XELJANZ PRESCRIBER BROCHURE

A guide to dosing, administration, monitoring, and risk management

XELJANZ®
(tofacitinib citrate)
5 mg tablets

Version: XELJ-MT-EM-V1.0
Date of approval: 25April2017

Therapeutic indication

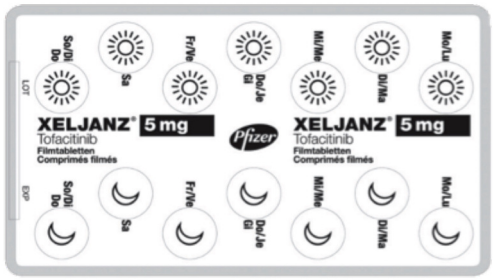
XELJANZ, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs. XELJANZ can be given as monotherapy in case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

Posology and method of administration

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

Oral Dosing XELJANZ is available in 5 mg tablets[1]

XELJANZ 5 mg BID
XELJANZ 5 mg BID Recommended dose is 5 mg administered daily



The blister strip shown does not represent the actual size

XELJANZ should be avoided in combination with biological DMARDs and potent immunosuppressants because of the possibility of increased immunosuppression and increased risk of infection.
XELJANZ dose should be reduced to 5 mg once daily in patients receiving potent inhibitors of cytochrome (CYP) P450 3A4 (e.g., ketoconazole). XELJANZ dosage should be reduced to 5 mg once daily in patients receiving one or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g., fluconazole).

Considerations for administration

Contraindications

- **Must not administer XELJANZ in patients:**
  - With hypersensitivity to the active substance(s) or to any of the excipients listed in Summary of Product Characteristics (SmPC)
  - With active tuberculosis (TB) or other severe infections such as sepsis or opportunistic infections
  - With Severe hepatic impairment
  - That are pregnant and lactating

Prior to administering XELJANZ

- Discuss the risks with patients using the **patient alert card and XELJANZ treatment initiation checklist** (see enclosed checklist for more details).
- Consider the risks and benefits of XELJANZ treatment carefully in patients who are at higher risk of developing serious infections including patients:
  - with recurrent infections
  - who have been exposed to TB
  - with a history of a serious or an opportunistic infection
  - who have resided or travelled in areas of endemic TB or endemic mycoses
  - who have underlying conditions that may predispose them to infections, such as diabetes mellitus.
- Evaluate and test the patient for latent or active TB infection. Patients with latent TB should be treated with standard antimycobacterial therapy before administering XELJANZ.
- All patients should be brought up to date with all immunisations in agreement with current immunisation guidelines. Viral reactivation and cases of herpes virus reactivation (e.g. herpes zoster) were observed in clinical studies with XELJANZ. The risk of herpes zoster appears to be higher in Japanese and Korean patients treated with XELJANZ.
- Screening for viral hepatitis should be performed in accordance with clinical guidelines.
- Consider the risks and benefits of XELJANZ treatment prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy
- Check patients' laboratory parameters including lymphocytes, neutrophils, haemoglobin, lipids, and hepatic enzymes. Initiating treatment is not recommended in patients with:
  - Low lymphocyte count (<750 cells/mm^3)
  - Low absolute neutrophil count (<1000 cells/mm^3)
  - Low haemoglobin (<9 g/dl)

Patients treated with XELJANZ should be given a patient alert card. An adequate supply will be provided to prescribers for distribution to patients (through Pfizer local country office distribution channels). Additional copies can be downloaded via the prescriber website (see section Risk Communication for more details). **Patients should be advised to keep this card with them for at least 2 months after taking the last dose of XELJANZ.**

Monitoring of laboratory parameters:

Laboratory parameters	Routine Monitoring	Laboratory value	Recommended Actions
Lymphocytes	At baseline, then every 3 months	Greater than or equal to 750 cells/mm^3	Dose should be maintained
		Between 500 and 750 cells/mm^3 (confirmed by repeat testing)	Dosing should be interrupted until lymphocyte count is greater than 750 cells/mm^3 When lymphocyte count is greater than or equal to 750, resume 5 mg twice daily.
		Less than 500 cells/mm^3 (confirmed by repeat testing)	Dosing should be discontinued.
Neutrophils	At baseline, after 4 to 8 weeks of treatment, and then every 3 months	ANC greater than 1000 cells/mm^3	Dose should be maintained
		ANC 500•1000 cells/mm^3	For persistent decreases in this range, interrupt dosing until ANC is greater than 1000 cells/mm^3. When ANC is greater than 1000, cells/mm^3 resume 5 mg twice daily.
		ANC less than 500 cells/mm^3	Dosing should be discontinued
Haemoglobin	At baseline, after 4 to 8 weeks of treatment, and then every 3 months	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)	Interrupt dosing until haemoglobin values have normalised
Lipids	After 8 weeks following initiation of therapy	NA	Managed according to clinical guide lines for the management of hyperlipidaemia
Liver enzymes	Routine monitoring	NA	Following initiation, routine monitoring of liver tests and prompt investigation of the causes of liver enzyme elevations is recommended to identify potential cases of drug-induced liver injury

ANC=absolute neutrophil counts; **NA**=not applicable

Special warnings and precautions for use

Combination with other RA therapies

- XELJANZ has not been studied and its use should be avoided in RA patients in combination with biological DMARDs such as TNF antagonists, IL-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators and potent immunosuppressants such as azathioprine, cyclosporine and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

- There is a higher incidence of adverse events for the combination of XELJANZ plus MTX versus XELJANZ as monotherapy

Serious infections

- The most common serious infections reported with XELJANZ were pneumonia, cellulitis, herpes zoster, urinary tract infection, diverticulitis, and appendicitis. Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus, BK virus infections and listeriosis were reported with XELJANZ. Some patients have presented with disseminated rather than localised disease, and rheumatoid arthritis patients were often taking concomitant immunomodulating agents such as MTX or corticosteroids which, in addition to rheumatoid arthritis, may predispose them to infections. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis). The risk of opportunistic infections is higher in Asian geographic regions.
- Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ. Treatment must be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with XELJANZ should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, appropriate antimicrobial therapy should be initiated, and the patient should be closely monitored.
- Caution is recommended when XELJANZ treatment is used in the following patients:
    - Elderly and diabetic patients given there is a higher incidence of infections in general
    - Patients with a history of chronic lung disease as they may be more prone to infections.
    - Patients with lymphopenia

Tuberculosis

- The risks and benefits of treatment should be considered prior to initiating XELJANZ in patients:
    - who have been exposed to TB
    - who have resided or travelled in areas of endemic TB or endemic mycoses
- Patients should be evaluated and tested for latent or active infection prior to and per applicable guidelines during administration of XELJANZ.

Viral reactivation

- Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. In patients treated with XELJANZ, the incidence of herpes zoster appears to be increased in Japanese and Korean patients, as well as in those patients with long standing rheumatoid arthritis who have received two or more biological DMARDs. Patients with an absolute lymphocyte count (ALC) less than 1,000 cells/mm^3 may have an increased risk of herpes zoster.
- The impact of XELJANZ on chronic viral hepatitis reactivation is unknown. Screening for viral hepatitis should be performed in accordance with clinical guidelines before starting therapy with XELJANZ.

Malignancies and lymphoproliferative disorder [Excluding Non-melanoma Skin Cancer (NMSC)]

- The risks and benefits of XELJANZ treatment should be considered prior to initiating therapy in patients with current or a history of malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing XELJANZ in patients who develop a malignancy. The possibility exists for XELJANZ to affect host defences against malignancies.
- Lymphomas have been observed in patients treated with XELJANZ. Patients with RA, particularly those with highly active disease may be at a higher risk (up to several-fold) than the general population for the development of lymphoma. The role of XELJANZ in the development of lymphoma is uncertain.
- Other malignancies were observed in clinical studies and the post-marketing setting, including, but not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.
- The effect of XELJANZ on the development and course of malignancies is not known.

Non-melanoma skin cancer

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

Interstitial Lung Disease

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

Gastrointestinal perforations

- Events of gastrointestinal perforation have been reported in clinical trials although the role of Janus- kinase inhibition in these events is not known.
- XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis and patients with concomitant use of corticosteroids and/or non-steroidal anti-inflammatory medicinal products). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Vaccination

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

- Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular consideration should be given to patients with longstanding rheumatoid arthritis who have received two or more prior biological DMARDs. If live zoster vaccine is administered; it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus (VZV). If the history of chickenpox is considered doubtful or unreliable it is recommended to test for antibodies against VZV.
- Vaccination with live vaccines should occur at least 2 weeks but preferably 4 weeks prior to initiation of XELJANZ or in accordance with current vaccination guidelines regarding immunomodulatory medicinal products.

Use in Special Populations

Patients with renal impairment

- No dose adjustment is required in patients with mild (creatinine clearance 50-80 mL/min) or moderate renal impairment (creatinine clearance 30-49 mL/min).
- XELJANZ dose should be reduced to 5 mg once daily in patients with severe renal impairment (creatinine clearance <30 mL/min).

Patients with hepatic impairment

- No dose adjustment is required in patients with mild hepatic impairment (Child Pugh A).
- XELJANZ dose should be reduced to 5 mg once daily in patients with moderate hepatic impairment (Child Pugh B).
- XELJANZ should not be used in patients with severe hepatic impairment (Child Pugh C).

Paediatric patients

- The safety and efficacy of XELJANZ in children aged from 2 years to less than 18 years of age have not yet been established. No data are available. There is no relevant use of XELJANZ in patients aged less than 2 years for the indication of juvenile idiopathic arthritis.

Pregnancy and lactation

- Use of XELJANZ during pregnancy is contraindicated.
- Use of XELJANZ during breastfeeding is contraindicated.

Women of childbearing potential

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

FOR MORE DETAILS ON PRESCRIBING XELJANZ,
PLEASE REFER TO THE SUMMARY OF PRODUCT CHARACTERISTICS.

Patient Counselling

It is important for you to discuss the risks associated with use of tofacitinib with your patients, and in applicable instances, with their caregivers.

A patient alert card has been developed to help patients understand the risks associated with XELJANZ, and remind them to seek immediate medical attention if they experience any listed signs and symptoms.

It is important for physicians to:

- provide the patient alert card to each patient who is prescribed with XELJANZ.
- remind patients to use the patient alert card.
- discuss the risks with each patient and ensure patient understanding of the treatment potential risks.
- ensure patients to carry the patient alert card with them, particularly when they visit doctors£ office and/or the emergency room.

You should remind patients to seek immediate medical attention if they experience any of the following signs and symptoms.

- Experience possible symptoms of allergic reactions such as chest tightness, wheezing, severe dizziness or light headedness, swelling of the lips, tongue or throat, itching or skin rash when taking XELJANZ, or soon after taking XELJANZ.
- Develop symptoms of an infection, such as fever, persistent cough, weight loss, or excessive tiredness.
- Develop symptoms of herpes zoster, such as painful rash or blisters.
- Develop symptoms of interstitial lung diseases, such as shortness of breath
- Have been in close contact with a person with TB.
- Develop abdominal signs and symptoms such as stomach pain, abdominal pain, blood in stool, or any change in bowel habits with fever.
- Develop yellow skin, nausea, or vomiting.
- Are due to receive any vaccine. Patients should not receive certain types of vaccines while taking XELJANZ.
- Become pregnant or plan on becoming pregnant.

To order more copies of the patient alert card, please call Pfizer£s Local Representative, Vivian Corporation Ltd.: 00356 22588600 or visit the website: www.tofacitinib-rmp.com.mt

Reporting of Adverse Events

If you become aware of any suspected adverse reactions in association with use of XELJANZ, please report the event promptly to:

ADR Reporting
www.medicinesauthority.gov.mt/adrportal
Malta Medicines Authority, Sir Temi Zammit Buildings,
Malta Life Sciences Park, San Gwann, SGN 3000,
Malta Website: www.medicinesauthority.gov.mt/adrportal
e-mail: postlicensing.medicinesauthority@gov.mt

Also, please contact Pfizer Hellas S.A. Medical Information at +30 210 67 85 800.
Local Representative: V.J. Salomone Pharma Ltd. Tel. +356 21220174

Risk Management Plan (RMP)

A risk management system, described in the risk management plan (RMP), is a set of pharmacovigilance activities and interventions required by the European Medicines Agency (EMA) to ensure that the benefits of the medicinal product outweigh its risks.
The XELJANZ RMP is developed:

- To identify, characterise, prevent or minimise risks relating to XELJANZ including the assessment of the effectiveness of those activities and interventions.

Risk Communication

In order to communicate certain risks about XELJANZ, Pfizer has worked with the EMA to develop a detailed communication plan to communicate the risks described in the summary of product characteristics, including the following items: patient alert card

- patient alert card
- prescriber brochure
- prescriber treatment initiation checklist
- prescriber treatment maintenance checklist

Two treatment checklists: initiation checklist and maintenance checklists, are developed for you to be used prior to and during XELJANZ treatment. They intend to remind you of the risks associated with use of XELJANZ and the recommended tests before and during the XELJANZ treatment.

References and Summary of Product Characteristics

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

1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect

Each tablet contains 59.44 mg lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, round tablet of 7.9 mm diameter, debossed ™Pfizerî on one side and ™JKI 5î on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

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

4.2 Posology and method of administration

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

Posology

The recommended dose is 5 mg administered twice daily.

Dose adjustment

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

Dose interruption and discontinuation

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

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia and anaemia. As described in Tables 1, 2 and 3 below, recommendations for temporary dose interruption or permanent discontinuation of treatment are made according to the severity of laboratory abnormalities. (see section 4.4)

It is recommended not to initiate dosing in patients with an absolute lymphocyte count less than 750 cells/mm^3.

Table 1: Low Absolute Lymphocyte Count

Low Absolute Lymphocyte Count (ALC) (see section 4.4)

Lab Value (cells/mm^3)	Recommendation
ALC greater than or equal to 750	Dose should be maintained.
ALC 500-750	For persistent (2 sequential values in this range on routine testing) decrease in this range, dosing should be interrupted until ALC is greater than 750. When ALC is greater than 750, resume 5 mg twice daily.
ALC less than 500	If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.

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

Table 2: Low Absolute Neutrophil Count

Low Absolute Neutrophil Count (ANC) (see section 4.4)

Lab Value (cells/mm^3)	Recommendation
ANC greater than 1,000	Dose should be maintained.
ANC 500-1,000	For persistent (2 sequential values in this range on routine testing) decreases in this range, dosing should be interrupted until ANC is greater than 1,000. When ANC is greater than 1,000, resume 5 mg twice daily.
ANC less than 500	If lab value confirmed by repeat testing within 7 days, dosing should be discontinued.

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

Table 3: Low Haemoglobin Value

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

Special populations

Renal impairment

No dose adjustment is required in patients with mild (creatinine clearance 50-80 mL/min) or moderate (creatinine clearance 30-49 mL/min) renal impairment. XELJANZ dose should be reduced to 5 mg once daily in patients with severe (creatinine clearance <30 mL/min) renal impairment (see sections 4.4 and 5.2). Patients with severe renal impairment should remain on a reduced dose of 5 mg once daily even after haemodialysis.

Hepatic impairment

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

Elderly

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

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

Paediatric population

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

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

Drug-drug interactions

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

Method of administration

Oral use.

XELJANZ is given orally with or without food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Combination with other RA therapies

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

There is a higher incidence of adverse events for the combination of XELJANZ with MTX versus XELJANZ as monotherapy.

Serious infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in RA patients receiving XELJANZ. The risk of opportunistic infections is higher in Asian geographic regions (see section 4.8). XELJANZ should not be initiated in patients with active infections, including localised infections.

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

- with recurrent infections,
- with a history of a serious or an opportunistic infection,
- who have resided or travelled in areas of endemic mycoses,

- who have underlying conditions that may predispose them to infection.

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

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

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

Tuberculosis

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

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

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

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

Antituberculosis therapy should also be considered prior to administration of XELJANZ in patients who test negative for TB but who have a past history of latent or active TB and where an adequate course of treatment cannot be confirmed; or those who test negative but who have risk factors for TB infection. Consultation with a healthcare professional with expertise in the treatment of TB is recommended to aid in the decision about whether initiating antituberculosis therapy is appropriate for an individual patient. Patients should be closely monitored for the development of signs and symptoms of TB, including patients who tested negative for latent TB infection prior to initiating therapy.

Viral reactivation

Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) were observed in clinical studies with XELJANZ. In patients treated with XELJANZ, the incidence of herpes zoster appears to be increased in Japanese and Korean patients, as well as in those patients with long standing RA who have previously received two or more biological DMARDs. Patients with an absolute lymphocyte count (ALC) less than 1,000 cells/mm3 may have an increased risk of herpes zoster (see section 4.2).

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

Malignancy and lymphoproliferative disorder

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

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

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

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

Non-melanoma skin cancer

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

Interstitial lung disease

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

Gastrointestinal perforations

Events of gastrointestinal perforation have been reported in clinical trials although the role of JAK inhibition

in these events is not known. XELJANZ should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis, patients with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory drugs). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Cardiovascular risk

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

1.

2. Liver enzymes

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

Laboratory parameters

Lymphocytes

Treatment with XELJANZ was associated with an increased incidence of lymphopenia compared to placebo. Lymphocyte counts less than 750 cells/mm3 were associated with an increased incidence of serious infections. It is not recommended to initiate or continue XELJANZ treatment in patients with a confirmed lymphocyte count less than 750 cells/mm3. Lymphocytes should be monitored at baseline and every 3 months thereafter. For recommended modifications based on lymphocyte counts, see section 4.2.

Neutrophils

Treatment with XELJANZ was associated with an increased incidence of neutropenia (less than 2,000 cells/mm3) compared to placebo. It is not recommended to initiate XELJANZ treatment in patients with an ANC less than 1,000 cells/mm^3. ANC should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on ANC, see section 4.2.

Haemoglobin

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

Lipid monitoring

Treatment with XELJANZ was associated with increases in lipid parameters such as total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum effects were generally observed within 6 weeks. Assessment of lipid parameters should be performed after 8 weeks following initiation of XELJANZ therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia. Increases in total and LDL cholesterol associated with XELJANZ may be decreased to pretreatment levels with statin therapy.

Vaccinations

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

Prophylactic zoster vaccination should be considered in accordance with vaccination guidelines. Particular consideration should be given to patients with longstanding RA who have previously received two or more biological DMARDs. If live zoster vaccine is administered; it should only be administered to patients with a known history of chickenpox or those that are seropositive for varicella zoster virus (VZV). If the history of chickenpox is considered doubtful or unreliable it is recommended to test for antibodies against VZV.

Vaccination with live vaccines should occur at least 2 weeks but preferably 4 weeks prior to initiation of XELJANZ or in accordance with current vaccination guidelines regarding immunomodulatory medicinal products. No data are available on the secondary transmission of infection by live vaccines to patients receiving XELJANZ.

Elderly

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

Lactose

XELJANZ contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase de-

ficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to influence the PK of XELJANZ

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

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

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

Figure 1. Impact of Other Drugs on PK of XELJANZ

Note: Reference group is administration of XELJANZ alone

Potential for XELJANZ to influence the PK of other medicinal products

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

In vitro studies indicate that tofacitinib does not significantly inhibit the activity of the major human drug metabolizing uridine 5'-diphospho-glucuronosyltransferases (UGTs), [UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7] at concentrations exceeding 535 and 893 times the steady state total and free Cmax of a 5 mg twice daily dose in RA patients.

In vitro data indicate that the potential for XELJANZ to inhibit transporters such as P glycoprotein, organic anion transporting polypeptide, organic anionic or cationic transporters at therapeutic concentrations is also low.

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Women of childbearing potential/contraception in females

Women of childbearing potential should be advised to

use effective contraception during treatment with XELJANZ and for at least 4 weeks after the last dose.

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The safety data includes 6 double-blind, controlled, multicentre studies of varying durations from 6 24 months (Studies I-VI, see section 5.1). A total of 6194 patients (Phases 1, 2, 3 and long-term extension studies) were treated with any dose of XELJANZ, with a mean duration of 3.13 years, with 19405.8 patient-years of accumulated total drug exposure based on up to 8 years of continous exposure to XELJANZ.

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

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

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

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

Tabulated list of adverse reactions

The ADRs listed in the table below 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) or rare (≥1/10,000 to <1/1,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Adverse Drug Reactions

System Organ Class	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
Infections and infestations	Nasopharyngitis	Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Pharyngitis	Sepsis Tuberculosis Pneumonia pneumococcal Pneumonia bacterial Diverticulitis Pyelonephritis Cellulitis Arthritis bacterial Herpes simplex Gastroenteritis viral Viral infection	TB of central nervous system Meningitis cryptococcal Urosepsis Disseminated TB Necrotizing fasciitis Bacteraemia Staphylococcal bacteraemia *Pneumocystis jirovecii* pneumonia Encephalitis Atypical mycobacterial infection *Mycobacterium avium* complex infection Cytomegalovirus infection

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Non-melanoma skin cancers	
Blood and lymphatic system disorders		Leukopenia Anaemia	Lymphopenia Neutropenia	
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia	Dehydration	
Psychiatric disorders		Insomnia		
Nervous system disorders		Headache	Paraesthesia	
Vascular disorders Respiratory, thoracic and mediastinal disorders		Hypertension Dyspnoea Cough	Sinus congestion	
Gastrointestinal disorders		Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia		
Hepatobiliary disorders			Hepatic steatosis	
Skin and subcutaneous tissue disorders		Rash	Erythema Pruritus	TB of central nervous system Meningitis cryptococcal Urosepsis Disseminated TB Necrotizing fasciitis Bacteraemia Staphylococcal bacteraemia *Pneumocystis jirovecii* pneumonia Encephalitis Atypical mycobacterial infection *Mycobacterium avium* complex infection Cytomegalovirus infection
Musculoskeletal and connective tissue disorders		Musculoskeletal pain Arthralgia	Joint swelling Tendonitis	
General disorders and administration site conditions Investigations		Pyrexia Oedema peripheral Fatigue Hepatic enzyme increased Blood cholesterol increased Weight increased Blood creatine	Transaminases increased Liver function test abnormal increased Gamma glutamyl-transferase	

		phosphokinase increased	Blood creatinine increased Low density lipoprotein increased	
Injury, poisoning and procedural complications			Ligament sprain Muscle strain	

Description of selected adverse reactions

Overall infections

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

The most commonly reported infections were upper respiratory tract infections and nasopharyngitis (3.7% and 3.2%, respectively).

The overall incidence rate of infections with XELJANZ in the long-term safety all exposure population (total 4867 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 1750) 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 3117) on background DMARDs, the rates were 41.0 and 50.3 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively.

Serious infections

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

In studies of 6-, 12-, or 24-month duration, the rates of serious infections in the 5 mg twice daily and 10 mg twice daily XELJANZ plus DMARD groups were 3.6 and 3.4 patients with events per 100 patient-years, respectively, compared to 1.7 patients with events per 100 patient-years in the placebo plus DMARD group.

In the long-term safety all exposure population, the overall rates of serious infections were 2.4 and 3.0 patients with events per 100 patient-years for 5 mg and 10 mg twice daily XELJANZ groups, respectively. The most common serious infections included pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis and diverticulitis. Cases of opportunistic infections have been reported (see section 4.4).

Serious infections in the elderly

Of the 4271 patients who enrolled in Studies I-VI (see section 5.1), a total of 608 RA patients were 65 years of age and older, including 85 patients 75 years and older. The frequency of serious infection among XELJANZ-treated patients 65 years of age and older was higher than those under the age of 65 (4.8 per 100 patient-years vs. 2.4 per 100 patient-years, respectively). As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly (see section 4.4).

Viral reactivation

In XELJANZ clinical trials, Japanese and Korean patients appeared to have a higher rate of herpes zoster than that observed in other populations, as do patients with long standing RA who have previously received two or more biological DMARDs. Patients with an ALC less than 1,000 cells/mm^3 may have an increased risk of herpes zoster (see section 4.4).

Laboratory tests

Lymphocytes

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

In the long-term safety population, confirmed decreases in ALC below 500 cells/mm3 occurred in 1.3% of patients and for ALC between 500 and 750 cells/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/mm3 were associated with an increased incidence of serious infections (see section 4.4).
Neutrophils
In the controlled clinical studies, confirmed decreases in ANC below 1,000 cells/mm3 occurred in 0.08% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. There were no confirmed decreases in ANC below 500 cells/mm3 observed in any treatment group. There was no clear relationship between neutropenia and the occurrence of serious infections.
In the 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 patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of XELJANZ, or reduction in XELJANZ dose, resulted in decrease or normalisation of liver enzymes.
In the controlled portion of the Phase 3 monotherapy study (0-3 months), (Study I, see section 5.1), ALT elevations greater than 3x ULN were observed in 1.65%, 0.41%, and 0% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 1.65%, 0.41% and 0% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively.
In the Phase 3 monotherapy study (0-24 months) (Study VI, see section 5.1), ALT elevations greater than 3x ULN were observed in 7.1%, 3.0%, and 3.0% of patients receiving MTX, XELJANZ 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 3.3%, 1.6% and 1.5% of patients receiving MTX, XELJANZ 5 mg and 10 mg twice daily, respectively.
In the controlled portion of the Phase 3 studies on background DMARDs (0-3 months), (Study II-V, see section 5.1), ALT elevations greater than 3x ULN were observed in 0.9%, 1.24% and 1.14% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively. In these studies, AST elevations greater than 3x ULN were observed in 0.72%, 0.5% and 0.31% of patients receiving placebo, XELJANZ 5 mg and 10 mg twice daily, respectively.
In the long-term extension studies, on monotherapy, ALT elevations greater than 3x ULN were observed in 1.1% and 1.4% of patients receiving XELJANZ 5 mg and 10 mg twice daily, respectively. AST elevations greater than 3x ULN were observed in <1.0% in both the tofacitinib 5 mg and 10 mg twice daily groups.
In the long-term extension studies, on background DMARDs, ALT elevations greater than 3x ULN were observed in 1.8% and 1.6% of patients receiving XELJANZ 5 mg and 10 mg twice daily, respectively. AST elevations greater than 3x ULN were observed in <1.0% in both the XELJANZ 5 mg and 10 mg twice daily groups.
Lipids
Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were first assessed at one month following initiation of XELJANZ in the controlled double-blind clinical trials of RA. Increases were observed at this time point and remained stable thereafter.
Changes in lipid parameters from baseline through the end of the study (6-24 months) in the controlled clinical studies in RA are summarised below:

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

Upon withdrawal of XELJANZ treatment, lipid levels returned to baseline.
Mean LDL cholesterol/HDL cholesterol ratios and Apolipoprotein B (ApoB)/ApoA1 ratios were essentially unchanged in XELJANZ-treated patients.
In a controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pretreatment levels in response to statin therapy.
In the long-term safety populations, elevations in the lipid parameters remained consistent with what was seen in the controlled clinical studies.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the na-

tional 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 XELJANZ. Treatment should be symptomatic and supportive.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Selective Immunosuppressants; ATC code: L04AA29

Mechanism of action

Tofacitinib is a potent, selective inhibitor of the JAK family. In enzymatic assays, tofacitinib inhibits JAK1, JAK2, JAK3, and to a lesser extent TyK2. In contrast, tofacitinib has a high degree of selectivity against other kinases in the human genome. In human cells, tofacitinib preferentially inhibits signalling by heterodimeric cytokine receptors that associate with JAK3 and/or JAK1 with functional selectivity over cytokine receptors that signal via pairs of JAK2. Inhibition of JAK1 and JAK3 by tofacitinib attenuates signalling of interleukins (IL-2, -4, -6, -7, -9, -15, -21) and type I and type II interferons, which will result in modulation of the immune and inflammatory response.

Pharmacodynamic effects

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

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

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

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

Vaccine studies

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

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

Clinical efficacy and safety

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

Table 5: Phase 3 Clinical Trials of Tofacitinib 5 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)
Population Control	DMARD-IR Placebo	DMARD-IR Placebo	MTX-IR Placebo	MTX-IR Placebo	TNFi-IR Placebo	MTX-naovea MTX
Background treatment	None[b]	csDMARDs	MTX	MTX	MTX	None[b]
Key features	Monotherapy	Various csD MARDs	Active control (adalimumab)	X-Ray	TNFi-IR	Monotherapy, Active comparator (MTX), X-Ray
Number of patients treated	610	792	717	797	399	956
Total study duration	6 months	1 year	1 year	2 years	6 months	2 years
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

• a. ≤3 weekly doses (MTX-naove). • 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.

Clinical response

ACR response

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

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, or disease status. Time to onset was rapid (as early as Week 2 in Studies ORAL Solo, ORAL Sync, and ORAL Step) and the magnitude of response continued to improve with duration of treatment. As with the overall ACR response in patients treated with 5 mg or 10 mg twice daily tofacitinib, each of the components of the ACR response was consistently improved from baseline including: tender and swollen joint counts; patient and physician global assessment; disability index scores; pain assessment and CRP compared to patients receiving placebo plus MTX or other DMARDs in all studies.

Table 6: Proportion (%) of Patients with an ACR Response

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-naove				
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***

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

DAS28-4(ESR) response

Patients in the Phase 3 studies had a mean Disease Activity Score (DAS28-4[ESR]) of 6.1 6.7 at baseline. Significant reductions in DAS28-4(ESR) from baseline (mean improvement) of 1.8-2.0 and 1.9-2.2 were observed in patients treated with 5 mg and 10 mg twice daily doses, respectively, compared to placebo-treated patients (0.7-1.1) at Month 3. The proportion of patients achieving a DAS28 clinical remission (DAS28-4(ESR) <2.6) in ORAL Step, ORAL Sync, and ORAL Standard is shown in Table 7.

Table 7: Number (%) of Subjects Achieving DAS28-4(ESR) <2.6 Remission at Months 3 and 6

	Time Point	N	%
ORAL Step: TNF Inhibitor Inadequate Responders			
Tofacitinib 5 mg twice daily + MTX	Month 3	1336	
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 vs. placebo plus MTX).

Table 8: 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					
Month 6	33 (42)	31 (48)	-	37 (54)	-
Month 12	0.5 (2.0)	0.1 (1.7)	-0.3 (-0.7, 0.0)	0.1 (2.0)	-0.4 (-0.8, 0.0)
	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-naove					
	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					
Month 6	16 (29)	20 (41)	-	19 (39)	-
Month 12	0.9 (2.7)	0.2 (2.3)	-0.7 (-1.0, -0.3)	0.0 (1.2)	-0.8 (-1.2, -0.4)
	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)

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

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

Physical function response and health-related outcomes

XELJANZ, alone or in combination with MTX, has shown improvements in physical function, as measured by the HAQ-DI. Patients receiving tofacitinib 5 or 10 mg twice daily demonstrated significantly greater improvement from baseline in physical functioning compared to placebo at Month 3 (Studies ORAL Solo, ORAL Sync, ORAL Standard, and ORAL Step) and Month 6 (Studies ORAL Sync and ORAL Standard). Tofacitinib 5 or 10 mg twice daily-treated patients demonstrated significantly greater improvement in physical functioning compared to placebo as early as Week 2 in ORAL Solo and ORAL Sync. Changes from baseline in HAQ-DI in studies ORAL Standard, ORAL Step and ORAL Sync are shown in Table 9.

Table 9: 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 vs. placebo + MTX, LS = least squares, N = number of patients, QOW = every other week, NA = not applicable, HAQ-DI = Health Assessment Questionnaire Disability Index

Health-related quality of life was assessed by the Short Form Health Survey (SF-36). Patients receiving either 5 or 10 mg tofacitinib twice daily experienced significantly greater improvement from baseline compared to placebo in all 8 domains as well as the Physical Component Summary and Mental Component Summary scores at Month 3 in ORAL Solo, ORAL Scan and ORAL Step. In ORAL Scan, mean SF-36 improvements were maintained to 12 months in tofacitinib-treated patients.

Improvement in fatigue was evaluated by the Functional Assessment of Chronic Illness Therapy Fatigue (FACIT-F) scale at Month 3 in all studies. Patients receiving tofacitinib 5 or 10 mg twice daily demonstrated significantly greater improvement from baseline in fatigue compared to placebo in all 5 studies. In ORAL Standard and ORAL Scan, mean FACIT-F improvements were maintained to 12 months in tofacitinib-treated patients.

Improvement in sleep was assessed using the Sleep Problems Index I and II summary scales of the Medical Outcomes Study Sleep (MOS-Sleep) measure at Month 3 in all studies. Patients receiving tofacitinib 5 or 10 mg twice daily demonstrated significantly greater improvement from baseline in both scales compared to placebo in ORAL Sync, ORAL Standard and ORAL Scan. In ORAL Standard and ORAL Scan, mean improvements in both scales were maintained to 12 months in tofacitinib-treated patients.

Durability of clinical responses

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

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

Paediatric population

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

5.2 Pharmacokinetic properties

The pharmacokinetic (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 Cmax was reduced by 32%. In clinical trials, tofacitinib was administered without regard to meal.

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

Metabolism and elimination

Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabeled study, more than 65% of the total circulating radioactivity was accounted for by unchanged active substance, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. All metabolites have been observed in animal species and are predicted to have less than 10-fold potency than tofacitinib for JAK1/3 inhibition. No evidence of stereo conversion in human samples was detected. The pharmacologic activity of tofacitinib is attributed to the parent molecule.

Pharmacokinetics in RA patients

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

Population PK analysis in RA patients indicated that systemic exposure (AUC) of tofacitinib in the extremes of body weight (40 kg, 140 kg) were similar (within 5%) to that of a 70 kg patient. Elderly patients 80 years of age were estimated to have less than 5% higher AUC relative to the mean age of 55 years. Women were estimated to have 7% lower AUC compared to men. The available data have also shown that there are no major differences in tofacitinib AUC between White, Black and Asian patients. An approximate linear relationship between body weight and volume of distribution was observed, resulting in higher peak (Cmax) and lower

trough (Cmin) concentrations in lighter patients. However, this difference is not considered to be clinically relevant. The between-subject variability (percentage coefficient of variation) in AUC of tofacitinib is estimated to be approximately 27%.

Renal impairment

Patients 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 with healthy patients (see section 4.2). In patients 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 patients with ESRD based on concentrations measured on a non-dialysis day was approximately 40% (90% confidence intervals: 1.5-95%) higher compared with patients with normal renal function. In clinical trials, XELJANZ was not evaluated in patients with baseline creatinine clearance values (estimated by Cockroft-Gault equation) less than 40 mL/min (see section 4.2).

Hepatic impairment

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

5.3 Preclinical safety data

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

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

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib was not carcinogenic in mice at exposures up to 38 times the clinical exposure level. Benign testicular interstitial (Leydig) cell tumours were observed in rats: benign Leydig cell tumours in rats are not associated with a risk of Leydig cell tumours in humans. Hibernomas (malignancy of brown adipose tissue) were observed in female rats at exposures greater than or equal to 83 times the clinical exposure level. Benign thymomas were observed in female rats at 187 times the clinical exposure level.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
microcrystalline cellulose
lactose monohydrate
croscarmellose sodium
magnesium stearate

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

Store in the original, bottle and/or blister, in order to protect from moisture.

6.5 Nature and contents of container

HDPE bottles with silica gel desiccant and child-resis-

tant caps containing 60 or 180 film-coated tablets.
Aluminium foil/PVC backed aluminium foil blisters containing 14 film-coated tablets. Each pack contains 56 or 182 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2017

10. DATE OF REVISION OF THE TEXT

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

Prescriber website

All the educational materials including patient alert card and treatment initiation/maintenance checklist are available at www.tofacitinib-rmp.com.mt
Please visit this website for more details.

Ongoing Risk Assessment

In order to continue to characterise the risks relating to XELJANZ, Pfizer has committed to participate in 4 established European RA registries including one in UK (i.e., BSRBR), one in Germany (i.e., RABBIT), one in Sweden (i.e., ARTIS), and one in Spain (i.e., BIOBADASER).

The purpose of the registry surveillance studies is to collect additional longitudinal safety data from the clinical practice setting regarding the use of XELJANZ in patients with rheumatoid arthritis.

Physicians from those countries can register their patients treated with XELJANZ by contacting the registries via the following contact information:

- BSRBR:
http://www.rheumatology.org.uk/resources/bsr_biologics_registers/bsrbr_rheumatoid_arthritis_register/default.aspx.
- RABBIT • Rheumatoide Arthritis: Beobachtung der Biologika-Therapie:
http://www.biologika-register.de; contact form available at: http://www.biologika-register.de/index.php?page=kontakt&lang=de, and information can be retrieved/requested via Info@biologika-register.de.
- ARTIS
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https://biobadaser.ser.es/biobadaser/eng/

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or website www.medicinesauthority.gov.mt/adrportal, if you have any questions.**