 and ASAS40 Responses (%) by Treatment History at Week 16, Study AS-I

Prior Treatment History	**Efficacy Endpoint**					
	ASAS20			**ASAS40**		
	Placebo N	**Tofacitinib 5 mg Twice Daily N**	**Difference from Placebo (95% CI)**	**Placebo N**	**Tofacitinib 5 mg Twice Daily N**	**Difference from Placebo (95% CI)**
bDMARD-Naïve	105	102	28 (15, 41)	105	102	31 (19, 43)
TNFi-IR or bDMARD Use (Non-IR)	31	31	23 (1, 44)	31	31	19 (2, 37)

Prior Treatment History	Efficacy Endpoint					
	ASAS20			ASAS40		
	Placebo N	Tofacitinib 5 mg Twice Daily N	Difference from Placebo (95% CI)	Placebo N	Tofacitinib 5 mg Twice Daily N	Difference from Placebo (95% CI)

ASAS20 = An improvement from Baseline ≥ 20% and ≥ 1 unit increase in at least 3 domains on a scale of 0 to 10, and no worsening of ≥ 20% and ≥ 1 unit in the remaining domain; ASAS40 = An improvement from Baseline ≥ 40% and ≥ 2 units in at least 3 domains on a scale of 0 to 10 and no worsening at all in the remaining domain; bDMARD = biologic disease-modifying anti-rheumatic drug; CI = confidence interval; Non-IR = non-inadequate response; TNFi-IR = tumour necrosis factor inhibitor inadequate response.

The improvements in the components of the ASAS response and other measures of disease activity were higher in tofacitinib 5 mg twice daily compared to placebo at Week 16 as shown in Table 21. The improvements were maintained from Week 16 through to Week 48 in patients receiving tofacitinib 5 mg twice daily.

Table 21: ASAS Components and Other Measures of Disease Activity at Week 16, Study AS-I

	Placebo (N=136)		Tofacitinib 5 mg Twice Daily (N=133)		
	Baseline (mean)	Week 16 (LSM change from Baseline)	Baseline (mean)	Week 16 (LSM change from Baseline)	Difference from Placebo (95% CI)
ASAS Components					
– Patient Global Assessment of Disease Activity (0-10)[a,*]	7.0	-0.9	6.9	-2.5	-1.6 (-2.07, -1.05)**
– Total spinal pain (0-10)[a,*]	6.9	-1.0	6.9	-2.6	-1.6 (-2.10, -1.14)**
– BASFI (0-10)[b,*]	5.9	-0.8	5.8	-2.0	-1.2 (-1.66, -0.80)**
– Inflammation (0-10)[c,*]	6.8	-1.0	6.6	-2.7	-1.7 (-2.18, -1.25)**
BASDAI Score[d]	6.5	-1.1	6.4	-2.6	-1.4 (-1.88, -1.00)**
BASMI[e,*]	4.4	-0.1	4.5	-0.6	-0.5 (-0.67, -0.37)**
hsCRP[f,*] (mg/dL)	1.8	-0.1	1.6	-1.1	-1.0 (-1.20, -0.72)**
ASDAScrp[g,*]	3.9	-0.4	3.8	-1.4	-1.0 (-1.16, -0.79)**

* type I error-controlled.
** $p < 0.0001$.
[a] Measured on a numerical rating scale with 0 = not active or no pain, 10 = very active or most severe pain.
[b] Bath Ankylosing Spondylitis Functional Index measured on a numerical rating scale with 0 = easy and 10 = impossible.
[c] Inflammation is the mean of two patient-reported stiffness self-assessments in BASDAI.
[d] Bath Ankylosing Spondylitis Disease Activity Index total score.
[e] Bath Ankylosing Spondylitis Metrology Index.
[f] High sensitivity C-reactive protein.
[g] Ankylosing Spondylitis Disease Activity Score with C-reactive protein.
LSM = least squares mean

Other health-related outcomes
Patients treated with tofacitinib 5 mg twice daily achieved greater improvements from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) (-4.0 vs -2.0) and Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) Total score (6.5 vs 3.1) compared to placebo-treated patients at Week 16 ($p<0.001$). Patients treated with tofacitinib 5 mg twice daily achieved consistently greater improvements from baseline in the Short Form health survey version 2 (SF-36v2), Physical Component Summary (PCS) domain compared to placebo-treated patients at Week 16.

Ulcerative colitis
The efficacy and safety of tofacitinib film-coated tablets 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 22 provides additional information regarding pertinent study design and population characteristics.

Table 22: 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 23.

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

Table 23: 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 24).

Table 24. 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 25.

Table 25: 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 26). 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 26: 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.

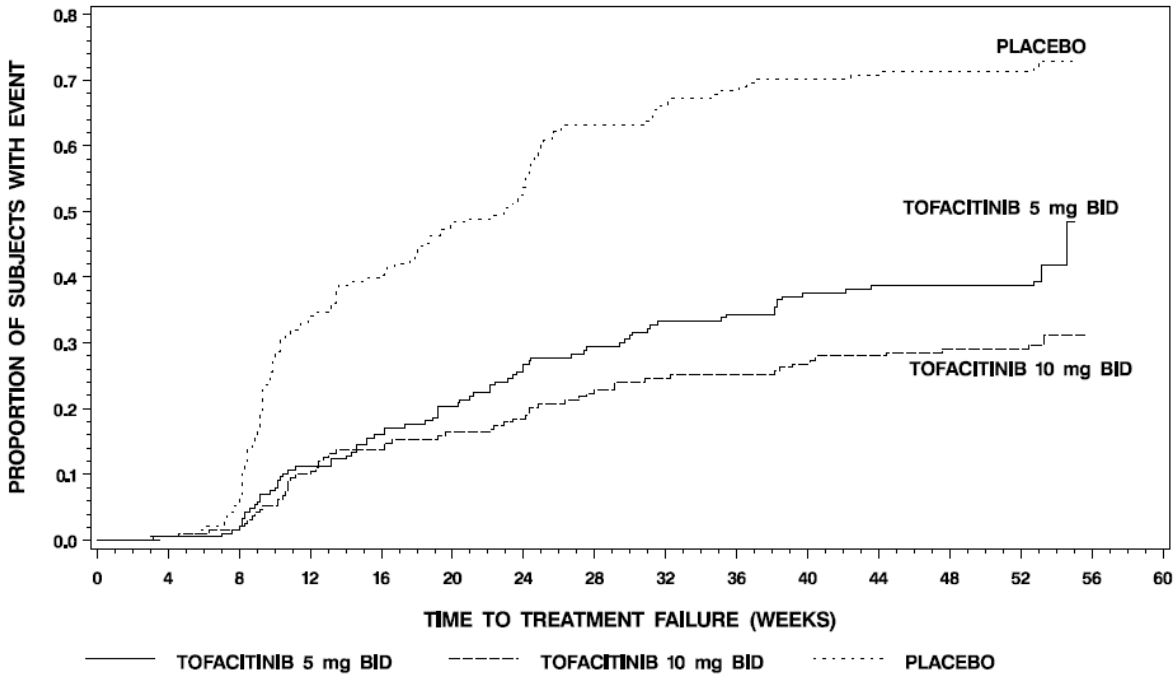
b. Included TNF Inhibitor naïve patients.

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 other rarer types of juvenile idiopathic arthritis and in ulcerative colitis (see section 4.2 for information on paediatric use).

Polyarticular juvenile idiopathic arthritis and juvenile PsA

The tofacitinib Phase 3 program for JIA consisted of one completed Phase 3 trial (Study JIA-I [A3921104]) and one ongoing long-term extension (LTE) (A3921145) trial. In these studies the following JIA subgroups were included: patients with either RF+ or RF- polyarthritis, extended oligoarthritis, systemic JIA with active arthritis and no current systemic symptoms (referred as pJIA dataset) and two separate subgroups of patients with juvenile PsA and enthesitis-related arthritis (ERA). However, the pJIA efficacy population only includes the subgroups with either RF+ or RF- polyarthritis or extended oligoarthritis; inconclusive results have been seen in the subgroup of patients with systemic JIA with active arthritis and no current systemic symptoms. Patients with juvenile PsA are included as separate efficacy subgroup. ERA patients are not included in the efficacy analysis.

All eligible patients in Study JIA-I received open-label tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily for 18 weeks (run-in phase); patients who achieved at least a JIA ACR30 response at the end of the open-label phase were randomised (1:1) to either active tofacitinib 5 mg film-coated tablets or tofacitinib oral solution, or placebo in the 26-week double-blind, placebo-controlled phase. Patients who did not achieve a JIA ACR30 response at the end of the open-label run-in phase or experienced a single episode of disease flare at any time were discontinued from the study. A total of 225 patients were enrolled in the open-label run-in phase. Of these, 173 (76.9%) patients were eligible to be randomised into the double-blind phase to either active tofacitinib 5 mg film-coated tablets or tofacitinib oral solution weight-based equivalent twice daily (n=88) or placebo (n=85). There were 58 (65.9%) patients in the tofacitinib group and 58 (68.2%) patients in the placebo group taking MTX during the double-blind phase, which was permitted but not required per the protocol.

There were 133 patients with pJIA [RF+ or RF- polyarthritis and extended oligoarthritis] and 15 with juvenile PsA randomised into the double-blind phase of the study and included in the efficacy analyses presented below.

Signs and symptoms
A significantly smaller proportion of patients with pJIA in Study JIA-I treated with tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily flared at Week 44 compared with patients treated with placebo. A significantly greater proportion of patients with pJIA treated with tofacitinib 5 mg film-coated tablets or tofacitinib oral solution achieved JIA ACR30, 50, and 70 responses compared to patients treated with placebo at Week 44 (Table 27).

The occurrence of disease flare and JIA ACR30/50/70 results were favourable to tofacitinib 5 mg twice daily in comparison to placebo across the RF+ polyarthritis, RF- polyarthritis, extended oligoarthritis, and jPsA JIA subtypes and were consistent with those for the overall study population.
The occurrence of disease flare and JIA ACR30/50/70 results were favourable to tofacitinib 5 mg twice daily in comparison to placebo for pJIA patients who received tofacitinib 5 mg twice daily with concomitant MTX use on Day 1 [n=101 (76%)] and those who were on tofacitinib monotherapy [n=32 (24%)]. In addition, the occurrence of disease flare and JIA ACR30/50/70 results were also favourable to tofacitinib 5 mg twice daily compared to placebo for pJIA patients who had prior bDMARD experience [n=39 (29%)] and those who were bDMARD naïve [n=94 (71%)].

In Study JIA-I at Week 2 of the open-label run-in phase, the JIA ACR30 response in patients with pJIA was 45.03%.

Table 27: Primary and secondary efficacy endpoints in patients with pJIA at Week 44* in Study JIA-I (all p-values<0.05)

Primary endpoint (Type I error controlled)	**Treatment group**	**Occurrence rate**	**Difference (%) from placebo (95% CI)**
Occurrence of disease flare	Tofacitinib 5 mg Twice Daily (N=67)	28%	-24.7 (-40.8, -8.5)
	Placebo (N=66)	53%	
Secondary endpoints (Type I error controlled)	**Treatment group**	**Response rate**	**Difference (%) from placebo (95% CI)**
JIA ACR30	Tofacitinib 5 mg Twice Daily (N=67)	72%	24.7 (8.50, 40.8)
	Placebo (N=66)	47%	
JIA ACR50	Tofacitinib 5 mg Twice Daily (N=67)	67%	20.2 (3.72, 36.7)
	Placebo (N=66)	47%	
JIA ACR70	Tofacitinib 5 mg Twice Daily (N=67)	55%	17.4 (0.65, 34.0)
	Placebo (N=66)	38%	
Secondary endpoint (Type I error controlled)	**Treatment group**	**LS mean (SEM)**	**Difference from placebo (95% CI)**
Change from Baseline in CHAQ Disability Index	Tofacitinib 5 mg Twice Daily (N=67; n=46)	-0.11 (0.04)	-0.11 (-0.22, -0.01)
	Placebo (N=66; n=31)	0.00 (0.04)	

ACR = American College of Rheumatology; CHAQ = childhood health assessment questionnaire; CI = confidence interval; LS = least squares; n = number of patients with observations at the visit; N = total number of patients; JIA = juvenile idiopathic arthritis; SEM = standard error of the mean
* The 26-week double-blind phase is from Week 18 through Week 44 on and after randomisation day.
The Type-I error-controlled endpoints are tested in this order: Disease Flare, JIA ACR50, JIA ACR30, JIA ACR70, CHAQ Disability Index.

In the double-blind phase, each of the components of the JIA ACR response showed greater improvement from the open-label baseline (Day 1) at Week 24, and Week 44 for patients with pJIA treated with tofacitinib oral solution dosed as 5 mg twice daily or weight-based equivalent twice daily compared with those receiving placebo in Study JIA-I.

Physical function and health-related quality of life
Changes in physical function in Study JIA-I were measured by the CHAQ Disability Index. The mean change from the double-blind baseline in CHAQ-Disability Index in patients with pJIA was significantly lower in the tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily compared to placebo at Week 44 (Table 27). The mean change from the double-blind baseline in CHAQ Disability Index results were favourable to tofacitinib 5 mg twice daily in comparison to placebo across the RF+ polyarthritis, RF- polyarthritis, extended oligoarthritis, and jPsA JIA subtypes and were consistent with those for the overall study population.

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 studies, 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, moderate to severe UC or AS 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 studies, tofacitinib was not evaluated in patients with baseline creatinine clearance values (estimated by Cockcroft-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 studies, 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.

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.

Comparison of PK of prolonged-release and film-coated tablet formulations

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

Paediatric population

Pharmacokinetics in paediatric patients with juvenile idiopathic arthritis
Population PK analysis based on results from both tofacitinib 5 mg film-coated tablets twice daily and tofacitinib oral solution weight-based equivalent twice daily indicated that tofacitinib clearance and volume of distribution both decreased with decreasing body weight in JIA patients. The available data indicated that there were no clinically relevant differences in tofacitinib exposure (AUC), based on age, race, gender, patient type or baseline disease severity. The between-subject variability (% coefficient of variation) in (AUC) was estimated to be approximately 24%.

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. In studies conducted in juvenile rats and monkeys, there were no tofacitinib-related effects on bone development in males or females, at exposures similar to those achieved at approved doses in humans.

No tofacitinib-related findings were observed in juvenile animal studies that indicate a higher sensitivity of paediatric populations compared with adults. In the juvenile rat fertility study, there was no evidence of developmental toxicity, no effects on sexual maturation, and no evidence of reproductive toxicity (mating and fertility) was noted after sexual maturity. In 1-month juvenile rat and 39-week juvenile monkey studies tofacitinib-related effects on immune and haematology parameters consistent with JAK1/3 and JAK2 inhibition were observed. These effects were reversible and consistent with those also observed in adult animals at similar exposures.

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
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

4 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
Date of renewal of the authorisation: 04 March 2022

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.

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 tablet

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

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 (DMARDs) (see section 5.1). 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).

Ankylosing spondylitis

Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

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, psoriatic arthritis, and ankylosing spondylitis

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

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

For information on switching between tofacitinib film-coated tablets and tofacitinib prolonged-release tablets see Table 1.

Table 1: Switching between tofacitinib film-coated tablets and tofacitinib prolonged-release tablets

Switching between tofacitinib 5 mg film-coated tablets and tofacitinib 11 mg prolonged-release tablet[a]	Treatment with tofacitinib 5 mg film-coated tablets twice daily and tofacitinib 11 mg prolonged-release tablet once daily may be switched between each other on the day following the last dose of either tablet.

[a] See section 5.2 for comparison of pharmacokinetics of prolonged-release and film-coated formulations.

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 2, 3 and 4 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 2: Low absolute lymphocyte count

Low absolute lymphocyte count (ALC) (see section 4.4)	
Laboratory 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. When ALC is greater than 750, treatment should be resumed as clinically appropriate.
ALC less than 500	If laboratory 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 3: Low absolute neutrophil count

Low absolute neutrophil count (ANC) (see section 4.4)	
Laboratory 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. When ANC is greater than 1,000, treatment should be resumed as clinically appropriate.
ANC less than 500	If laboratory 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 4: Low haemoglobin value

Low haemoglobin value (Section 4.4)	
Laboratory 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.

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 film-coated tablet once daily in patients receiving 11 mg prolonged-release tablet once daily.

Dose discontinuation in AS

Available data suggest that clinical improvement in AS is observed within 16 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no clinical improvement within this timeframe.

Special populations

Elderly

No dose adjustment is required in patients 65 years of age and older. There are limited data in patients aged 75 years and older. See section 4.4 for Use in patients 65 years of age and older.

Hepatic impairment

Table 5: 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 tablet 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 6: 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 prolonged-release formulation 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

Tofacitinib should only be used if no suitable treatment alternatives are available in patients: -65 years of age and older; -patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers); -patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

Use in patients 65 years of age and older

Considering the increased risk of serious infections, myocardial infarction, malignancies and all cause mortality with tofacitinib in patients 65 years of age and older , tofacitinib should only be used in these patients if no suitable treatment alternatives are available (see further details below in section 4.4 and section 5.1).

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, ciclosporin 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. In a randomised post-authorisation safety study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, a dose dependent increased risk for VTE was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

In a post hoc exploratory analysis within this study, in patients with known VTE risk factors, occurrences of subsequent VTEs were observed more frequently in tofacitinib-treated patients that, at 12 months treatment, had D-dimer level ≥2× ULN versus those with D-dimer level <2×ULN; this was not evident in TNF inhibitor-treated patients. Interpretation is limited by the low number of VTE events and restricted D-dimer test availability (only assessed at Baseline, Month 12, and at the end of the study). In patients who did not have a VTE during the study, mean D-dimer levels were significantly reduced at Month 12 relative to Baseline across all treatment arms. However, D-dimer levels ≥2× ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D-Dimer testing in this study.

In patients with MACE or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events (MACE)” and “Malignancy”) tofacitinib should only be used if no suitable treatment alternatives are available.

In patients with VTE risk factors other than MACE or malignancy risk factors, tofacitinib should be used with caution. VTE risk factors other than MACE or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone

replacement therapy, inherited coagulation disorder. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.

For patients with RA with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is ≥ 2× ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib.

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

Retinal venous thrombosis

Retinal venous thrombosis (RVT) has been reported in patients treated with tofacitinib (see section 4.8). The patients should be advised to promptly seek medical care in case they experience symptoms suggestive of RVT.

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 (see section 4.8). 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.

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 65 years of age and older, tofacitinib should only be used if no suitable treatment alternatives are 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) have been observed in patients receiving tofacitinib (see section 4.8).

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 studies. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with tofacitinib.

Major adverse cardiovascular events (including myocardial infarction)

Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib.

In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1). In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1).

Malignancies and lymphoproliferative disorder

Tofacitinib may affect host defences against malignancies.

In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies particularly NMSC, lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

NMSC lung cancers and lymphoma in patients treated with tofacitinib have also been observed in other clinical studies and in the post marketing setting.

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

In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1). Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer (see Table 7 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 studies 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 studies 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.

Fractures

Fractures have been observed in patients treated with tofacitinib.

Tofacitinib should be used with caution in patients with known risk factors for fractures such as elderly patients, female patients and patients with corticosteroid use, regardless of indication and dosage.

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 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.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of tofacitinib in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycaemia occurs.

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 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 contents

Tofacitinib prolonged-release tablets contain 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

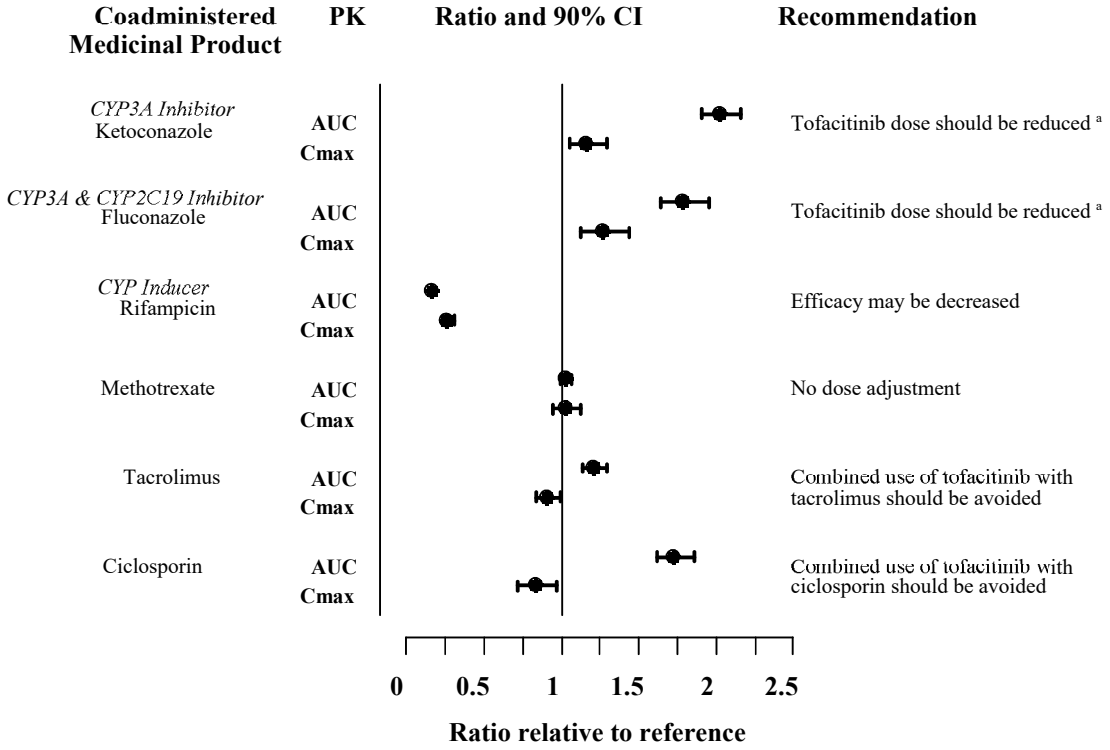
Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib

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 ciclosporin (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, ciclosporin 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

Rheumatoid arthritis
The most common serious adverse reactions were serious infections (see section 4.4). In the long-term safety all exposure population, the most common serious infections reported with tofacitinib were pneumonia (1.7%), herpes zoster (0.6%), urinary tract infection (0.4%), cellulitis (0.4%), diverticulitis (0.3%), and appendicitis (0.2%). Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus infection, 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 of the double-blind, placebo or MTX controlled clinical studies were headache (3.9%), upper respiratory tract infections (3.8%), viral upper respiratory tract infection (3.3%), diarrhoea (2.9%), nausea (2.7%), and hypertension (2.2%).

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 during the first 3 months in controlled clinical studies were herpes zoster (0.19%) and pneumonia (0.15%).

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.

Ankylosing spondylitis
Overall, the safety profile observed in patients with active AS treated with tofacitinib was consistent with the safety profile observed in patients with RA treated with tofacitinib.

Tabulated list of adverse reactions

The adverse reactions listed in the table below are from clinical studies in patients with RA, PsA, AS, 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, adverse reactions are presented in the order of decreasing seriousness.

Table 7: Adverse 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 Bacteraemia *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal Pneumonia bacterial Cytomegalovirus infection Arthritis bacterial	Tuberculosis of central nervous system Meningitis cryptococcal Necrotizing fasciitis Encephalitis Staphylococcal bacteraemia *Mycobacterium avium* complex infection Atypical mycobacterial infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Lung cancer Non-melanoma skin cancers	Lymphoma		
Blood and lymphatic system disorders	Lymphopenia Anaemia	Leukopenia Neutropenia			
Immune system disorders					Hypersensitivity * Angioedema* Urticaria*
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia Dehydration			
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache	Paraesthesia			
Cardiac disorders		Myocardial infarction			
Vascular disorders	Hypertension	Venous thromboembolism**			
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea Sinus congestion			
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia				
Hepatobiliary disorders		Hepatic steatosis Hepatic enzyme increased Transaminases increased Gamma glutamyl-transferase increased	Liver function test abnormal		
Skin and subcutaneous tissue disorders	Rash	Erythema Pruritus			

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)
Musculoskeletal and connective tissue disorders	Arthralgia	Joint swelling Tendonitis	Musculoskeletal pain		
General disorders and administration site conditions	Oedema peripheral	Pyrexia 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, DVT, and Retinal Venous Thrombosis

Description of selected adverse reactions

Venous thromboembolism

Rheumatoid arthritis
In a large (N=4,362), randomised post-authorisation safety study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors (see section 5.1). The majority of these events were serious and some resulted in death. The incidence rates (95% CI) for PE for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.17 (0.08-0.33), 0.50 (0.32-0.74), and 0.06 (0.01-0.17) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for PE was 2.93 (0.79-10.83) and 8.26 (2.49, 27.43) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, respectively (see section 5.1). In tofacitinib-treated patients where PE was observed, the majority (97%) had VTE risk factors.

Ankylosing spondylitis
In the combined Phase 2 and Phase 3 randomised controlled clinical trials, there were no VTE events in 420 patients (233 patient-years of observation) receiving tofacitinib up to 48 weeks.

Overall infections

Rheumatoid arthritis
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.

Ankylosing spondylitis
In the combined Phase 2 and Phase 3 clinical trials, during the placebo-controlled period of up to 16 weeks, the frequency of infections in the tofacitinib 5 mg twice daily group (185 patients) was 27.6% and the frequency in the placebo group (187 patients) was 23.0%. In the combined Phase 2 and Phase 3 clinical trials, among the 316 patients treated with tofacitinib 5 mg twice daily for up to 48 weeks, the frequency of infections was 35.1%.

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).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, a dose-dependent increase in serious infections was observed with tofacitinib compared to TNF inhibitors (see section 4.4).

The incidence rates (95% CI) for serious infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 2.86 (2.41, 3.37), 3.64 (3.11, 4.23), and 2.44 (2.02, 2.92) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for serious infections was 1.17 (0.92, 1.50) and 1.48 (1.17, 1.87) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily, respectively.

Ankylosing spondylitis
In the combined Phase 2 and Phase 3 clinical trials, among the 316 patients treated with tofacitinib 5 mg twice daily for up to 48 weeks, there was one serious infection (aseptic meningitis) yielding a rate of 0.43 patients with events per 100 patient-years.

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).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, an increase in serious infections was observed in patients 65 years of age and older for tofacitinib 10 mg twice daily compared to TNF inhibitors and to tofacitinib 5 mg twice daily (see section 4.4). The incidence rates (95% CI) for serious infections in patients ≥65 years were 4.03 (3.02, 5.27), 5.85 (4.64, 7.30), and 3.73 (2.81, 4.85) patients with events per 100 patient-years for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors, respectively.

Compared with TNF inhibitors, the hazard ratio (HR) for serious infections in patients ≥65 years of age was 1.08 (0.74, 1.58) and 1.55 (1.10, 2.19) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, respectively.

Serious infections from non-interventional post approval safety study
Data from a non-interventional post approval safety study that evaluated tofacitinib in RA patients from a registry (US Corrona) showed that a numerically higher incidence rate of serious infection was observed for the 11 mg prolonged-release tablet administered once daily than the 5 mg film-coated tablet administered twice daily. Crude incidence rates (95% CI) (i.e., not adjusted for age or sex) from availability of each formulation at 12 months following initiation of treatment were 3.45 (1.93, 5.69) and 2.78 (1.74, 4.21) and at 36 months were 4.71 (3.08, 6.91) and 2.79 (2.01, 3.77) patients with events per 100 patient-years in the 11 mg prolonged-release tablet once daily and 5 mg film-coated tablet twice daily groups, respectively. The unadjusted hazard ratio was 1.30 (95% CI: 0.67, 2.50) at 12 months and 1.93 (95% CI: 1.15, 3.24) at 36 months for the 11 mg prolonged-release once daily dose compared to the 5 mg film-coated twice daily dose. Data is based on a small number of patients with events observed with relatively large confidence intervals and limited follow up time.

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).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, an increase in herpes zoster events was observed in patients treated with tofacitinib compared to TNF inhibitors. The incidence rates (95% CI) for herpes zoster for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 3.75 (3.22, 4.34), 3.94 (3.38, 4.57), and 1.18 (0.90, 1.52) patients with events per 100 patient-years, respectively.

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).

Platelets
Patients in the Phase 3 controlled clinical studies (RA, PsA, AS) were required to have a platelet count ≥ 100,000 cells/mm^3 to be eligible for enrolment, therefore, there is no information available for patients with a platelet count < 100,000 cells/mm^3 before starting treatment with tofacitinib.

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 a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, ALT elevations greater than or equal to 3x ULN were observed in 6.01%, 6.54% and 3.77% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors respectively. AST elevations greater than or equal to 3x ULN were observed in 3.21%, 4.57% and 2.38% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors respectively.

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 studies 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 study, 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 a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, changes in lipid parameters from baseline through 24 months are summarised below:

- Mean LDL cholesterol increased by 13.80%, 17.04%, and 5.50% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor, respectively, at month 12. At month 24, the increase was 12.71%, 18.14%, and 3.64%, respectively,
- Mean HDL cholesterol increased by 11.71%, 13.63%, and 2.82% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor, respectively, at month 12. At month 24, the increase was 11.58%, 13.54%, and 1.42%, respectively.

Myocardial infarction

Rheumatoid arthritis
In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for non-fatal myocardial infarction for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), and 0.16 (0.07, 0.31) patients with events per 100 patient-years, respectively. Few fatal myocardial infarctions were reported with rates similar in patients treated with tofacitinib compared to TNF inhibitors (see sections 4.4 and 5.1). The study required at least 1500 patients to be followed for 3 years.

Malignancies excluding NMSC

Rheumatoid arthritis
In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for lung cancer for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.23 (0.12, 0.40), 0.32 (0.18, 0.51), and 0.13 (0.05, 0.26) patients with events per 100 patient-years, respectively (see sections 4.4 and 5.1). The study required at least 1500 patients to be followed for 3 years.

The incidence rates (95% CI) for lymphoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), and 0.02 (0.00, 0.10) patients with events per 100 patient-years, respectively (see sections 4.4 and 5.1).

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 study 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 herpes virus vaccine 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 medicinal product. 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 film-coated tablets 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 8 provides information regarding the pertinent study design and population characteristics.

Table 8: Phase 3 clinical studies 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
Number of patients treated	610	792	717	797	399	956	1,146

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)
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 9. 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 9: 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 10.

Table 10: 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 11, 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 11: 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 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 12.

Table 12: 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 5 years is also provided from data in a randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, as well as in completed open-label, long-term follow-up studies up to 8 years.

Long-term controlled safety data

Study ORAL Surveillance (A3921133) was a large (N=4362), randomised active-controlled post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional 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, anaemia of chronic disease, pulmonary manifestations). The majority (more than 90%) of tofacitinib patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively. Patients were required to be on a stable dose of methotrexate at study entry; dose adjustment was permitted during the study.

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 were adjudicated malignancies excluding NMSC and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessment of endpoints were blinded. The study was an event-powered study that also required at least 1500 patients to be followed for 3 years. The study treatment of tofacitinib 10 mg twice daily was stopped and patients were switched to 5 mg twice daily because of a dose-dependent signal of venous thromboembolic events (VTE). For patients in the tofacitinib 10 mg twice daily treatment arm, the data collected before and after the dose switch were analysed in their originally randomised treatment group.

The study did not meet the non-inferiority criterion for the primary comparison of the combined tofacitinib doses to TNF inhibitor since the upper limit of the 95% CI for HR exceeded the pre-specified non-inferiority criterion of 1.8 for adjudicated MACE and adjudicated malignancies excluding NMSC.

The results for adjudicated MACE, adjudicated malignancies excluding NMSC, and selected other events are provided below.

MACE (including myocardial infarction) and venous thromboembolism (VTE)
An increase in non-fatal myocardial infarction was observed in patients treated with tofacitinib compared to TNF inhibitor. A dose-dependent increase in VTE events was observed in patients treated with tofacitinib compared to TNF inhibitor (see sections 4.4 and 4.8).

Table 13: Incidence rate and hazard ratio for MACE, myocardial infarction and venous thromboembolism

	Tofacitinib 5 mg twice daily	**Tofacitinib 10 mg twice daily[a]**	**All Tofacitinib[b]**	**TNF inhibitor (TNFi)**
MACE[c]				
IR (95% CI) per 100 PY	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.98 (0.79, 1.19)	0.73 (0.52, 1.01)
HR (95% CI) vs TNFi	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)	
Fatal MI[c]				
IR (95% CI) per 100 PY	0.00 (0.00, 0.07)	0.06 (0.01, 0.18)	0.03 (0.01, 0.09)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	0.00 (0.00, Inf)	1.03 (0.21, 5.11)	0.50 (0.10, 2.49)	
Non-fatal MI[c]				
IR (95% CI) per 100 PY	0.37 (0.22, 0.57)	0.33 (0.19, 0.53)	0.35 (0.24, 0.48)	0.16 (0.07, 0.31)
HR (95% CI) vs TNFi	2.32 (1.02, 5.30)	2.08 (0.89, 4.86)	2.20 (1.02, 4.75)	
VTE[d]				
IR (95% CI) per 100 PY	0.33 (0.19, 0.53)	0.70 (0.49, 0.99)	0.51 (0.38, 0.67)	0.20 (0.10, 0.37)
HR (95% CI) vs TNFi	1.66 (0.76, 3.63)	3.52 (1.74, 7.12)	2.56 (1.30, 5.05)	
PE[d]				
IR (95% CI) per 100 PY	0.17 (0.08, 0.33)	0.50 (0.32, 0.74)	0.33 (0.23, 0.46)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	2.93 (0.79, 10.83)	8.26 (2.49, 27.43)	5.53 (1.70, 18.02)	

DVT[d]				
IR (95% CI) per 100 PY	0.21 (0.11, 0.38)	0.31 (0.17, 0.51)	0.26 (0.17, 0.38)	0.14 (0.06, 0.29)
HR (95% CI) vs TNFi	1.54 (0.60, 3.97)	2.21 (0.90, 5.43)	1.87 (0.81, 4.30)	

[a] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.
[b] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
[c] Based on events occurring on treatment or within 60 days of treatment discontinuation.
[d] Based on events occurring on treatment or within 28 days of treatment discontinuation.
Abbreviations: MACE = major adverse cardiovascular events, MI = myocardial infarction, VTE = venous thromboembolism, PE = pulmonary embolism, DVT = deep vein thrombosis, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, Inf = infinity

The following predictive factors for development of MI (fatal and non-fatal) were identified using a multivariate Cox model with backward selection: age ≥65 years, male, current or past smoking, history of diabetes, and history of coronary artery disease (which includes myocardial infarction, coronary heart disease, stable angina pectoris, or coronary artery procedures) (see sections 4.4 and 4.8).

Malignancies

An increase in malignancies excluding NMSC, particularly lung cancer, lymphoma and an increase in NMSC was observed in patients treated with tofacitinib compared to TNF inhibitor.

Table 14: Incidence rate and hazard ratio for malignancies[a]

	Tofacitinib 5 mg twice daily	**Tofacitinib 10 mg twice daily[b]**	**All Tofacitinib[c]**	**TNF inhibitor (TNFi)**
Malignancies excluding NMSC				
IR (95% CI) per 100 PY	1.13 (0.87, 1.45)	1.13 (0.86, 1.45)	1.13 (0.94, 1.35)	0.77 (0.55, 1.04)
HR (95% CI) vs TNFi	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)	
Lung cancer				
IR (95% CI) per 100 PY	0.23 (0.12, 0.40)	0.32 (0.18, 0.51)	0.28 (0.19, 0.39)	0.13 (0.05, 0.26)
HR (95% CI) vs TNFi	1.84 (0.74, 4.62)	2.50 (1.04, 6.02)	2.17 (0.95, 4.93)	
Lymphoma				
IR (95% CI) per 100 PY	0.07 (0.02, 0.18)	0.11 (0.04, 0.24)	0.09 (0.04, 0.17)	0.02 (0.00, 0.10)
HR (95% CI) vs TNFi	3.99 (0.45, 35.70)	6.24 (0.75, 51.86)	5.09 (0.65, 39.78)	
NMSC				
IR (95% CI) per 100 PY	0.61 (0.41, 0.86)	0.69 (0.47, 0.96)	0.64 (0.50, 0.82)	0.32 (0.18, 0.52)
HR (95% CI) vs TNFi	1.90 (1.04, 3.47)	2.16 (1.19, 3.92)	2.02 (1.17, 3.50)	

[a] For malignancies excluding NMSC, lung cancer, and lymphoma, based on events occurring on treatment or after treatment discontinuation up to the end of the study. For NMSC based on events occurring on treatment or within 28 days of treatment discontinuation.
[b] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.
[c] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
Abbreviations: NMSC = non melanoma skin cancer, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years

The following predictive factors for development of malignancies excluding NMSC were identified using a Multivariate Cox model with backward selection: age ≥65 years and current or past smoking (see section 4.4 and 4.8).

Mortality

Increased mortality was observed in patients treated with tofacitinib compared to TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies.

Table 15: Incidence rate and hazard ratio for mortality[a]

	Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily[b]	All Tofacitinib[c]	TNF inhibitor (TNFi)
Mortality (all cause)				
IR (95% CI) per 100 PY	0.50 (0.33, 0.74)	0.80 (0.57, 1.09)	0.65 (0.50, 0.82)	0.34 (0.20, 0.54)
HR (95% CI) vs TNFi	1.49 (0.81, 2.74)	2.37 (1.34, 4.18)	1.91 (1.12, 3.27)	
Fatal infections				
IR (95% CI) per 100 PY	0.08 (0.02, 0.20)	0.18 (0.08, 0.35)	0.13 (0.07, 0.22)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	1.30 (0.29, 5.79)	3.10 (0.84, 11.45)	2.17 (0.62, 7.62)	
Fatal CV events				
IR (95% CI) per 100 PY	0.25 (0.13, 0.43)	0.41 (0.25, 0.63)	0.33 (0.23, 0.46)	0.20 (0.10, 0.36)
HR (95% CI) vs TNFi	1.26 (0.55, 2.88)	2.05 (0.96, 4.39)	1.65 (0.81, 3.34)	
Fatal Malignancies				
IR (95% CI) per 100 PY	0.10 (0.03, 0.23)	0.00 (0.00, 0.08)	0.05 (0.02, 0.12)	0.02 (0.00, 0.11)
HR (95% CI) vs TNFi	4.88 (0.57, 41.74)	0 (0.00, Inf)	2.53 (0.30, 21.64)	

[a] Based on events occurring on treatment or within 28 days of treatment discontinuation.
[b] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.
[c] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
Abbreviations: TNF = tumor necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, CV = cardiovascular, Inf = infinity

Psoriatic arthritis
The efficacy and safety of tofacitinib film-coated tablets 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 16.

Table 16: 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 twice daily-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 twice daily 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 twice daily, adalimumab and placebo treated patients, respectively (tofacitinib 5 mg twice daily 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 twice daily and placebo treated patients, respectively, however tofacitinib 5 mg twice daily 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 17).

Table 17: 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 $p \leq 0.05$).

Ankylosing spondylitis
The tofacitinib clinical development program to assess the efficacy and safety included one placebo-controlled confirmatory trial (Study AS-I). Study AS-I was a randomised, double-blind, placebo-controlled, 48-week treatment clinical trial in 269 adult patients who had an inadequate response (inadequate clinical response or intolerance) to at least 2 NSAIDs. Patients were randomised and treated with tofacitinib 5 mg twice daily or placebo for 16 weeks of blinded treatment and then all were advanced to tofacitinib 5 mg twice daily for an additional 32 weeks. Patients had active disease as defined by both Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and back pain score (BASDAI question 2) of greater or equal to 4 despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or DMARD therapy.

Approximately 7% and 21% of patients used concomitant methotrexate or sulfasalazine, respectively, from baseline to Week 16. Patients were allowed to receive a stable low dose of oral corticosteroids (8.6% received) and/or NSAIDs (81.8% received) from baseline to Week 48. Twenty-two percent of patients had an inadequate response to 1 or 2 TNF blockers. The primary endpoint was to evaluate the proportion of patients who achieved an ASAS20 response at Week 16.

Clinical response
Patients treated with tofacitinib 5 mg twice daily achieved greater improvements in ASAS20 and ASAS40 responses compared to placebo at Week 16 (Table 18). The responses were maintained from Week 16 through to Week 48 in patients receiving tofacitinib 5 mg twice daily.

Table 18: ASAS20 and ASAS40 Responses at Week 16, Study AS-I

	Placebo (N=136)	**Tofacitinib 5 mg Twice Daily (N=133)**	**Difference from Placebo (95% CI)**
ASAS20 response*, %	29	56	27 (16, 38)**
ASAS40 response*, %	13	41	28 (18, 38)**

* type I error-controlled.
** $p<0.0001$.

The efficacy of tofacitinib was demonstrated in bDMARD naïve and TNF-inadequate responders (IR)/bDMARD experienced (non-IR) patients (Table 19).

Table 19: ASAS20 and ASAS40 Responses (%) by Treatment History at Week 16, Study AS-I

Prior Treatment History	**Efficacy Endpoint**					
	ASAS20			**ASAS40**		
	Placebo N	**Tofacitinib 5 mg Twice Daily N**	**Difference from Placebo (95% CI)**	**Placebo N**	**Tofacitinib 5 mg Twice Daily N**	**Difference from Placebo (95% CI)**
bDMARD-Naïve	105	102	28 (15, 41)	105	102	31 (19, 43)
TNFi-IR or bDMARD Use (Non-IR)	31	31	23 (1, 44)	31	31	19 (2, 37)

Prior Treatment History	Efficacy Endpoint					
	ASAS20			ASAS40		
	Placebo N	Tofacitinib 5 mg Twice Daily N	Difference from Placebo (95% CI)	Placebo N	Tofacitinib 5 mg Twice Daily N	Difference from Placebo (95% CI)

ASAS20 = An improvement from Baseline ≥ 20% and ≥ 1 unit increase in at least 3 domains on a scale of 0 to 10, and no worsening of ≥ 20% and ≥ 1 unit in the remaining domain; ASAS40 = An improvement from Baseline ≥ 40% and ≥ 2 units in at least 3 domains on a scale of 0 to 10 and no worsening at all in the remaining domain; bDMARD = biologic disease-modifying anti-rheumatic drug; CI = confidence interval; Non-IR = non-inadequate response; TNFi-IR = tumour necrosis factor inhibitor inadequate response.

The improvements in the components of the ASAS response and other measures of disease activity were higher in tofacitinib 5 mg twice daily compared to placebo at Week 16 as shown in Table 20. The improvements were maintained from Week 16 through to Week 48 in patients receiving tofacitinib 5 mg twice daily.

Table 20: ASAS Components and Other Measures of Disease Activity at Week 16, Study AS-I

	Placebo (N=136)		Tofacitinib 5 mg Twice Daily (N=133)		
	Baseline (mean)	Week 16 (LSM change from Baseline)	Baseline (mean)	Week 16 (LSM change from Baseline)	Difference from Placebo (95% CI)
ASAS Components					
– Patient Global Assessment of Disease Activity (0-10)[a,*]	7.0	-0.9	6.9	-2.5	-1.6 (-2.07, -1.05)**
– Total spinal pain (0-10)[a,*]	6.9	-1.0	6.9	-2.6	-1.6 (-2.10, -1.14)**
– BASFI (0-10)[b,*]	5.9	-0.8	5.8	-2.0	-1.2 (-1.66, -0.80)**
– Inflammation (0-10)[c,*]	6.8	-1.0	6.6	-2.7	-1.7 (-2.18, -1.25)**
BASDAI Score[d]	6.5	-1.1	6.4	-2.6	-1.4 (-1.88, -1.00)**
BASMI[e,*]	4.4	-0.1	4.5	-0.6	-0.5 (-0.67, -0.37)**
hsCRP[f,*] (mg/dL)	1.8	-0.1	1.6	-1.1	-1.0 (-1.20, -0.72)**
ASDAScrp[g,*]	3.9	-0.4	3.8	-1.4	-1.0 (-1.16, -0.79)**

* type I error-controlled.
** p<0.0001.
[a] Measured on a numerical rating scale with 0 = not active or no pain, 10 = very active or most severe pain.
[b] Bath Ankylosing Spondylitis Functional Index measured on a numerical rating scale with 0 = easy and 10 = impossible.
[c] Inflammation is the mean of two patient-reported stiffness self-assessments in BASDAI.
[d] Bath Ankylosing Spondylitis Disease Activity Index total score.
[e] Bath Ankylosing Spondylitis Metrology Index.
[f] High sensitivity C-reactive protein.
[g] Ankylosing Spondylitis Disease Activity Score with C-reactive protein.
LSM = least squares mean.

Other health-related outcomes
Patients treated with tofacitinib 5 mg twice daily achieved greater improvements from baseline in Ankylosing Spondylitis Quality of Life (ASQoL) (-4.0 vs -2.0) and Functional Assessment of Chronic

Illness Therapy - Fatigue (FACIT-F) Total score (6.5 vs 3.1) compared to placebo-treated patients at Week 16 ($p<0.001$). Patients treated with tofacitinib 5 mg twice daily achieved consistently greater improvements from baseline in the Short Form health survey version 2 (SF-36v2), Physical Component Summary (PCS) compared to placebo-treated patients at Week 16.

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%.

Results from population PK analysis in patients with active PsA or AS 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 studies, tofacitinib was not evaluated in patients with baseline creatinine clearance values (estimated by Cockcroft-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 studies, 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.

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.

Comparison of PK of prolonged-release and film-coated tablet formulations

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

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. In studies conducted in juvenile rats and monkeys, there were no tofacitinib-related effects on bone development in males or females, at exposures similar to those achieved at approved doses in humans.

No tofacitinib-related findings were observed in juvenile animal studies that indicate a higher sensitivity of paediatric populations compared with adults. In the juvenile rat fertility study, there was no evidence of developmental toxicity, no effects on sexual maturation, and no evidence of reproductive toxicity (mating and fertility) was noted after sexual maturity. In 1-month juvenile rat and 39-week juvenile monkey studies tofacitinib-related effects on immune and haematology parameters consistent with JAK1/3 and JAK2 inhibition were observed. These effects were reversible and consistent with those also observed in adult animals at similar exposures.

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)
titanium dioxide (E171)
triacetin
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
Date of renewal of the authorisation: 04 March 2022

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.

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 1 mg/mL oral solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of oral solution contains tofacitinib citrate, equivalent to 1 mg tofacitinib.

Excipient(s) with known effect

Each mL of oral solution contains 2.39 mg propylene glycol.

Each mL of oral solution contains 0.9 mg of sodium benzoate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Tofacitinib is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with disease modifying antirheumatic drugs (DMARDs).

Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

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

Tofacitinib may be used as monotherapy or in combination with methotrexate (MTX).

The recommended dose in patients 2 years of age and older is based upon the following weight categories:

Table 1: Tofacitinib dose for patients with polyarticular juvenile idiopathic arthritis and juvenile PsA two years of age and older

Body weight (kg)	Dose regimen
10 - < 20	3.2 mg (3.2 mL of oral solution) twice daily
20 - < 40	4 mg (4 mL of oral solution) twice daily
≥ 40	5 mg (5 mL of oral solution or 5 mg film-coated tablet) twice daily

Patients ≥ 40 kg treated with tofacitinib 5 mL oral solution twice daily may be switched to tofacitinib 5 mg film-coated tablets twice daily. Patients < 40 kg cannot be switched from tofacitinib oral solution.

Dose adjustment

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

Dose interruption and discontinuation

Available data suggest that clinical improvement is observed within 18 weeks of initiation of treatment with tofacitinib. Continued therapy should be carefully reconsidered in a patient exhibiting no improvement within this timeframe.

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 2, 3 and 4 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 paediatric patients with an absolute lymphocyte count (ALC) less than 750 cells/mm^3.

Table 2: Low absolute lymphocyte count

Low absolute lymphocyte count (ALC) (see section 4.4)	
Laboratory 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 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 laboratory value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in paediatric patients with an absolute neutrophil count (ANC) less than 1,200 cells/mm^3.

Table 3: Low absolute neutrophil count

Low absolute neutrophil count (ANC) (see section 4.4)	
Laboratory 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 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 laboratory value confirmed by repeat testing within 7 days, dosing should be discontinued.

It is recommended not to initiate dosing in paediatric patients with haemoglobin less than 10 g/dL.

Table 4: Low haemoglobin value

Low haemoglobin value (see section 4.4)	
Laboratory 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.

Interactions

Tofacitinib total daily dose should be reduced to 5 mg film-coated tablet once daily or weight-based equivalent once daily in patients receiving 5 mg film-coated tablets or weight-based equivalent twice daily 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).

Special populations

Elderly

The safety and efficacy of tofacitinib oral solution has not been established in the elderly.

Hepatic impairment

Table 5: Dose adjustment for hepatic impairment

Hepatic impairment category	**Classification**	**Dose adjustment in hepatic impairment for oral solution**
Mild	Child Pugh A	No dose adjustment required.
Moderate	Child Pugh B	Dose should be reduced to 5 mg or weight-based equivalent once daily when the indicated dose in the presence of normal hepatic function is 5 mg or weight-based equivalent 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 6: Dose adjustment for renal impairment

Renal impairment category	**Creatinine clearance**	**Dose adjustment in renal impairment for oral solution**
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 or weight-based equivalent once daily when the indicated dose in the presence of normal renal function is 5 mg or weight-based equivalent twice daily. Patients with severe renal impairment should remain on a reduced dose even after haemodialysis (see section 5.2).

Paediatric population (children below 2 years of age)
The safety and efficacy of tofacitinib in children below 2 years of age has not been established. No data are available.

Method of administration

Oral use.

Tofacitinib oral solution should be administered using the included press-in bottle adapter and oral dosing syringe.

Tofacitinib is given orally with or without food.

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

Tofacitinib should only be used if no suitable treatment alternatives are available in patients: -65 years of age and older; -patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers); -patients with malignancy risk factors (e.g. current malignancy or history of malignancy)

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, ciclosporin 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. In a randomised post-authorisation safety study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, a dose dependent increased risk for VTE was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

In a post hoc exploratory analysis within this study, in patients with known VTE risk factors, occurrences of subsequent VTEs were observed more frequently in tofacitinib-treated patients that, at 12 months treatment, had D-dimer level ≥2× ULN versus those with D-dimer level <2×ULN; this was not evident in TNF inhibitor-treated patients. Interpretation is limited by the low number of VTE events and restricted D-dimer test availability (only assessed at Baseline, Month 12, and at the end of the study). In patients who did not have a VTE during the study, mean D-dimer levels were significantly reduced at Month 12 relative to Baseline across all treatment arms. However, D-dimer levels ≥2× ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D-Dimer testing in this study.

In patients with MACE or malignancy risk factors (see also section 4.4 “Major adverse cardiovascular events (MACE)” and “Malignancy”) tofacitinib should only be used if no suitable treatment alternatives are available.

In patients with VTE risk factors other than MACE or malignancy risk factors, tofacitinib should be used with caution. VTE risk factors other than MACE or malignancy risk factors include previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk.

For patients with RA with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is ≥ 2× ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib.

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

Retinal venous thrombosis

Retinal venous thrombosis (RVT) has been reported in patients treated with tofacitinib (see section 4.8). The patients should be advised to promptly seek medical care in case they experience symptoms suggestive of RVT.

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 (see section 4.8). 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.

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 65 years of age and older, tofacitinib should only be used if no suitable treatment alternatives are 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) have been observed in patients receiving tofacitinib (see section 4.8).

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).

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

Major adverse cardiovascular events (including myocardial infarction)

Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib.

In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1). In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1).

Malignancies and lymphoproliferative disorder

Tofacitinib may affect host defences against malignancies.

In a randomised post authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies particularly NMSC, lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

NMSC lung cancers and lymphoma in patients treated with tofacitinib have also been observed in other clinical studies and in the post marketing setting.

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

In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1). Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer (see Table 7 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 studies 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 studies 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.

Fractures

Fractures have been observed in patients treated with tofacitinib.

Tofacitinib should be used with caution in patients with known risk factors for fractures such as elderly patients, female patients and patients with corticosteroid use, regardless of indication and dosage.

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 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 adult patients with an ANC less than 1,000 cells/mm^3 and in paediatric patients with an ANC less than

1,200 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 adult patients with a haemoglobin value less than 9 g/dL and in paediatric patients with haemoglobin value less than 10 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.

Hypoglycaemia in patients treated for diabetes

There have been reports of hypoglycaemia following initiation of tofacitinib in patients receiving medication for diabetes. Dose adjustment of anti-diabetic medication may be necessary in the event that hypoglycaemia occurs.

Vaccinations

Prior to initiating tofacitinib, it is recommended that all patients, particularly pJIA and jPsA 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 contents

Propylene glycol
This medicinal product contains 2.39 mg propylene glycol in each mL.

Examples of propylene glycol exposures based on daily doses (see section 4.2) are as follows:
- A dose of 3.2 mg twice daily of XELJANZ 1 mg/mL oral solution administered to a child weighing 10 kg to < 20 kg would result in a propylene glycol exposure of 1.53 mg/kg/day.
- A dose of 4 mg twice daily of XELJANZ 1 mg/mL oral solution administered to a child weighing 20 kg to <40 kg would result in a propylene glycol exposure of 0.96 mg/kg/day.

- A dose of 5 mg twice daily of XELJANZ 1 mg/mL oral solution administered to a child weighing ≥40 kg would result in a propylene glycol exposure of 0.60 mg/kg/day.

Sodium benzoate
This medicinal product contains 0.9 mg sodium benzoate in each mL.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

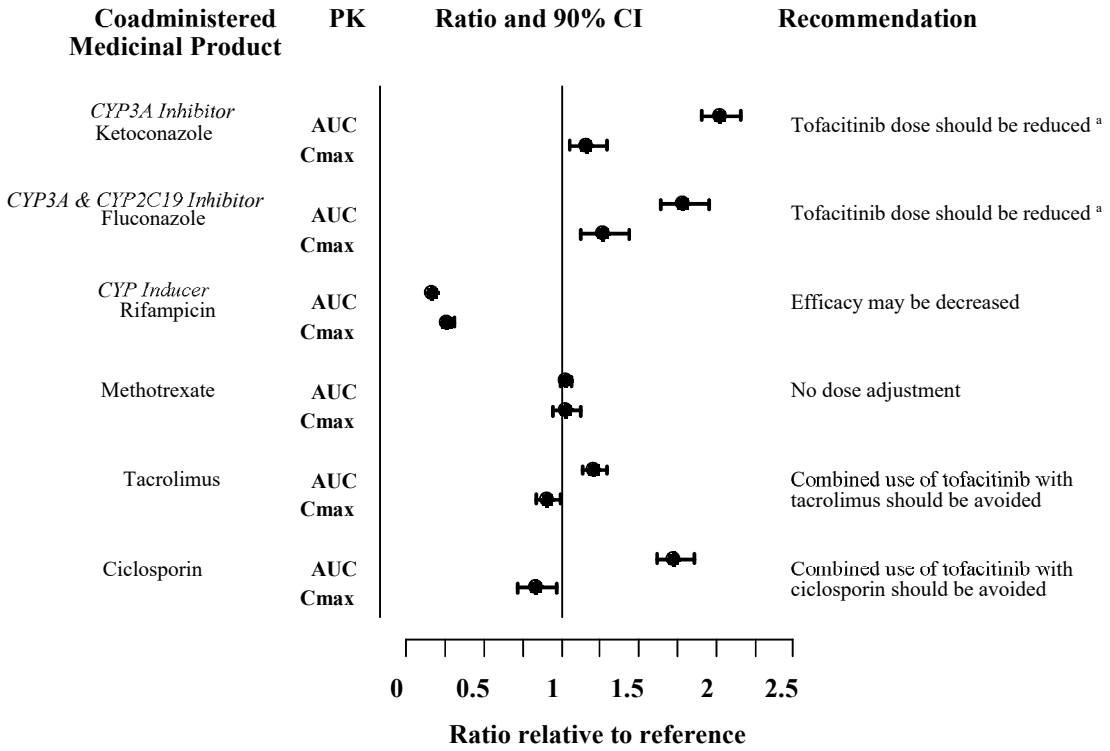
Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib

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 ciclosporin (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, ciclosporin 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 film-coated tablet once daily or oral solution weight-based equivalent in patients receiving 5 mg or weight-based equivalent 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.

Paediatric population

Interaction studies have only been performed in adults.

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). In the long-term safety all exposure population, the most common serious infections reported with tofacitinib were pneumonia (1.7%), herpes zoster (0.6%), urinary tract infection (0.4%), cellulitis (0.4%), diverticulitis (0.3%), and appendicitis (0.2%). Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus infection, 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 of the double-blind, placebo or MTX controlled clinical studies were headache (3.9%), upper respiratory tract infections (3.8%), viral upper respiratory tract infection (3.3%), diarrhoea (2.9%), nausea (2.7%), and hypertension (2.2%).

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 during the first 3 months in controlled clinical studies were herpes zoster (0.19%) and pneumonia (0.15%).

Tabulated list of adverse reactions

The adverse reactions listed in the table below are from clinical studies in adult 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, adverse reactions are presented in the order of decreasing seriousness.

Table 7: Adverse 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 Bacteraemia *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal Pneumonia bacterial Cytomegalovirus infection Arthritis bacterial	Tuberculosis of central nervous system Meningitis cryptococcal Necrotizing fasciitis Encephalitis Staphylococcal bacteraemia *Mycobacterium avium* complex infection Atypical mycobacterial infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Lung cancer Non-melanoma skin cancers	Lymphoma		
Blood and lymphatic system disorders	Lymphopenia Anaemia	Leukopenia Neutropenia			
Immune system disorders					Hypersensitivity * Angioedema* Urticaria*
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia Dehydration			
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache	Paraesthesia			
Cardiac disorders		Myocardial infarction			
Vascular disorders	Hypertension	Venous thromboembolism**			
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea Sinus congestion			
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia				
Hepatobiliary disorders		Hepatic steatosis Hepatic enzyme increased Transaminases increased Gamma glutamyl-transferase increased	Liver function test abnormal		
Skin and subcutaneous tissue disorders	Rash	Erythema Pruritus			

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)
Musculoskeletal and connective tissue disorders	Arthralgia	Joint swelling Tendonitis	Musculoskeletal pain		
General disorders and administration site conditions	Oedema peripheral	Pyrexia 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, DVT, and Retinal Venous Thrombosis

Description of selected adverse reactions

Venous thromboembolism

Rheumatoid arthritis
In a large (N=4,362), randomised post-authorisation safety study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular (CV) risk factor, VTE was observed at an increased and dose-dependent incidence in patients treated with tofacitinib compared to TNF inhibitors (see section 5.1). The majority of these events were serious and some resulted in death. The incidence rates (95% CI) for PE for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.17 (0.08-0.33), 0.50 (0.32-0.74), and 0.06 (0.01-0.17) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for PE was 2.93 (0.79-10.83) and 8.26 (2.49, 27.43) for tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily, respectively (see section 5.1). In tofacitinib-treated patients where PE was observed, the majority (97%) had VTE risk factors

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.

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).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, a dose-dependent increase in serious infections was observed with tofacitinib compared to TNF inhibitors (see section 4.4).

The incidence rates (95% CI) for serious infections for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 2.86 (2.41, 3.37), 3.64 (3.11, 4.23), and 2.44 (2.02, 2.92) patients with events per 100 patient-years, respectively. Compared with TNF inhibitors, the hazard ratio (HR) for serious infections was 1.17 (0.92, 1.50) and 1.48 (1.17, 1.87) for tofacitinib 10 mg twice daily and tofacitinib 5 mg twice daily, respectively.

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).

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, an increase in herpes zoster events was observed in patients treated with tofacitinib compared to TNF inhibitors. The incidence rates (95% CI) for herpes zoster for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 3.75 (3.22, 4.34), 3.94 (3.38, 4.57), and 1.18 (0.90, 1.52) patients with events per 100 patient-years, respectively.

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.

In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, ALT elevations greater than or equal to 3x ULN were observed in 6.01%, 6.54% and 3.77% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors respectively. AST elevations greater than or equal to 3x ULN were observed in 3.21%, 4.57% and 2.38% of patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors respectively.

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 studies 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 study, 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 a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years or older with at least one additional cardiovascular risk factor, changes in lipid parameters from baseline through 24 months are summarised below:

- Mean LDL cholesterol increased by 13.80%, 17.04%, and 5.50% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor, respectively, at month 12. At month 24, the increase was 12.71%, 18.14%, and 3.64%, respectively,
- Mean HDL cholesterol increased by 11.71%, 13.63%, and 2.82% in patients receiving tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitor, respectively, at month 12. At month 24, the increase was 11.58%, 13.54%, and 1.42%, respectively.

Myocardial infarction

<u>*Rheumatoid arthritis*</u>
In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for non-fatal myocardial infarction for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), and 0.16 (0.07, 0.31) patients with events per 100 patient-years, respectively. Few fatal myocardial infarctions were reported with rates similar in patients treated with tofacitinib compared to TNF inhibitors (see sections 4.4 and 5.1). The study required at least 1500 patients to be followed for 3 years.

Malignancies excluding NMSC

<u>*Rheumatoid arthritis*</u>
In a large (N=4,362) randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, the incidence rates (95% CI) for lung cancer for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.23 (0.12,

0.40), 0.32 (0.18, 0.51), and 0.13 (0.05, 0.26) patients with events per 100 patient-years, respectively (see sections 4.4 and 5.1). The study required at least 1500 patients to be followed for 3 years.

The incidence rates (95% CI) for lymphoma for tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, and TNF inhibitors were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), and 0.02 (0.00, 0.10) patients with events per 100 patient-years, respectively (see sections 4.4 and 5.1).

Paediatric population

Polyarticular juvenile idiopathic arthritis and juvenile PsA
The adverse reactions in JIA patients in the clinical development program were consistent in type and frequency with those seen in adult RA patients, with the exception of some infections (influenza, pharyngitis, sinusitis, viral infection) and gastrointestinal or general disorders (abdominal pain, nausea, vomiting, pyrexia, headache, cough), which were more common in JIA paediatric population. MTX was the most frequent concomitant csDMARD used (on Day 1, 156 of 157 patients on csDMARDs took MTX). There are insufficient data regarding the safety profile of tofacitinib used concomitantly with any other csDMARDs.

Infections
In the double-blind portion of the pivotal Phase 3 trial (Study JIA-I), infection was the most commonly reported adverse reaction (44.3%). The infections were generally mild to moderate in severity.

In the integrated safety population, 7 patients had serious infections during treatment with tofacitinib within the reporting period (up to 28 days after the last dose of study medication), representing an incidence rate of 1.92 patients with events per 100 patient-years: pneumonia, epidural empyema (with sinusitis and subperiosteal abscess), pilonidal cyst, appendicitis, escherichia pyelonephritis, abscess limb, and UTI.

In the integrated safety population, 3 patients had non-serious events of herpes zoster within the reporting window representing an incidence rate of 0.82 patients with events per 100 patient-years. One (1) additional patient had an event of serious HZ outside the reporting window.

Hepatic events

Patients in the JIA pivotal study were required to have AST and ALT levels less than 1.5 times the upper limit of normal to be eligible for enrolment. In the integrated safety population, there were 2 patients with ALT elevations ≥3 times the ULN at 2 consecutive visits. Neither event met Hy's Law criteria. Both patients were on background MTX therapy and each event resolved after discontinuation of MTX and permanent discontinuation of tofacitinib.

Laboratory tests

Changes in laboratory tests in JIA patients in the clinical development program were consistent with those seen in adult RA patients. Patients in the JIA pivotal study were required to have a platelet count ≥100,000 cells/mm^3 to be eligible for enrolment, therefore, there is no information available for JIA patients with a platelet count <100,000 cells/mm^3 before starting treatment with tofacitinib.

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 study 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 herpes virus vaccine 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 medicinal product. This patient subsequently made a robust, though delayed, humoral and cellular response to the vaccine (see section 4.4).

Clinical efficacy and safety

Clinical response

The tofacitinib Phase 3 program for JIA consisted of one completed Phase 3 trial (Study JIA-I [A3921104]) and one ongoing long-term extension (LTE) (A3921145) trial. In these studies the following JIA subgroups were included: patients with either RF+ or RF- polyarthritis, extended oligoarthritis, systemic JIA with active arthritis and no current systemic symptoms (referred as pJIA dataset) and two separate subgroups of patients with juvenile PsA and enthesitis-related arthritis (ERA). However, the pJIA efficacy population only includes the subgroups with either RF+ or RF- polyarthritis or extended oligoarthritis; inconclusive results have been seen in the subgroup of patients with systemic JIA with active arthritis and no current systemic symptoms. Patients with juvenile PsA are included as separate efficacy subgroup. ERA patients are not included in the efficacy analysis.

All eligible patients in Study JIA-I received open-label tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily for 18 weeks (run-in phase); patients who achieved at least a JIA ACR30 response at the end of the open-label phase were randomised (1:1) to either active tofacitinib 5 mg film-coated tablets or tofacitinib oral solution, or placebo in the 26-week double-blind, placebo-controlled phase. Patients who did not achieve a JIA ACR30 response at the end of the open-label run-in phase or experienced a single episode of disease flare at any time were discontinued from the study. A total of 225 patients were enrolled in the open-label run-in phase. Of these, 173 (76.9%) patients were eligible to be randomised into the double-blind phase to either active tofacitinib 5 mg film-coated tablets or tofacitinib oral solution weight-based equivalent twice daily (n=88) or placebo (n=85). There were 58 (65.9%) patients in the tofacitinib group and 58 (68.2%) patients in the placebo group taking MTX during the double-blind phase, which was permitted but not required per the protocol.

There were 133 patients with pJIA [RF+ or RF- polyarthritis and extended oligoarthritis] and 15 with juvenile PsA randomised into the double-blind phase of the study and included in the efficacy analyses presented below.

Signs and symptoms
A significantly smaller proportion of patients with pJIA in Study JIA-I treated with tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily flared at Week 44 compared with patients treated with placebo. A significantly greater proportion of patients with

pJIA treated with tofacitinib 5 mg film-coated tablets or tofacitinib oral solution achieved JIA ACR30, 50, and 70 responses compared to patients treated with placebo at Week 44 (Table 8).

The occurrence of disease flare and JIA ACR30/50/70 results were favourable to tofacitinib 5 mg twice daily in comparison to placebo across the RF+ polyarthritis, RF- polyarthritis, extended oligoarthritis, and jPsA JIA subtypes and were consistent with those for the overall population.

The occurrence of disease flare and JIA ACR30/50/70 results were favourable to tofacitinib 5 mg twice daily in comparison to placebo for pJIA patients who received tofacitinib 5 mg twice daily with concomitant MTX use on Day 1 [n=101 (76%)] and those who were on tofacitinib monotherapy [n=32 (24%)]. In addition, the occurrence of disease flare and JIA ACR30/50/70 results were also favourable to tofacitinib 5 mg twice daily compared to placebo for pJIA patients who had prior bDMARD experience [n=39 (29%)] and those who were bDMARD naïve [n=94 (71%)].

In Study JIA-I, at Week 2 of the open-label run-in phase, the JIA ACR30 response in patients with pJIA was 45.03%.

Table 8: Primary and secondary efficacy endpoints in patients with pJIA at Week 44* in Study JIA-I (all p-values<0.05)

Primary endpoint (Type I error controlled)	**Treatment group**	**Occurrence rate**	**Difference (%) from placebo (95% CI)**
Occurrence of disease flare	Tofacitinib 5 mg Twice Daily (N=67)	28%	-24.7 (-40.8, -8.5)
	Placebo (N=66)	53%	
Secondary endpoints (Type I error controlled)	**Treatment group**	**Response rate**	**Difference (%) from placebo (95% CI)**
JIA ACR30	Tofacitinib 5 mg Twice Daily (N=67)	72%	24.7 (8.50, 40.8)
	Placebo (N=66)	47%	
JIA ACR50	Tofacitinib 5 mg Twice Daily (N=67)	67%	20.2 (3.72, 36.7)
	Placebo (N=66)	47%	
JIA ACR70	Tofacitinib 5 mg Twice Daily (N=67)	55%	17.4 (0.65, 34.0)
	Placebo (N=66)	38%	

Secondary endpoint (Type I error controlled)	Treatment group	LS mean (SEM)	Difference from placebo (95% CI)
Change from Double-Blind Baseline in CHAQ Disability Index	Tofacitinib 5 mg Twice Daily (N=67; n=46)	-0.11 (0.04)	-0.11 (-0.22, -0.01)
	Placebo (N=66; n=31)	0.00 (0.04)	

ACR = American College of Rheumatology; CHAQ = childhood health assessment questionnaire; CI = confidence interval; JIA = juvenile idiopathic arthritis; LS = least squares; n = number of patients with observations at the visit; N = total number of patients; SEM = standard error of the mean
* The 26-week double-blind phase is from Week 18 through Week 44 on and after randomisation day.
The Type-I error-controlled endpoints are tested in this order: Disease Flare, JIA ACR50, JIA ACR30, JIA ACR70, CHAQ Disability Index.

In the double-blind phase, each of the components of the JIA ACR response showed greater improvement from the open-label baseline (Day 1) at Week 24 and Week 44 for patients with pJIA treated with tofacitinib oral solution dosed as 5 mg twice daily or weight-based equivalent twice daily compared with those receiving placebo in Study JIA-I.

Physical function and health-related quality of life
Changes in physical function in Study JIA-I were measured by the CHAQ Disability Index. The mean change from the double-blind baseline in CHAQ-Disability Index in patients with pJIA was significantly lower in the tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily compared to placebo at Week 44 (Table 8). The mean change from the double-blind baseline in CHAQ Disability Index results were favourable to tofacitinib 5 mg twice daily in comparison to placebo across the RF+ polyarthritis, RF- polyarthritis, extended oligoarthritis, and jPsA JIA subtypes and were consistent with those for the overall study population.

Long-term controlled safety data in RA

Study ORAL Surveillance (A3921133) was a large (N=4362), randomised active-controlled post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional 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, anaemia of chronic disease, pulmonary manifestations). The majority (more than 90%) of tofacitinib patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively. Patients were required to be on a stable dose of methotrexate at study entry; dose adjustment was permitted during the study.

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 were adjudicated malignancies excluding NMSC and adjudicated major adverse cardiovascular events (MACE); cumulative incidence and statistical assessment of endpoints were blinded. The study was an event-powered study that also required at least 1500 patients to be followed for 3 years. The study treatment of tofacitinib 10 mg twice daily was stopped and patients were switched to 5 mg twice daily because of a dose-dependent signal of venous thromboembolic events (VTE). For patients in the tofacitinib 10 mg twice daily treatment arm, the data collected before and after the dose switch were analysed in their originally randomised treatment group.

The study did not meet the non-inferiority criterion for the primary comparison of the combined tofacitinib doses to TNF inhibitor since the upper limit of the 95% CI for HR exceeded the pre-specified non-inferiority criterion of 1.8 for adjudicated MACE and adjudicated malignancies excluding NMSC.

The results for adjudicated MACE, adjudicated malignancies excluding NMSC, and selected other events are provided below.

MACE (including myocardial infarction) and venous thromboembolism (VTE)
An increase in non-fatal myocardial infarction was observed in patients treated with tofacitinib compared to TNF inhibitor. A dose-dependent increase in VTE events was observed in patients treated with tofacitinib compared to TNF inhibitor (see sections 4.4 and 4.8).

Table 9: Incidence rate and hazard ratio for MACE, myocardial infarction and venous thromboembolism

	Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily[a]	All Tofacitinib[b]	TNF inhibitor (TNFi)
MACE[c]				
IR (95% CI) per 100 PY	0.91 (0.67, 1.21)	1.05 (0.78, 1.38)	0.98 (0.79, 1.19)	0.73 (0.52, 1.01)
HR (95% CI) vs TNFi	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)	
Fatal MI[c]				
IR (95% CI) per 100 PY	0.00 (0.00, 0.07)	0.06 (0.01, 0.18)	0.03 (0.01, 0.09)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	0.00 (0.00, Inf)	1.03 (0.21, 5.11)	0.50 (0.10, 2.49)	
Non-fatal MI[c]				
IR (95% CI) per 100 PY	0.37 (0.22, 0.57)	0.33 (0.19, 0.53)	0.35 (0.24, 0.48)	0.16 (0.07, 0.31)
HR (95% CI) vs TNFi	2.32 (1.02, 5.30)	2.08 (0.89, 4.86)	2.20 (1.02, 4.75)	
VTE[d]				
IR (95% CI) per 100 PY	0.33 (0.19, 0.53)	0.70 (0.49, 0.99)	0.51 (0.38, 0.67)	0.20 (0.10, 0.37)
HR (95% CI) vs TNFi	1.66 (0.76, 3.63)	3.52 (1.74, 7.12)	2.56 (1.30, 5.05)	
PE[d]				
IR (95% CI) per 100 PY	0.17 (0.08, 0.33)	0.50 (0.32, 0.74)	0.33 (0.23, 0.46)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	2.93 (0.79, 10.83)	8.26 (2.49, 27.43)	5.53 (1.70, 18.02)	
DVT[d]				
IR (95% CI) per 100 PY	0.21 (0.11, 0.38)	0.31 (0.17, 0.51)	0.26 (0.17, 0.38)	0.14 (0.06, 0.29)
HR (95% CI) vs TNFi	1.54 (0.60, 3.97)	2.21 (0.90, 5.43)	1.87 (0.81, 4.30)	

[a] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.
[b] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.
[c] Based on events occurring on treatment or within 60 days of treatment discontinuation.
[d] Based on events occurring on treatment or within 28 days of treatment discontinuation.
Abbreviations: MACE = major adverse cardiovascular events, MI = myocardial infarction, VTE = venous thromboembolism, PE = pulmonary embolism, DVT = deep vein thrombosis, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, Inf = infinity

The following predictive factors for development of MI (fatal and non-fatal) were identified using a multivariate Cox model with backward selection: age ≥65 years, male, current or past smoking, history of diabetes, and history of coronary artery disease (which includes myocardial infarction, coronary heart disease, stable angina pectoris, or coronary artery procedures) (see sections 4.4 and 4.8).

Malignancies

An increase in malignancies excluding NMSC, particularly lung cancer, lymphoma and an increase in NMSC was observed in patients treated with tofacitinib compared to TNF inhibitor.

Table 10: Incidence rate and hazard ratio for malignancies[a]

	Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily[b]	All Tofacitinib[c]	TNF inhibitor (TNFi)
Malignancies excluding NMSC				
IR (95% CI) per 100 PY	1.13 (0.87, 1.45)	1.13 (0.86, 1.45)	1.13 (0.94, 1.35)	0.77 (0.55, 1.04)
HR (95% CI) vs TNFi	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)	
Lung cancer				
IR (95% CI) per 100 PY	0.23 (0.12, 0.40)	0.32 (0.18, 0.51)	0.28 (0.19, 0.39)	0.13 (0.05, 0.26)
HR (95% CI) vs TNFi	1.84 (0.74, 4.62)	2.50 (1.04, 6.02)	2.17 (0.95, 4.93)	
Lymphoma				
IR (95% CI) per 100 PY	0.07 (0.02, 0.18)	0.11 (0.04, 0.24)	0.09 (0.04, 0.17)	0.02 (0.00, 0.10)
HR (95% CI) vs TNFi	3.99 (0.45, 35.70)	6.24 (0.75, 51.86)	5.09 (0.65, 39.78)	
NMSC				
IR (95% CI) per 100 PY	0.61 (0.41, 0.86)	0.69 (0.47, 0.96)	0.64 (0.50, 0.82)	0.32 (0.18, 0.52)
HR (95% CI) vs TNFi	1.90 (1.04, 3.47)	2.16 (1.19, 3.92)	2.02 (1.17, 3.50)	

[a] For malignancies excluding NMSC, lung cancer, and lymphoma, based on events occurring on treatment or after treatment discontinuation up to the end of the study. For NMSC based on events occurring on treatment or within 28 days of treatment discontinuation.

[b] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.

[c] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.

Abbreviations: NMSC = non melanoma skin cancer, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years

The following predictive factors for development of malignancies excluding NMSC were identified using a Multivariate Cox model with backward selection: age ≥65 years and current or past smoking (see section 4.4 and 4.8).

Mortality

Increased mortality was observed in patients treated with tofacitinib compared to TNF inhibitors. Mortality was mainly due to cardiovascular events, infections and malignancies.

Table 11: Incidence rate and hazard ratio for mortality[a]

	Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily[b]	All Tofacitinib[c]	TNF inhibitor (TNFi)
Mortality (all cause)				
IR (95% CI) per 100 PY	0.50 (0.33, 0.74)	0.80 (0.57, 1.09)	0.65 (0.50, 0.82)	0.34 (0.20, 0.54)
HR (95% CI) vs TNFi	1.49 (0.81, 2.74)	2.37 (1.34, 4.18)	1.91 (1.12, 3.27)	
Fatal infections				
IR (95% CI) per 100 PY	0.08 (0.02, 0.20)	0.18 (0.08, 0.35)	0.13 (0.07, 0.22)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	1.30 (0.29, 5.79)	3.10 (0.84, 11.45)	2.17 (0.62, 7.62)	
Fatal CV events				
IR (95% CI) per 100 PY	0.25 (0.13, 0.43)	0.41 (0.25, 0.63)	0.33 (0.23, 0.46)	0.20 (0.10, 0.36)
HR (95% CI) vs TNFi	1.26 (0.55, 2.88)	2.05 (0.96, 4.39)	1.65 (0.81, 3.34)	
Fatal Malignancies				
IR (95% CI) per 100 PY	0.10 (0.03, 0.23)	0.00 (0.00, 0.08)	0.05 (0.02, 0.12)	0.02 (0.00, 0.11)
HR (95% CI) vs TNFi	4.88 (0.57, 41.74)	0 (0.00, Inf)	2.53 (0.30, 21.64)	

[a] Based on events occurring on treatment or within 28 days of treatment discontinuation.

[b] The tofacitinib 10 mg twice daily treatment group includes data from patients that were switched from tofacitinib 10 mg twice daily to tofacitinib 5 mg twice daily as a result of a study modification.

[c] Combined tofacitinib 5 mg twice daily and tofacitinib 10 mg twice daily.

Abbreviations: TNF = tumor necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, CV = cardiovascular, Inf = infinity

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 studies, 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.

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 studies, tofacitinib was not evaluated in patients with baseline creatinine clearance values (estimated by Cockcroft-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 studies, 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.

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.

Pharmacokinetics in paediatric patients with juvenile idiopathic arthritis
Population PK analysis based on results from both tofacitinib 5 mg film-coated tablets twice daily and tofacitinib oral solution weight-based equivalent twice daily indicated that tofacitinib clearance and volume of distribution both decreased with decreasing body weight in JIA patients. The available data indicated that there were no clinically relevant differences in tofacitinib exposure (AUC), based on age, race, gender, patient type or baseline disease severity. The between-subject variability (% coefficient of variation) in (AUC) was estimated to be approximately 24%.

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. In studies conducted in juvenile rats and monkeys, there were no tofacitinib-related effects on bone development in males or females, at exposures similar to those achieved at approved doses in humans.

No tofacitinib-related findings were observed in juvenile animal studies that indicate a higher sensitivity of paediatric populations compared with adults. In the juvenile rat fertility study, there was no evidence of developmental toxicity, no effects on sexual maturation, and no evidence of reproductive toxicity (mating and fertility) was noted after sexual maturity. In 1-month juvenile rat and 39-week juvenile monkey studies tofacitinib-related effects on immune and haematology parameters consistent with JAK1/3 and JAK2 inhibition were observed. These effects were reversible and consistent with those also observed in adult animals at similar exposures.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Grape flavour [containing propylene glycol (E1520), glycerin (E422), and natural flavours]
Hydrochloric acid

Lactic acid (E270)
Purified water
Sodium benzoate (E211)
Sucralose (E955)
Xylitol (E967)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

Shelf life after first opening

Should be discarded after 60 days of first opening.

6.4 Special precautions for storage

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

Store in the original bottle and package in order to protect from light.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

White coloured HDPE 250 mL bottles containing 240 mL of oral solution with a child resistant, polypropylene cap with PP liner sealed by aluminium-foil heat-induction seal and a 5 mL oral dosing syringe with 3.2 mL, 4 mL, and 5 mL graduations.

The container closure system also includes a low-density polyethylene (LDPE) press-in bottle adapter (PIBA).

Pack size: each pack contains one bottle, one press-in bottle adapter, and one oral dosing syringe.

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/1/17/1178/015

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2017
Date of renewal of the authorisation: 04 March 2022

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

Pfizer Service Company BVBA
Hoge Wei 10
1930 Zaventem
Belgium

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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 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 all-cause mortality, serious infections, venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), cardiovascular risk (excluding myocardial infarction [MI]), MI, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy (particularly lymphoma and lung cancer), NMSC, gastrointestinal perforations, interstitial lung disease, and laboratory abnormalities.

The MAH shall ensure that in each Member State where XELJANZ is marketed, all healthcare professionals and patients/carers who are expected to prescribe or use XELJANZ have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

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

- **The Guide for healthcare professionals** shall contain the following key elements:
    - Relevant information of the safety concerns addressed by the aRMM (e.g. seriousness, severity, frequency, time to onset, reversibility of the AE as applicable)
    - Details of the population at higher risk for the safety concern addressed by the aRMM (i.e. contraindications, risk factors, increased risk by interactions with certain medicine)
    - Details of the populations at higher risk for VTE, cardiovascular risk including MI, and malignancy (including lymphoma and lung cancer)
    - Details on use of XELJANZ in patients 65 years of age and older, including information on the specific risks in this population (e.g. serious infections, myocardial infarction, malignancy, all-cause mortality), and details on how to minimise the risks of tofacitinib in patients 65 years of age and older in clinical practice, i.e. the recommendation that tofacitinib should only be used in patients 65 years of age and older if no suitable treatment alternatives are available
    - Details on how to minimise the safety concerns addressed by the aRMM through appropriate monitoring and management (i.e. who may receive the medicine, 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 dose according to laboratory measurements, signs and symptoms)
    - Details on how to minimise the risks of VTE, cardiovascular risk including MI, and malignancy (including lymphoma, lung cancer, and NMSC) in clinical practice, i.e.:
        - VTE: Tofacitinib should be used with caution in patients with known VTE risk factors.
        - MACE and MI: In patients 65 years of age and older, patients who are current or past long-time smokers and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available
        - Malignancies: In patients 65 years of age and older, patients who are current or past long-time smokers and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer), tofacitinib should only be used if no suitable treatment alternatives are available

    - Posology UC maintenance treatment: Tofacitinib 10 mg twice daily is not recommended for maintenance treatment in patients with UC who have known VTE, MACE and malignancy risk factors, unless there is no suitable alternative treatment available

  - Key message to convey in patients counselling
  - Instructions on how to handle possible adverse events
  - Information about the BSRBR, ARTIS, RABBIT, BIODABASER, UC registries, and polyarticular juvenile idiopathic arthritis (pJIA) and juvenile psoriatic arthritis registries and the importance of contributing to these
  - Vaccination course to be completed before treatment as it is recommended that live vaccines not be given concurrently with tofacitinib

- **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
  - Guidance to minimise the risk of cardiovascular events including MI and malignancy (including lymphoma, lung cancer, and NMSC), i.e.:
    - MACE and MI: In patients 65 years of age and older, patients who are current or past long-time smokers and patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available
    - Malignancies: In patients 65 years of age and older, patients who are current or past long-time smokers and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer), tofacitinib should only be used if no suitable treatment alternatives are available
    - Guidance that in patients 65 years of age and older tofacitinib should only be used if no suitable treatment alternatives are available
  - 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 all-cause mortality, infections, venous thromboembolism (deep vein thrombosis [DVT] and pulmonary embolism [PE]), cardiovascular risk (excluding MI), MI, herpes zoster, tuberculosis (TB) and other opportunistic infections, malignancy (including lymphoma and lung cancer), 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, malignancies (including lung cancer, lymphoma), 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]), myocardial infarction (MI), herpes zoster reactivation, malignancies (including lung cancer, lymphoma), 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, 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
  - Instructions for use

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

Other ingredients include 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

Other ingredients include 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/1/17/1178/001 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

Other ingredients include 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

Other ingredients include 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

Other ingredients include 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

Other ingredients include 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

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR BOTTLE

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 1 mg/mL oral solution
tofacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral solution contains 1 mg of tofacitinib (as tofacitinib citrate).

3. LIST OF EXCIPIENTS

Contains propylene glycol (E1520), sodium benzoate (E211). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

240 mL Oral solution
One bottle of oral solution, one press-in bottle adapter, and one oral dosing syringe

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
Discard after 60 days of first opening
Open date:

9. SPECIAL STORAGE CONDITIONS

Store in the original bottle and package in order to protect from light.

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/1/17/1178/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

XELJANZ 1 mg/mL

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 INNER PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 1 mg/mL oral solution
tofacitinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each mL of oral solution contains 1 mg of tofacitinib (as tofacitinib citrate).

3. LIST OF EXCIPIENTS

Contains propylene glycol (E1520), sodium benzoate (E211). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

240 mL Oral solution
One bottle of oral solution, one press-in bottle adapter, and one oral dosing syringe

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
Discard after 60 days of first opening
Open date:

9. SPECIAL STORAGE CONDITIONS

Store in the original botte and package in order to protect from light.

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/1/17/1178/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER - 2D BARCODE

18. UNIQUE IDENTIFIER-HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient
XELJANZ 5 mg film-coated tablets
XELJANZ 10 mg film-coated tablets
tofacitinib

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
- ankylosing spondylitis
- polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis

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

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

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

Psoriatic arthritis
XELJANZ is used to treat adult patients with 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.

Ankylosing spondylitis
XELJANZ is used to treat a condition called ankylosing spondylitis. This condition is an inflammatory disease of the spine.

If you have ankylosing spondylitis, you may first be given other medicines. If you do not respond well enough to these medicines, you will be given XELJANZ. XELJANZ can help to reduce back pain, and improve physical function. These effects can ease your normal daily activities and so improve your quality of life.

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

Polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis
XELJANZ is used for the treatment of active polyarticular juvenile idiopathic arthritis a long-term disease that mainly causes pain and swelling of your joints, in patients 2 years of age and older.

XELJANZ is also used for the treatment of juvenile psoriatic arthritis, a condition that is an inflammatory disease of the joints often accompanied by psoriasis, in patients 2 years of age and older.

XELJANZ can be used together with methotrexate when previous treatment for polyarticular juvenile idiopathic arthritis or juvenile psoriatic arthritis 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.

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 are 65 years of age and older, if you have ever had any type of cancer, and also if you are a current or past smoker. XELJANZ may increase your risk of certain cancers. White blood cell cancer, lung cancer and other cancers (such as breast, skin, 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 known risk of fractures, e.g., if you are 65 years of age and older, you are a female, or take corticosteroids (e.g., prednisone).
- Cases of non-melanoma skin cancer have been observed in patients taking XELJANZ. Your doctor may recommend that you have regular skin examinations while taking XELJANZ. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.
- 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, high cholesterol, and also if you are a current or past smoker

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 currently or in the past, 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.

Talk to your doctor straight away if you experience acute changes to your eyesight (blurry vision, partial or complete loss of vision), as this may be a sign of blood clots in the eyes.

There have been reports of patients treated with XELJANZ who have had a heart problem, including heart attack. Your doctor will evaluate your risk to develop a heart problem and determine if XELJANZ is appropriate for you. Talk to your doctor straight away if you develop signs and symptoms of a heart attack including severe chest pain or tightness (that may spread to arms, jaw, neck, back), shortness of breath, cold sweat, light headedness or sudden dizziness.

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, some of which may be serious, in patients 65 years of age and older. Tell your doctor as soon as you notice any signs or symptoms of infections.

Patients 65 years of age and older may be at increased risk of infections, heart attack and some types of cancer. Your doctor may decide that XELJANZ is not suitable for you.

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
The safety and benefits of XELJANZ in children have not yet been established in patients less than 2 years of age.

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

Tell your doctor if you have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you need less anti-diabetic medicine while taking tofacitinib.

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

Serious infections and fractures 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.

XELJANZ contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

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.

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

Ankylosing spondylitis
- The recommended dose is 5 mg twice a day.
- Your doctor may decide to stop XELJANZ if XELJANZ does not work for you within 16 weeks.

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 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 your treatment is interrupted, your doctor may decide to restart your treatment.

Use in children and adolescents

Polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis

- The recommended dose is 5 mg twice a day for patients ≥40 kg.

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.

Side effects in patients with polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis were consistent with those seen in adult rheumatoid arthritis patients with the exception of some infections (influenza, pharyngitis, sinusitis, viral infection) and gastrointestinal or general disorders (abdominal pain, nausea, vomiting, fever, headache, cough), which were more common in juvenile idiopathic arthritis paediatric population.

Possible serious side effects
In rare cases, infection may be life-threatening. Lung cancer, white blood cell cancer and heart attack have also been reported.

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 (perforations) 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 or eyes (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
- acute changes in eyesight

Signs of a heart attack (uncommon) include
- severe chest pain or tightness (that may spread to arms, jaw, neck, back)
- shortness of breath
- cold sweat
- light headedness or sudden dizziness

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 white blood cell counts, low red blood cell count (anaemia), swelling of the feet and hands, headache, high blood pressure (hypertension), cough, rash.

Uncommon (may affect up to 1 in 100 people): lung cancer, tuberculosis, kidney infection, skin infection, herpes simplex or cold sores (oral herpes), blood creatinine increased (a possible sign of kidney problems), increased cholesterol (including increased LDL), fever, fatigue (tiredness), weight gain, dehydration, muscle strain, 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), lymphoma (white blood cell cancer), disseminated tuberculosis involving bones and other organs, other unusual infections, joint infections, increased liver enzymes in the blood (sign of liver problems), pain in the muscles and joints.

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

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 blister pack, bottle, or carton. 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 “XELJANZ contains lactose”), croscarmellose sodium (see section 2 “XELJANZ contains sodium”), magnesium stearate, hypromellose (E464), titanium dioxide (E171), macrogol, and triacetin.

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 “XELJANZ contains lactose”), croscarmellose sodium (see section 2 “XELJANZ contains sodium”), magnesium stearate, hypromellose (E464), titanium dioxide (E171), macrogol, triacetin, 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.

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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

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
- ankylosing spondylitis

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 adult patients with 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.

Ankylosing spondylitis
XELJANZ is used to treat a condition called ankylosing spondylitis. This condition is an inflammatory disease of the spine.

If you have ankylosing spondylitis, you may first be given other medicines. If you do not respond well enough to these medicines, you will be given XELJANZ. XELJANZ can help to reduce back pain, and improve physical function. These effects can ease your normal daily activities and so improve your quality of life.

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 are 65 years of age and older, if you have ever had any type of cancer, and also if you are a current or past smoker. XELJANZ may increase your risk of certain cancers. White blood cell cancer, lung cancer and other cancers (such as breast, skin, 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 known risk of fractures, e.g., if you are 65 years of age and older, you are a female, or take corticosteroids (e.g., prednisone).
- Cases of non-melanoma skin cancer have been observed in patients taking XELJANZ. Your doctor may recommend that you have regular skin examinations while taking XELJANZ. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.
- 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, high cholesterol, and also if you are a current or past smoker
- 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 currently or in the past, 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.

Talk to your doctor straight away if you experience acute changes to your eyesight (blurry vision, partial or complete loss of vision), as this may be a sign of blood clots in the eyes.

There have been reports of patients treated with XELJANZ who have had a heart problem, including heart attack. Your doctor will evaluate your risk to develop a heart problem and determine if XELJANZ is appropriate for you. Talk to your doctor straight away if you develop signs and symptoms of a heart attack including severe chest pain or tightness (that may spread to arms, jaw, neck, back), shortness of breath, cold sweat, light headedness or sudden dizziness.

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, some of which may be serious, in patients 65 years of age and older. Tell your doctor as soon as you notice any signs or symptoms of infections.

Patients 65 years of age and older may be at increased risk of infections, heart attack and some types of cancer. Your doctor may decide that XELJANZ is not suitable for you.

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.

Tell your doctor if you have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you need less anti-diabetic medicine while taking tofacitinib.

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

Serious infections and fractures 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

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, psoriatic arthritis, and ankylosing spondylitis
The recommended dose is one 11 mg prolonged-release tablet administered once daily.

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.

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, psoriatic arthritis, or ankylosing spondylitis, your doctor may switch your tablets between XELJANZ 5 mg film-coated tablets twice daily and XELJANZ 11 mg prolonged-release tablet once daily. You can start the XELJANZ prolonged-release tablet once daily or XELJANZ film-coated tablets twice daily on the day following the last dose of either tablet. You should not switch between XELJANZ film-coated tablets and XELJANZ prolonged-release tablet unless instructed by your doctor.

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

Ankylosing spondylitis
- Your doctor may decide to stop XELJANZ if XELJANZ does not work for you within 16 weeks.

If you take more XELJANZ than you should
If you take more 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 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. Lung cancer, white blood cell cancer and heart attack have also been reported.

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 (perforations) 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 or eyes (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
- acute changes in eyesight

Signs of a heart attack (uncommon) include
- severe chest pain or tightness (that may spread to arms, jaw, neck, back)
- shortness of breath
- cold sweat
- light headedness or sudden dizziness

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 white blood cell counts, low red blood cell count (anaemia), swelling of the feet and hands, headache, high blood pressure (hypertension), cough, rash.

Uncommon (may affect up to 1 in 100 people): lung cancer, tuberculosis, kidney infection, skin infection, herpes simplex or cold sores (oral herpes), blood creatinine increased (a possible sign of kidney problems), increased cholesterol (including increased LDL), fever, fatigue (tiredness), weight gain, dehydration, muscle strain, 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), lymphoma (white blood cell cancer), disseminated tuberculosis involving bones and other organs, other unusual infections, joint infections, increased liver enzymes in the blood (sign of liver problems), pain in the muscles and joints.

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

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 blister pack, bottle, or carton. 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 “XELJANZ 11 mg prolonged-release tablet contains sorbitol”), hydroxyethyl cellulose, copovidone, magnesium stearate, cellulose acetate, hydroxypropyl cellulose (E463), hypromellose (E464), titanium dioxide (E171), triacetin, 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 tablets are provided in blisters containing 7 tablets. Each pack contains 28 or 91 tablets. The tablets are also available in bottles with silica gel desiccant containing 30 or 90 tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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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 1 mg/mL oral solution
tofacitinib

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 1 mg/mL oral solution is a medicine that contains the active substance tofacitinib.

XELJANZ 1 mg/mL oral solution is used for the treatment of active polyarticular juvenile idiopathic arthritis, a long-term disease that mainly causes pain and swelling of your joints, in patients 2 years of age and older.

XELJANZ 1 mg/mL oral solution is also used for the treatment of juvenile psoriatic arthritis, a condition that is an inflammatory disease of the joints often accompanied by psoriasis, in patients 2 years of age and older.

XELJANZ 1 mg/mL oral solution can be used together with methotrexate when previous treatment for polyarticular juvenile idiopathic arthritis or juvenile psoriatic arthritis was not sufficient or was not well tolerated. XELJANZ 1 mg/mL oral solution can also be taken on its own in those cases where methotrexate treatment is not tolerated or treatment with methotrexate is not advised.

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, and also if you are a current or past smoker. XELJANZ may increase your risk of certain cancers. White blood cell cancer, lung cancer and other cancers (such as breast, skin, 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 known risk of fractures, e.g., if you are 65 years of age and older, you are a female, or take corticosteroids (e.g., prednisone).
- Cases of non-melanoma skin cancer have been observed in patients taking XELJANZ. Your doctor may recommend that you have regular skin examinations while taking XELJANZ. If new skin lesions appear during or after therapy or if existing lesions change appearance, tell your doctor.
- 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, high cholesterol, and also if you are a current or past smoker

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), or if you smoke currently or in the past, 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.

Talk to your doctor straight away if you experience acute changes to your eyesight (blurry vision, partial or complete loss of vision), as this may be a sign of blood clots in the eyes.

There have been reports of patients treated with XELJANZ who have had a heart problem, including heart attack. Your doctor will evaluate your risk to develop a heart problem and determine if XELJANZ is appropriate for you. Talk to your doctor straight away if you develop signs and symptoms of a heart attack including severe chest pain or tightness (that may spread to arms, jaw, neck, back), shortness of breath, cold sweat, light headedness or sudden dizziness.

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
The safety and efficacy of tofacitinib 1 mg/mL oral solution has not been established in the elderly.

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
This medicine should not be given to patients less than 2 years of age.

This medicine contains propylene glycol and should be used with caution in patients 2 years of age and older and only if advised by the doctor (see "XELJANZ contains propylene glycol").

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

Tell your doctor if you have diabetes or are taking medicines to treat diabetes. Your doctor may decide if you need less anti-diabetic medicine while taking tofacitinib.

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

Serious infections and fractures 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 propylene glycol
This medicine contains 2.39 mg propylene glycol in each mL of oral solution.

XELJANZ contains sodium benzoate
This medicine contains 0.9 mg sodium benzoate in each mL of oral solution.

XELJANZ contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially ‘sodium-free’.

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.

The recommended dose in patients 2 years of age and older is based upon the following weight categories (see Table 1).

Table 1. XELJANZ dose for patients with polyarticular juvenile idiopathic arthritis and juvenile PsA two years of age and older:

Body weight (kg)	Dose regimen
10 - <20	3.2 mg (3.2 mL of oral solution) twice daily
20 - <40	4 mg (4 mL of oral solution) twice daily
≥ 40	5 mg (5 mL of oral solution or 5 mg film-coated tablet) twice 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 polyarticular juvenile idiopathic arthritis or juvenile psoriatic arthritis, your doctor may switch you from XELJANZ 5 mL oral solution twice daily to XELJANZ 5 mg film-coated tablets twice daily.

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

Try to take XELJANZ at the same time every day (once in the morning and once in the evening).

If you take more XELJANZ than you should
If you take more XELJANZ 1 mg/mL oral solution 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 dose. Take your next dose 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.

Side effects in patients with polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis were consistent with those seen in adult rheumatoid arthritis patients with the exception of some infections (influenza, pharyngitis, sinusitis, viral infection) and gastrointestinal or general disorders (abdominal pain, nausea, vomiting, fever, headache, cough), which were more common in juvenile idiopathic arthritis paediatric population.

Possible serious side effects
In rare cases, infection may be life-threatening. Lung cancer, white blood cell cancer and heart attack have also been reported.

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 (perforations) 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 or eyes (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
- acute changes in eyesight

Signs of a heart attack (uncommon) include
- severe chest pain or tightness (that may spread to arms, jaw, neck, back)
- shortness of breath
- cold sweat
- light headedness or sudden dizziness

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 white blood cell counts, low red blood cell count (anaemia), swelling of the feet and hands, headache, high blood pressure (hypertension), cough, rash.

Uncommon (may affect up to 1 in 100 people): lung cancer, tuberculosis, kidney infection, skin infection, herpes simplex or cold sores (oral herpes), blood creatinine increased (a possible sign of kidney problems), increased cholesterol (including increased LDL), fever, fatigue (tiredness), weight gain, dehydration, muscle strain, 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), lymphoma (white blood cell cancer), disseminated tuberculosis involving bones and other organs, other unusual infections, joint infections, increased liver enzymes in the blood (sign of liver problems), pain in the muscles and joints.

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

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 carton or bottle. 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 bottle and package in order to protect from light.

Discard after 60 days of first opening.

Do not use this medicine if you notice the solution shows visible signs of deterioration.

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 1 mL contains 1 mg of tofacitinib (as tofacitinib citrate).
- The other ingredients are grape flavour [containing propylene glycol (E1520) (see section 2 "XELJANZ contains propylene glycol"), glycerin (E422), and natural flavours], hydrochloric acid, lactic acid (E270), purified water, sodium benzoate (E211) (see section 2 "XELJANZ contains sodium benzoate" and "XELJANZ contains sodium"), sucralose (E955), and xylitol (E967).

What XELJANZ looks like and contents of the pack

XELJANZ 1 mg/mL oral solution is a clear, colourless solution.
The 1 mg/mL oral solution is provided in white coloured HDPE 250 mL bottles containing 240 mL of solution. Each pack contains one HDPE bottle, one press-in bottle adapter, and one oral dosing syringe with 3.2 mL, 4 mL, and 5 mL graduations.

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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.

7. Instructions for Use of XELJANZ oral solution

Read this Instructions for Use before you start taking XELJANZ oral solution. There may be new information.

Important information about measuring XELJANZ oral solution

Always use the oral dosing syringe that comes with your XELJANZ oral solution to measure and administer your prescribed dose. Ask your healthcare provider or pharmacist to show you how to measure your prescribed dose if you are not sure.

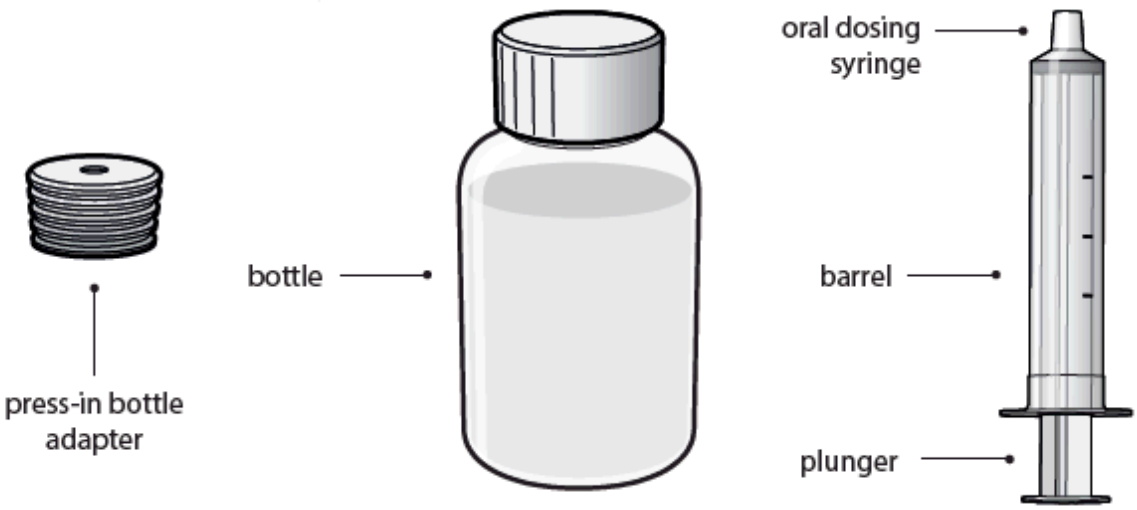
How should I store XELJANZ?

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

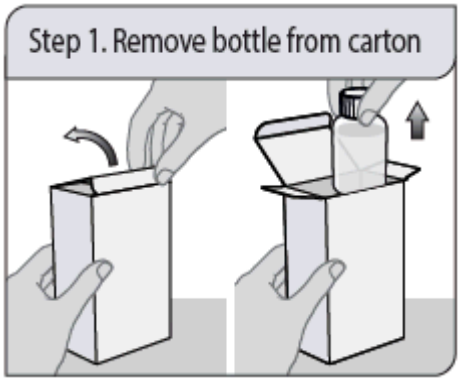
Discard remaining XELJANZ oral solution after 60 days.
To help you remember when to dispose of your XELJANZ bottle you can write the date of first use on the carton and below:
Date of first use ____ / ____ / ____.
Before each use:
Wash your hands with soap and water and place the items from the carton on a clean flat surface.

Each carton of XELJANZ oral solution contains

- 1 press-in bottle adapter
- 1 bottle of XELJANZ oral solution
- 1 oral dosing syringe

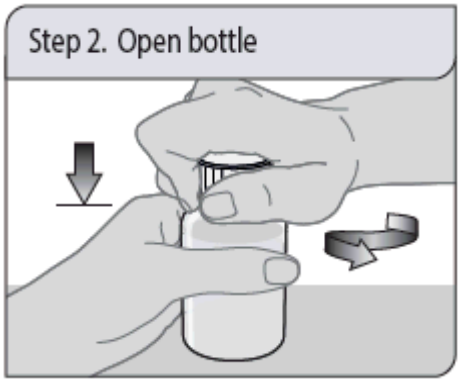


Step 1. Remove bottle from carton



Remove the bottle of XELJANZ oral solution from the carton.

Step 2. Open bottle

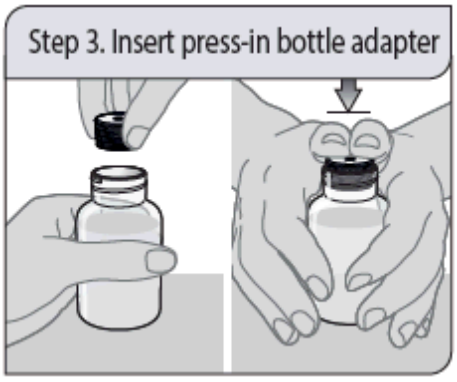


Open the bottle. Remove the seal off the top of the bottle (first time only).

Do not throw away the child-resistant cap.

Note: Bottle does **not** need to be shaken before use.

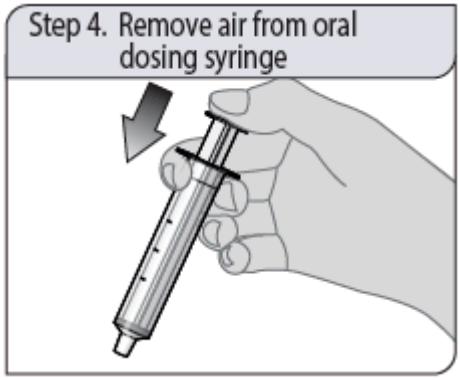
Step 3. Insert press-in bottle adapter



Remove the press-in bottle adapter and oral dosing syringe from the plastic overwrap. With the bottle on a flat surface, push the ribbed end of the press-in bottle adapter with your thumbs all the way into the neck of the bottle while holding the bottle firmly.

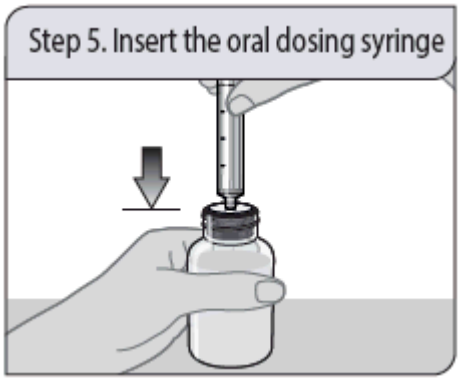
Note: Do not remove the press-in bottle adapter from the bottle after it is inserted.

Step 4. Remove air from oral dosing syringe



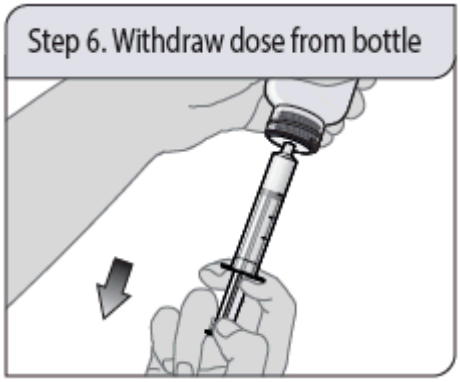
Push the oral dosing syringe plunger fully to the tip of the syringe barrel to remove excess air.

Step 5. Insert the oral dosing syringe



Insert the oral dosing syringe into the upright bottle through the opening of the press-in bottle adapter until it is firmly in place.

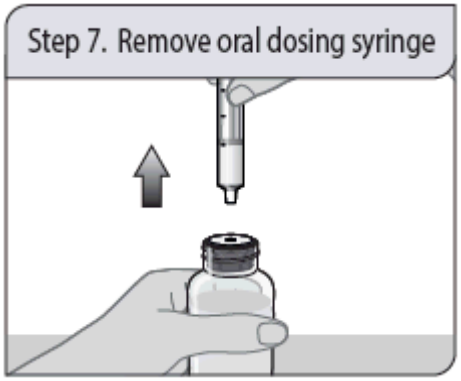
Step 6. Withdraw dose from bottle



With the oral dosing syringe in place, turn the bottle upside down. Pull back the plunger.

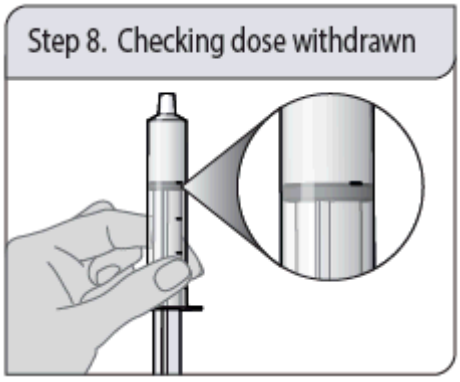
If you see air bubbles in the oral dosing syringe, fully push the plunger in to empty the oral solution back into the bottle. Then withdraw your prescribed dose of oral solution.

Step 7. Remove oral dosing syringe



Turn the bottle upright and place the bottle on a flat surface. Remove the oral dosing syringe from the bottle adapter and bottle by pulling straight up on the oral dosing syringe barrel.

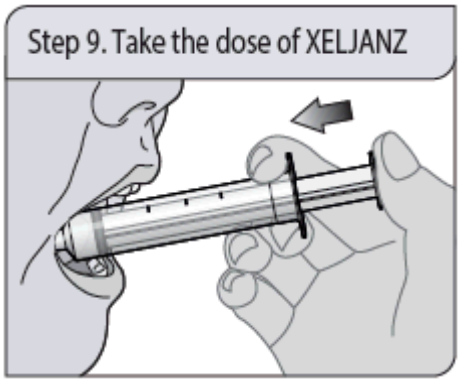
Step 8. Checking dose withdrawn



Check that the correct dose was drawn up into the oral dosing syringe.

If the dose is not correct, insert the oral dosing syringe tip firmly into the bottle adapter. Fully push in the plunger so that the oral solution flows back into the bottle. Repeat Steps 6 and 7.

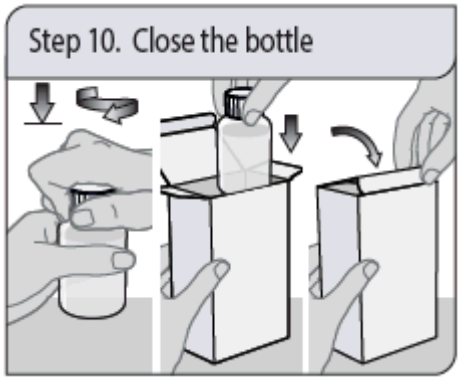
Step 9. Take the dose of XELJANZ



Place the tip of the oral dosing syringe into the inside of the patient’s cheek.

Slowly push the plunger all the way down to give all the medicine in the oral dosing syringe. Make sure the patient has time to swallow the medicine.

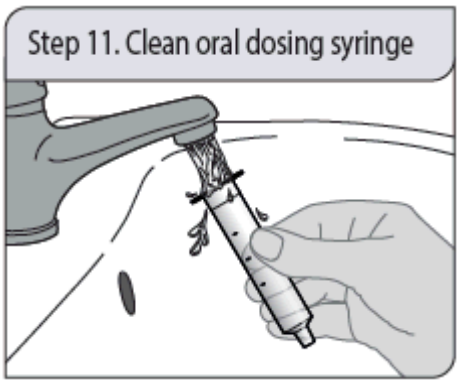
Step 10. Close the bottle



Close the bottle tightly by turning the child-resistant cap clockwise, leaving the press-in bottle adapter in place.

Place the bottle back into the carton and close the carton to protect XELJANZ oral solution from light.

Step 11. Clean oral dosing syringe



Remove the plunger from the barrel by pulling the plunger and the barrel away from each other.

Rinse both with water after each use.

Allow to air dry; then put the oral dosing syringe back together with oral solution in the carton.

Store the oral dosing syringe with the XELJANZ oral solution.

Do not throw away the oral dosing syringe.

ANNEX IV

SCIENTIFIC CONCLUSIONS

Scientific conclusions

On 28 January 2022, pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the Agency on whether the marketing authorisation of Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation by the PRAC

This referral procedure concerns JAKis approved for inflammatory disorders:

- Xeljanz (tofacitinib): rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), ulcerative colitis (UC) and juvenile idiopathic arthritis (JIA).
- Olumiant (barcitinib): RA, alopecia areata (AA) and atopic dermatitis (AD)
- Cibinqo (abrocitinib): AD
- Jyseleca (filgotinib): RA and UC
- Rinvoq (upadacitinib): RA, PsA, AS, non-radiographic axial spondyloarthritis (nr-axSpA), UC and AD

These medicinal products inhibit different JAK isoforms which attenuates signalling of interleukins and interferons, resulting in modulation of the immune and inflammatory response.

The background to this referral procedure is based on data from the ORAL Surveillance study A3921133. This is a Phase 3b/4 randomized study that evaluates the safety of tofacitinib at two doses (5 mg and 10 mg BID) versus TNFi. The study is a post marketing commitment to assess the risk of cardiovascular events in subjects 50 years of age and older with at least one cardiovascular risk factor with moderately or severely active RA.

Interim results from the ORAL Surveillance study were assessed in 2019 in an Article 20 referral procedure (EMEA/H/A-20/1485) and a preliminary analysis of the final results were included in signal procedure (EPITT 19382) which concluded in June 2021. The PRAC concluded that tofacitinib is associated with an increased risk of venous thromboembolism (VTE) and that there is a potential risk regarding increased mortality. This was partly driven by a higher mortality rate due to serious infections for tofacitinib and was particularly apparent for patients aged 65 years and above. Further, there was an increased incidence of major adverse cardiovascular events (MACE) and higher risk of malignancy with tofacitinib compared to TNFi. The PI of tofacitinib, but not the other JAKis, was updated accordingly.

The final results of the completed ORAL Surveillance study confirmed the findings observed in the preliminary analysis. No randomised controlled studies have been concluded with the other JAKis to specifically evaluate the safety concerns of interest. However, preliminary results on baricitinib were made available from the observational Study I4V-MC-B023 (B023) showed an increased rate of MACE and VTE with baricitinib compared to TNFi in RA patients. A safety referral was therefore triggered to assess whether the safety concerns on MACE, VTEs, serious infections, malignancies and mortality observed in rheumatoid arthritis patients with tofacitinib are a class effect and to assess its impact on the benefit risk balance of the JAKis used in the treatment of chronic inflammatory disorders.

Following assessment of the currently available mechanistic data, together with current knowledge of the safety profiles of these substances, the PRAC considered the main safety events observed during tofacitinib treatment in the ORAL Surveillance study as general JAKi class effects. This view was also supported by the Ad Hoc Expert Group.

It is acknowledged that the extent to which the tofacitinib ORAL Surveillance data on MACE, VTE, serious infections, malignancies and mortality are applicable to all JAKis approved for inflammatory conditions, across the target populations, depends also on the similarities of the respective populations including presence of risk factors for occurrence of the observed adverse events. Overall, the ORAL Surveillance study population is considered sufficiently similar to the populations covered by the adult arthritis indications RA and PsA to allow extrapolation of data. The target populations of the other

rheumatic disorders and UC are considered to be sufficiently similar, with regards to important disease characteristics and baseline risk factors, for the ORAL Surveillance data to be relevant.

For the AD population, the prevalence of risk factors (including age and co-morbidities) is different compared to a RA population, mainly explained by lower age and disease specific differences. Patients with AD are already due to their underlying disease at increased risk for cardiovascular comorbidities compared to the general population (e.g. Ivert et al., 2019), which supports extrapolation of the findings in RA in the ORAL surveillance study to AD. Regarding treatment of severe AA, the PRAC acknowledged that this patient group generally has less risk factors for the main serious safety outcomes compared with e.g. RA patients, as they are at least not associated to the underlying disease.

Nevertheless, as also pointed out by the Ad Hoc Expert Group, if a patient has risk factors in any of the authorised indications, the patient would be equally at risk for the safety findings being the focus of this review. JAKis are used for indications requiring chronic treatment, potentially exposing patients without risk factors for prolonged periods of time. Thus, even a small increase in absolute risk of serious adverse events may be clinically relevant. These risks are monitored and will be further characterised in ongoing PASSes.

Therefore, since the safety events are considered class effects and because the risk factors for these events can emerge in populations treated with any of the JAKis, the PRAC concluded that these important safety concerns are relevant to all approved indications including the AD and AA populations.

Impact of class effects on the benefit-risk balance of all JAKis under review

With regards to the benefits of the JAKis, no new data has emerged within this review. Importantly, in general, their benefits seem clinically relevant also for subjects not responding to anti-TNF (in the non-dermatological indications) or previous systemic AD-treatment, respectively.

Since data from the ORAL Surveillance study suggest that the risks for the major safety outcomes increase with dose, current dosing advice (SmPC section 4.2) is recommended to be revised for all products to lower the dose in patients with risk factors for MACE, VTEs, or malignancy and in patients 65 years of age and older, as applicable.

The special warnings and precautions (SmPC section 4.4) were updated for all products to align with the current recommendations for use for tofacitinib based on the ORAL Surveillance study. Currently, it is recommended that tofacitinib should be used only if no suitable treatment alternatives are available in patients over 65 years of age, in patients who are current or past smokers, and patients with other cardiovascular risk factors. Cautious use is recommended in patients with known risk factors for VTE.

The Ad Hoc Expert Group (AHEG) also recommended to strengthen the existing warning of Xeljanz to state that the product should be used with caution in patients with risk factors and being above 50 years of age, in accordance with the inclusion criteria of the ORAL Surveillance study. However, patients with similar risk factors as those included in the ORAL Surveillance study are already targeted by the existing warning of tofacitinib, as outlined above.

The warnings recommended during this review still included some updates to the existing warning for tofacitinib:

- The warning on MACE is updated to include *history of atherosclerotic cardiovascular disease* as risk factor, as supported by a post hoc analysis of the Oral Surveillance Study.
- The warnings on MACE and malignancies were updated to indicate that the risk factors apply to *long-time* smokers in accordance with the long duration of smoking for patients of the ORAL Surveillance study.
- All-cause mortality is added a risk for patients 65 years of age and older.
- The risk factors for VTE were updated to exclude those overlapping with malignancy and MACE, to avoid discrepant information across the warnings since different recommendations are given.

In order to specifically highlight the most important considerations for prescribers before and during use of these JAKis, the PRAC recommended the addition of a boxed warning in SmPC Section 4.4 to indicate the groups of patients for whom JAKis should be only used if no other treatment alternatives are available.

The impact of the safety concerns identified in the ORAL Surveillance study across all approved indications for all JAKis under review, were considered. The PRAC acknowledged the fact that, as also outlined by the AHEG, the ORAL Surveillance population constitutes a high CV-risk population which did not include individuals with low CV risk, based on inclusion criteria. This enriched population with respect to CV risk had a mean RA disease duration of more than 10 years (Ytterberg et al. 2022), which could in many aspects differ from the EU populations targeted by the approved JAKis indications. The PRAC also noted that the magnitude of the absolute risks observed in the ORAL Surveillance study likely is lower in populations with lower baseline risk. The main challenge is to estimate the magnitude of the absolute risks in different patient groups with lower baseline risk, and disease characteristics to weigh these risks against the observed/expected benefits and conclude on proportionate risk mitigation measures. For this evaluation, some guidance can be derived from the post hoc analysis of subgroups in the ORAL Surveillance study but there are also uncertainties deriving from e.g. the degree of generalisability of the ORAL Surveillance data to all populations targeted by the approved JAKi indications.

Taking all data available and the AHEG's view into account, the PRAC considered that an approach aiming at more precision and focus on readily identifiable individual risk factors, instead of limiting use across the respective target populations, is the preferred option to retain a positive benefit-risk balance without depriving patients with low risk of adverse events of an effective treatment option. Therefore, the PRAC recommended to implement warnings applicable to patients with certain risk factors in SmPC Section 4.4 of *all* approved JAKis to aid the prescribers in their assessment of benefits and risks for the individual patient.

For all products, the PRAC recommended also updates of the key elements of the existing educational materials according to the risk minimisation measures recommended during this procedure, to update the existing PASSes in place to monitor the new risks identified and to update the existing drug utilisation studies (DUSs), or to implement new DUS, in case none are in place to evaluate the effectiveness of the newly recommended risk minimisation measures. The PRAC acknowledged the recommendation from the AHEG to consider additional pharmacovigilance activities. However, the PRAC did not consider such additional activities necessary as there are a number of on-going PASS for the 5 JAKis. The PRAC agreed that a DHPC should be distributed to the HCP in order to inform on the recommended risk minimisation measures.

Benefit-risk balance of individual JAKis under review

Cibinqo (abrocitinib)

Cibinqo has recently been approved, for the treatment of AD. With regards to the benefit, abrocitinib has proven to be efficacious for the treatment of **AD**; both in monotherapy and combination studies. Effects in patients having received prior systemic immunosuppressant treatment were consistent with the results in the overall study population. Long-term prevention of AD flare was achieved in a majority of patients with the induction-maintenance regimen. The product is currently approved with a posology to use 200 mg QD as induction treatment, with an aim to rapidly achieve disease control followed by dose reduction to the lowest effective dose for maintenance treatment for most patients. A starting dose of 100 mg once daily is recommended for patients 65 years of age and older, and there is a reference to SmPC sections 4.4 and 4.8 for other patient groups who may benefit from a starting dose of 100 mg.

Regarding the established risks, the available long term safety data are limited. Nevertheless, thromboembolic events including pulmonary embolism are already listed as uncommon ADRs. Furthermore, herpes zoster including ophthalmic zoster (common), and pneumonia (uncommon) are already listed as ADRs. For MACE, although currently available data are still not mature for final conclusion, there is a trend for a dose dependency, and a higher occurrence than in the comparative arm in studies.

Considering the results from the ORAL Surveillance study, showing that increased risks for some of the key safety concerns only became apparent until after more than 2 years treatment, there are uncertainties regarding the long-term safety with abrocitinib. Nevertheless, as results from this study are considered relevant for all substances covered by this referral, the main outcomes are considered safety concerns also for abrocitinib. Therefore, product information updates were recommended by the PRAC to implement warnings across the class of JAKis. Further revisions of the warnings on malignancies and VTEs (SmPC section 4.4) were also made following review of abrocitinib specific data during this procedure.

In addition, since data from the ORAL Surveillance study suggest that the risks for the major safety outcomes of MACE, VTE and malignancy increase with dose, the PRAC recommended to update the posology (SmPC Section 4.2) to recommend a starting dose of 100 mg in patients at higher risks of VTE, MACE and malignancy and that the use of the 200 mg dose may be considered in patients who would benefit the most from a higher dose i.e. those with high disease burden but not at higher risk for MACE, VTE and malignancy or patients with an inadequate response to 100 mg. The dose should be decreased to 100 mg once daily upon disease control. In addition, the PRAC recommended the use of 100 mg once daily in patients 65 years of age and older.

Jyseleca (filgotinib)

With respect to the established benefit of filgotinib, the available data support that filgotinib is an effective treatment for **RA** and **UC.** Additionally, overall data presented by the MAH support that for patients with RA or UC, who failed to achieve therapeutic response to a TNF inhibitor, could still benefit from using filgotinib. The currently recommended dose for Jyseleca is 200 mg once daily, a starting dose of 100 mg is recommended in patients 75 years of age and older.

Overall, the main safety outcomes of the ORAL Surveillance study with increased risk for VTE, MACE, serious infections and malignancy with tofacitinib versus TNFi) are considered class effects relevant to all JAKis in their approved indications, and the SmPC Section 4.4 is updated to implement class warnings. Further, SmPC section 4.8 is updated following review of filgotinib specific data during this procedure, to add sepsis as an ADR (frequency: uncommon).

Since data from the ORAL Surveillance study suggest that the risks of MCAE, VTE and malignancy increase with dose, the PRAC recommended the use of 100 mg once daily for the treatment RA and for maintenance treatment of UC, in patients at increased risk of VTE, MACE, malignancy and in patients 65

years and older. The dose may be escalated to 200 mg once daily in case of insufficient disease control. For long term treatment, the lowest effective dose should be used.

Olumiant (baricitinib)

With respect to the established benefits of baricitinib, the available data support that baricitinib is an effective treatment in its approved indications.

For **AD**, the benefit/risk balance of baricitinib was considered positive in patients treated with systemic therapy (ciclosporin) prior to baricitinib, based on clinical studies. Dupilumab was the second available approved systemic therapy at the time of the application of baricitinib. No head-to-head comparison studies with ciclosporin or dupilumab have been performed. Regarding efficacy in AD patients treated with systemic therapy prior to baricitinib, the developmental programme comprised patients who are candidates for systemic therapy only. In the All BARI AD data set 51% of the patients received prior treatment, and one study was performed in patients previously treated with ciclosporin. In this study, the proportion of patients reaching EASI75 at week 16 was significantly larger than in placebo and secondary outcomes supported these findings. The effects lasted at least until 52 weeks.

For **AA**, two main studies in 1200 adults with severe alopecia areata showed that baricitinib was effective at reducing hair loss compared to placebo. In these studies, after 36 weeks of treatment, the extent of hair loss improved from over 50% to under 20% of scalp hair in 34% of the participants taking 4 mg of baricitinib and in 20% of the participants taking 2 mg of baricitinib, compared with 4% of the participants taking placebo.

The main source for comparison of safety between baricitinib and TNFi currently stems from the observational B023 study in **RA**, which suggests an increased risk for MACE (IRR 0.92; 1.27 – 2.91) and VTE (IRR 1.34; 0.84 – 2.14) for baricitinib versus TNFi. This higher risk for VTE was also found in a clinical trial directly comparing baricitinib and TNFi. VTE is already listed/known ADR for baricitinib and is included in the PI. Furthermore, the observed increased risks of MACE and VTE seem consistent across tofacitinib and baricitinib and taking the assumed JAKi class effect into account; the main safety outcomes of the ORAL Surveillance study are considered relevant also for baricitinib. Finally, there are data showing that baricitinib has a clinically relevant effect also in patients with previous inadequate response to adalimumab (TNFi).

Overall, the main safety outcomes of the ORAL surveillance study (increased risk for VTE, MACE, serious infections and malignancy (excluding NMSC) with tofacitinib versus TNFi) are considered class effects of all JAKis. Additionally, the available clinical study data on baricitinib show trends of increased incidence of some of the adverse events of interests also with baricitinib. Therefore, product information updates were recommended by the PRAC to implement warnings across the class of JAKis, and to apply to all indications of baricitinib, including the AA indication.

Since data from the ORAL Surveillance study suggest that the risks for the major safety outcomes of MACE, VTE and malignancy increase with dose, the current recommendation to use the 2mg dose in patients ≥75 years is updated to recommend the use of lower dose of 2mg once daily for patients 65 years and older and in patients at higher risk of VTE, MACE and malignancy. A dose of 4 mg once daily may be considered in case of inadequate response.

Rinvoq (updadacitinib)

The overall benefit of upadacitinib treatment is considered unchanged by the current procedure and thus consistent with the presentation of efficacy data in section 5.1 of the approved SmPC. The data presented by MAH support benefits of upadacitinib also in patients with RA, PsA and AS who previously failed to achieve therapeutic response to TNF inhibitors.

Regarding **AD**, upadacitinib has a clinically relevant efficacy, with short onset, and it is given via oral administration. Furthermore, long-term safety of upadacitinib is presently not established, which is an additional uncertainty.

For the recently approved indications i.e. UC and nr-axSpA, the safety profile and concerns regarding the benefit/risk are consistent with those of the other approved indications.

As concluded in the current review, the main safety outcomes of the ORAL Surveillance study data are considered class effects of all JAKis. Additionally, the available clinical study data on upadacitinib further support these being main safety concerns. Therefore, product information updates were recommended by the PRAC to implement warnings across the class of JAKis. Further revisions of the wording of warnings on serious infections and malignancy in SmPC Sections 4.4 and SmPC Section 4.8 were made following review of upadacitinib specific data to add sepsis (frequency: uncommon) and NMSC (frequency: common) as ADRs.

In light of the dose dependency of the safety events of MACE, VTE and malignancy observed in the ORAL Surveillance study that are considered relevant to the class of JAKis, the PRAC recommended to update the posology (SmPC Section 4.2) of Rinvoq to recommend for treatment of AD and maintenance treatment of UC, use of 15 mg once daily in patients with risk factors for VTE, MACE and malignancy. A dose of 30 mg once daily can be considered in patients who would benefit the most from a higher dose i.e. those with high disease burden but not at higher risk for VTE, MACE and malignancy, or for patients with an inadequate response to 15 mg. Lowest effective dose during maintenance treatment of both settings is also recommended.

Xeljanz (tofacitinib)

With respect to the established benefits of tofacitinib, the available data support that tofacitinib is an effective treatment in its approved indications. The MAH has now provided support also for the efficacy of tofacitinib in patients previously treated with TNFi.

The final results of the ORAL Surveillance study (A3921133) show an increased incidence for major safety risks that are known ADRs of tofacitinib, including MACE, MI, VTE, malignancy and death, NMSC and serious infections in patients treated with tofacitinib compared to TNFi, and this pattern was observed for both approved tofacitinib doses (i.e. 5 mg BID and 10 mg BID). Dose-dependency was observed for several safety outcomes, with increased risks of all-cause mortality, thromboembolic events and serious infections in tofacitinib 10 mg BID compared to tofacitinib 5 mg BID and TNFi.

The SmPC of tofacitinib is updated to include the final results of the ORAL Surveillance study in SmPC Sections 4.8 and 5.1.

The existing warning on VTE, malignancies and MACE in SmPC Section 4.4 is updated as described above.

Further, the PRAC recommended to update the posology recommendation on the 10 mg BID maintenance dose in UC patients in SmPC Section 4.2 to align with the warnings on MACE and malignancies in SmPC Section 4.4.

Overall, the PRAC concluded that the benefit risk balance of Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz remains positive subject to changes to the product information and implementation of risk minimisation measures recommended by the PRAC.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data for the JAKis used in the treatment of inflammatory disorders. The concerned products are Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz.
- The PRAC considered the totality of the data submitted during the referral in relation to the risks of major adverse cardiovascular events (MACEs), venous thromboembolism (VTE), malignancy, serious infections and all-cause mortality. This included the responses submitted by the marketing authorisation holders in writing and during oral explanations as well as the outcome of an Ad hoc expert group meeting.
- The PRAC concluded that, based on the currently available data, the increased risk for MACE, VTE, malignancy, serious infections and all-cause mortality observed in the ORAL Surveillance study with tofacitinib compared with TNF-inhibitors are considered JAKis class effects. The PRAC also concluded that these safety findings observed in patients with rheumatoid arthritis apply to all approved indications for the JAKis used in the treatment of chronic inflammatory disorders. However, the magnitude of the absolute risk depends on the background risk in the respective populations.
- To minimise these risks, the PRAC recommended implementing warnings for all JAKis included in this review that these products should only be used in patients 65 years of age and older, who are current or past long-time smoker, with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, or with other malignancy risk factors (e.g. current, or history of malignancy) if no suitable treatment alternatives are available. Cautious use is recommended in patients with known risk factors for VTE, other than those listed above.
- The PRAC recommended to revise current dosing advice to lower the dose in certain patient groups with risk factors since the occurrence of MACEs, VTEs, malignancies, serious infections and all-cause mortality have been observed in a dose dependent manner.
    - For Cibinqo, a lower starting dose is recommended in patients at higher risk for VTE, MACE, and malignancy with the possibility of a dose escalation in case of inadequate response. The lower dose is recommended for use in patients 65 years and older.
    - For Jyseleca, in the treatment of RA and for maintenance treatment of UC, a lower dose is recommended in patients at higher risk for VTE, MACE, and malignancy and in patients 65 years and older, with the possibility of a dose escalation in case of inadequate response.
    - For Olumiant, a lower dose is recommended for patients at higher risk of VTE, MACE and malignancy, for patients 65 years and older and for patients with history of chronic and recurrent infections, with the possibility of a dose escalation in case of inadequate response.
    - For Rinvoq, in the treatment of AD and maintenance treatment of UC, a lower dose is recommended in patients at higher risk for VTE, MACE, malignancy and in patients 65 years and older, with the possibility of a dose escalation in case of inadequate response.
    - For Xeljanz, the high dose is no longer recommended for the treatment of ulcerative colitis patients with CV and malignancy risk factors, unless there is no suitable alternative treatment available.
- Based on the clinical data presented, the PRAC recommended to include new adverse reactions for Jyseleca with the addition of sepsis (frequency: uncommon) and for Rinvoq with the addition of sepsis (frequency uncommon) and non-malignant skin cancer (frequency: common).
- The PRAC recommended an update of the key elements of the educational materials accordingly.
- PRAC recommended updates of the risk management plans including studies of drug utilisation accordingly.
- The PRAC also agreed on a direct healthcare professional communication, together with the timelines for its distribution.

In view of the above, the PRAC concluded that the benefit-risk balance of Cibinqo, Jyseleca, Olumiant, Rinvoq and Xeljanz

- is favourable subject to changes to the product information and other risk minimisation measures as described above.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.