SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

XELJANZ® 5 mg film-coated tablets

XELJANZ® 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

XELJANZ 5 mg film-coated tablets

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

Contains sugar (lactose monohydrate).

Excipient with known effect

Each film-coated tablet contains 59,44 mg of lactose monohydrate.

XELJANZ 10 mg film-coated tablets

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

Contains sugar (lactose monohydrate).

Excipient with known effect

Each film-coated tablet contains 118,88 mg of lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

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 indications

Rheumatoid arthritis

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

Psoriatic arthritis

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

Ulcerative colitis

XELJANZ 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 medicine (see section 5.1).

4.2. Posology and method of administration

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

Posology

Rheumatoid arthritis and psoriatic arthritis

The recommended dose is 5 mg administered twice daily.

Dose adjustment

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

Ulcerative colitis

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

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

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

Patients who experience a decrease in response on XELJANZ 5 mg twice daily maintenance therapy may benefit from an increase to XELJANZ 10 mg administered twice daily.

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

Retreatment in UC

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

Dose interruption and discontinuation

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

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

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

Table 1: Low absolute lymphocyte count

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

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

Table 2: Low absolute neutrophil count

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

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

Table 3: Low haemoglobin value

Low haemoglobin value (section 4.4)	
Lab value (g/dL)	Recommendation
Less than or equal to 2 g/dL decrease and greater than or equal to 9,0 g/dL	Dose should be maintained.
Greater than 2 g/dL decrease or less than 8,0 g/dL (confirmed by repeat testing)	Dosing should be interrupted until haemoglobin values have normalised.

Drug-drug interactions

XELJANZ 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 medicines 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) as follows:

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

Special populations

Elderly
No dose adjustment is required in patients aged 65 years and older. There are limited data in patients aged 75 years and older. A higher incidence and severity of adverse events in the elderly (> 65 yrs) is an important potential risk.

Hepatic impairment

Table 4: Dose adjustment for hepatic impairment

Hepatic impairment	Classification	Dose adjustment
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	XELJANZ should not be used in patients with severe hepatic impairment (see section 4.3).

Renal impairment

Table 5: Dose adjustment for renal impairment

Renal impairment	Creatinine clearance	Dose adjustment
Mild	50 - 80 mL/min	No dose adjustment required.
Moderate	30 - 49 mL/min	No dose adjustment required.
Severe	< 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 XELJANZ in children aged 0 to less than 18 years have not been established.

No data are available.

Method of administration

XELJANZ is given orally with or without food.

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

4.3 Contraindications

- Hypersensitivity to the tofacitinib or to any of the excipients listed in section 6.1
- Untreated pulmonary tuberculosis (active and latent) or untreated extra pulmonary tuberculosis, 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)
- Patients with treatment naïve / experienced HIV infections

XELJANZ 10 mg twice daily is contraindicated in patients who have one or more of the following conditions:

- Use of combined hormonal contraceptives or hormone replacement therapy
- Heart failure
- Previous venous thromboembolism, either deep venous thromboembolism or pulmonary embolism
- Inherited coagulation disorder
- Malignancy
- Patients undergoing major surgery

4.4 Special warnings and precautions for use

Combination with other therapies

XELJANZ has not been studied and its use should be avoided in combination with 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 XELJANZ with MTX versus XELJANZ as monotherapy in RA clinical studies.

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

Serious infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving XELJANZ. Rheumatoid arthritis patients taking corticosteroids may be predisposed to infection.

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.

Anti-tuberculosis 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 anti-tuberculosis 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:

- 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 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. The risk of NMSC may be higher in patients treated with XELJANZ 10 mg twice daily than in patients treated with 5 mg twice daily. Periodic skin examination is recommended for patients who are at increased risk for skin cancer (see Table 6 in section 4.8).

Pulmonary embolism

Pulmonary embolism (PE) has been observed in patients taking XELJANZ in clinical trials and post-marketing reports. XELJANZ 10 mg twice daily is contraindicated in patients who are at high risk for pulmonary embolism (see also section 4.3). Additional risk factors that should be considered in determining the patient's risk for PE are older age, obesity, smoking status, and immobilisation.

Interstitial lung disease

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

Gastrointestinal perforations

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

Cardiovascular risk

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

Liver enzymes

Treatment with XELJANZ was associated with an increased incidence of liver enzyme elevation in some patients (see section 4.8 liver enzyme tests). Caution should be exercised when considering initiation of XELJANZ treatment in patients with elevated alanine aminotransferase (ALT) or aspartate

aminotransferase (AST), particularly when initiated in combination with potentially hepatotoxic medicines such as MTX. Following initiation, routine monitoring of liver tests and prompt investigation of the causes of any observed liver enzyme elevations are recommended to identify potential cases of drug-induced liver injury. If drug-induced liver injury is suspected, the administration of XELJANZ should be interrupted until this diagnosis has been excluded.

Hypersensitivity

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

Laboratory parameters

Lymphocytes

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

Neutrophils

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

Haemoglobin

Treatment with XELJANZ has been associated with decreases in haemoglobin levels. It is not recommended to initiate XELJANZ treatment in patients with a haemoglobin value less than 9 g/dL.

Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on haemoglobin level, see section 4.2.

Lipid monitoring

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

Vaccinations

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

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

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

Excipients with known effect

XELJANZ contains lactose.

Patients with hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take XELJANZ. XELJANZ may have an effect on the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

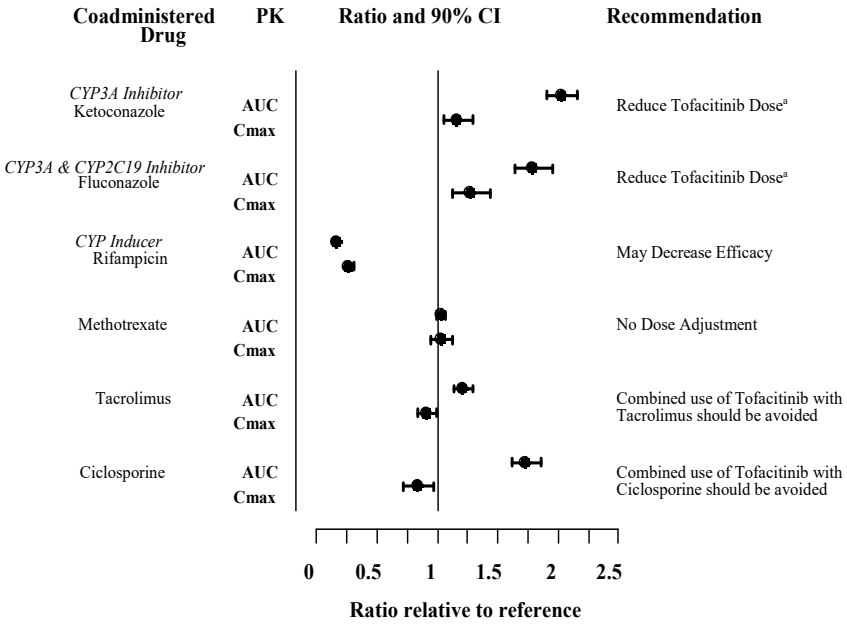
Potential for other medicines to influence the pharmacokinetics (PK) of tofacitinib.

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

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

Co-administration 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. Co-administration of tofacitinib with potent CYP inducers (e.g., rifampicin) may result in a loss of or reduced clinical response (see Figure 1). Co-administration of potent inducers of CYP3A4 with tofacitinib is not recommended. Co-administration with ketoconazole and fluconazole increased tofacitinib Cmax, while tacrolimus, ciclosporin and rifampicin decreased tofacitinib Cmax. 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 medicines on PK of tofacitinib.



Note: Reference group is administration of tofacitinib alone.

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

Potential for t*ofacitinib to influence the PK of other medicine*

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

In RA patients, co-administration of tofacitinib 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.

4.6 Fertility, pregnancy and lactation

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.

Pregnancy

There are no adequate and well-controlled studies on the use of XELJANZ in pregnant women. XELJANZ 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).

Breastfeeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Rheumatoid arthritis

The 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 Tabulated list of adverse reactions).

The proportion of patients who discontinued treatment due to adverse reactions during first 3 months of the double-blind, placebo or MTX controlled studies was 3,8 % for patients taking XELJANZ. The most common infections resulting in discontinuation of therapy were herpes zoster and pneumonia.

Psoriatic arthritis

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

Ulcerative colitis

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

In the induction and maintenance studies, across XELJANZ 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 XELJANZ was consistent with the safety profile of XELJANZ in the RA indication.

Tabulated list of adverse reactions

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

System organ class	Frequency	Side effect
Infections and infestations	Common	Pneumonia influenza herpes zoster urinary tract infection sinusitis bronchitis nasopharyngitis pharyngitis
	Uncommon	Tuberculosis diverticulitis pyelonephritis cellulitis herpes simplex viral gastroenteritis viral infection

	Rare	Sepsis urosepsis disseminated TB necrotizing fasciitis bacteraemia staphylococcal bacteraemia *Pneumocystis jirovecii* pneumonia pneumococcal pneumonia bacterial pneumonia encephalitis
		atypical mycobacterial infection cytomegalovirus infection bacterial arthritis
	Very rare	Tuberculosis of central nervous system cryptococcal meningitis *Mycobacterium avium* complex infection
Neoplasms benign and malignant and unspecified (including cysts and polyps)	Uncommon	Non-melanoma skin cancers

Blood and lymphatic system disorders	Common	Anaemia
	Uncommon	Leukopenia lymphopenia neutropenia
Immune system disorders	Not known	Drug hypersensitivity* angioedema* urticaria*
Metabolism and nutrition disorders	Uncommon	Dyslipidaemia hyperlipidaemia dehydration
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Common	Headache
	Uncommon	Paraesthesia
Vascular disorders	Common	Hypertension
Respiratory, thoracic and mediastinal disorders	Common	Cough
	Uncommon	Dyspnoea sinus congestion
Gastrointestinal disorders	Common	Abdominal pain vomiting diarrhoea nausea gastritis dyspepsia
Hepato-biliary disorders	Uncommon	Hepatic steatosis
	Common	Rash

Skin and subcutaneous tissue disorders	Uncommon	Erythema pruritus
Musculoskeletal and connective tissue disorders	Common	Arthralgia
	Uncommon	Musculoskeletal pain joint swelling tendonitis
General disorders and administration site conditions	Common	Pyrexia peripheral oedema fatigue
Investigations	Common	Increased blood creatine phosphokinase
	Uncommon	Increased hepatic enzyme increased transaminases abnormal liver function test increased gamma glutamyl-transferase increased blood creatinine increased blood cholesterol increased low density lipoprotein increased weight
Injury, poisoning and procedural complications	Uncommon	Ligament sprain muscle strain

*Spontaneous reporting data

Description of selected adverse reactions

Overall infections

Rheumatoid arthritis

In controlled Phase 3 clinical studies, the rates of infections over 0 - 3 months in the 5 mg twice daily (total 616 patients) and 10 mg twice daily (total 642 patients) tofacitinib monotherapy groups were 16,2 % (100 patients) and 17,9 % (115 patients), respectively, compared to 18,9 % (23 patients) in the placebo group (total 122 patients). In controlled Phase 3 clinical studies with background DMARDs, the rates of infections over 0 - 3 months in the 5 mg twice daily (total 973 patients) and 10 mg twice daily (total 969 patients) tofacitinib plus DMARD group were 21,3 % (207 patients) and 21,8 % (211 patients), respectively, compared to 18,4 % (103 patients) in the placebo plus DMARD group (total 559 patients).

The most commonly reported infections were upper respiratory tract infections and nasopharyngitis (3,7 % and 3,2 %, respectively).

The overall incidence rate of infections with tofacitinib in the long-term safety all exposure population (total 4 867 patients) was 46,1 patients with events per 100 patient-years (43,8 and 47,2 patients with events for 5 mg and 10 mg twice daily, respectively). For patients (total 1 750) on monotherapy, the rates were 48,9 and 41,9 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively. For patients (total 3 117) on background DMARDs, the rates were 41,0 and 50,3 patients with events per 100 patient-years for 5 mg and 10 mg twice daily, respectively.

Ulcerative colitis

In the randomised 8-week Phase 2/3 induction studies, the proportions of patients with infections were 21,1 % (198 patients) in the tofacitinib 10 mg twice daily group compared to 15,2 % (43 patients) in the placebo group. In the randomised 52-week Phase 3 maintenance study, the proportion of patients with infections were 35,9 % (71 patients) in the 5 mg twice daily and 39,8 % (78 patients) in the 10 mg twice daily tofacitinib groups, compared to 24,2 % (48 patients) in the placebo group.

In the entire treatment experience with tofacitinib, the most commonly reported infection was nasopharyngitis, occurring in 18,2 % of patients (211 patients).

In the entire treatment experience with tofacitinib, the overall incidence rate of infections was 60,3 events per 100 patient-years (involving 49,4 % of patients; total 572 patients).

Serious infections

Rheumatoid arthritis

In the 6-month and 24-month, controlled clinical studies, the rate of serious infections in the 5 mg twice daily tofacitinib monotherapy group was 1,7 patients with events per 100 patient-years. In the 10 mg twice daily tofacitinib monotherapy group the rate was 1,6 patients with events per 100 patient-years, the rate was 0 events per 100 patient-years for the placebo group, and the rate was 1,9 patients with events per 100 patient-years for the MTX group.

In studies of 6-, 12-, or 24-month duration, the rates of serious infections in the 5 mg twice daily and 10 mg twice daily tofacitinib plus DMARD groups were 3,6 and 3,4 patients with events per 100 patient-years, respectively, compared to 1,7 patients with events per 100 patient-years in the placebo plus DMARD group.

In the long-term safety all exposure population, the overall rates of serious infections were 2,4 and 3,0 patients with events per 100 patient-years for 5 mg and 10 mg twice daily tofacitinib groups, respectively. The most common serious infections included pneumonia, herpes zoster, urinary tract infection, cellulitis, gastroenteritis and diverticulitis. Cases of opportunistic infections have been reported (see section 4.4).

Ulcerative colitis

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

Serious infections in the elderly

Of the 4 271 patients who enrolled in RA studies I-VI (see section 5.1), a total of 608 RA patients were 65 years of age and older, including 85 patients 75 years and older. The frequency of serious infection among tofacitinib-treated patients 65 years of age and older was higher than those under the age of 65 (4,8 per 100 patient-years versus 2,4 per 100 patient-years, respectively). As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly (see section 4.4).

Viral reactivation

Patients with long standing RA who have previously received two or more biological DMARDs, or patients with an ALC less than 1 000 cells/mm^3, or patients treated with 10 mg twice daily may have an increased risk of herpes zoster (see section 4.4).

Laboratory tests

Lymphocytes

In the controlled RA clinical studies, confirmed decreases in ALC below 500 cells/mm^3 occurred in 0,3 % of patients and for ALC between 500 and 750 cells/mm^3 in 1,9 % of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

In the RA long-term safety population, confirmed decreases in ALC below 500 cells/mm^3 occurred in 1,3 % of patients and for ALC between 500 and 750 cells/mm^3 in 8,4 % of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

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

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

Neutrophils

In the controlled RA clinical studies, confirmed decreases in ANC below 1 000 cells/mm^3 occurred in 0,08 % of patients for the 5 mg twice daily and 10 mg twice daily doses combined. There were no confirmed decreases in ANC below 500 cells/mm^3 observed in any treatment group. There was no clear relationship between neutropenia and the occurrence of serious infections.

In the RA long-term safety population, the pattern and incidence of confirmed decreases in ANC remained consistent with what was seen in the controlled clinical studies (see section 4.4).

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

Liver enzyme tests

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

In the controlled portion of the RA Phase 3 monotherapy study (0 - 3 months) (study I, see section 5.1), ALT elevations greater than 3x ULN were observed in 1,65 %, 0,41 %, and 0 % of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 1,65 %, 0,41 % and 0 % of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the RA Phase 3 monotherapy study (0 - 24 months) (study VI, see section 5.1), ALT elevations greater than 3x ULN were observed in 7,1 %, 3,0 %, and 3,0 % of patients receiving MTX, tofacitinib 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 3,3 %, 1,6 % and 1,5 % of patients receiving MTX, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the controlled portion of the RA Phase 3 studies on background DMARDs (0 - 3 months) (studies II-V, see section 5.1), ALT elevations greater than 3x ULN were observed in 0,9 %, 1,24 % and 1,14 % of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively. In these studies, AST elevations greater than 3x ULN were observed in 0,72 %, 0,5 % and 0,31 % of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively.

In the RA long-term extension studies, on monotherapy, ALT elevations greater than 3x ULN were observed in 1,1 % and 1,4 % of patients receiving tofacitinib 5 mg and 10 mg twice daily, respectively. AST elevations greater than 3x ULN were observed in < 1,0 % in both the tofacitinib 5 mg and 10 mg twice daily groups.

In the RA long-term extension studies, on background DMARDs, ALT elevations greater than 3x ULN were observed in 1,8 % and 1,6 % of patients receiving tofacitinib 5 mg and 10 mg twice daily, respectively. AST elevations greater than 3x ULN were observed in < 1,0 % in both the tofacitinib 5 mg and 10 mg twice daily groups.

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

Lipids

Elevations in lipid parameters (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides) were first assessed at 1 month following initiation of tofacitinib in the controlled double-blind clinical trials of RA. Increases were observed at this time point and remained stable thereafter.

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

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

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

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

In an RA controlled clinical trial, elevations in LDL cholesterol and ApoB decreased to pre-treatment levels in response to statin therapy.

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8.

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 groups: Immunosuppressants, Selective Immunosuppressants. ATC code: L04AA29

Mechanism of action

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

Pharmacodynamic effects

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

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

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

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

Vaccine studies

In a controlled clinical trial of patients with RA initiating tofacitinib 10 mg twice daily or placebo, the number of responders to influenza vaccine was similar in both groups: tofacitinib (57 %) and placebo (62 %). For pneumococcal polysaccharide vaccine the number of responders was as follows: 32 % in patients receiving both tofacitinib and MTX; 62 % for tofacitinib monotherapy; 62 % for MTX monotherapy; and 77 % for

placebo. The clinical significance of this is unknown, however, similar results were obtained in a separate vaccine study with influenza and pneumococcal polysaccharide vaccines in patients receiving long-term tofacitinib 10 mg twice daily.

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

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 %. Co-administration 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.

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 radio-labelled 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. 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). *In vitro*, tofacitinib is a substrate for MDR1, but not for breast cancer resistance protein (BCRP), OATP1B1/1B3, or OCT1/2, and is not an inhibitor of MDR1, OATP1B1/1B3, OCT2, OAT1/3, or MRP at clinically meaningful concentrations.

Pharmacokinetics in patients

The enzymatic activity of CYP enzymes is reduced in RA patients due to chronic inflammation. In RA patients, the oral clearance of 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 and Black 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 %.

Results from population PK analysis in patients with active PsA or moderate to severe UC were consistent with those in patients with RA.

Renal impairment

Subjects with mild (creatinine clearance 50 - 80 mL/min), moderate (creatinine clearance 30 - 49 mL/min), and severe (creatinine clearance < 30 mL/min) renal impairment had 37 %, 43 % and 123 % higher AUC, respectively, compared to subjects with normal renal function (see section 4.2). In subjects with end stage renal disease (ESRD), contribution of dialysis to the total clearance of tofacitinib was relatively small. Following a single dose of 10 mg, mean AUC in subjects with ESRD based on concentrations measured on a non-dialysis day was approximately 40 % (90 % confidence intervals: 1,5 - 95 %) higher compared to subjects with normal renal function. In clinical trials, tofacitinib was not evaluated in patients with baseline creatinine clearance values (estimated by Cockroft-Gault equation) less than 40 mL/min (see section 4.2).

Hepatic impairment

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

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 post-dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

XELJANZ 5 mg and 10 mg film-coated tablets

Tablet core

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Film coat:

Hypromellose 6cP (E464)

Lactose monohydrate

Macrogol 3350

Titanium dioxide (E171)

Triacetin (E1518)

FD&C Blue #2/Indigo Carmine Aluminium Lake (E132) (10 mg strength only)

FD&C Blue #1/Brilliant Blue FCF Aluminium Lake (E133) (10 mg strength only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

XELJANZ 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

XELJANZ 5 mg film coated tablets

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

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

XELJANZ 10 mg film-coated tablets

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

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton, 2196

South Africa

Tel: +27(0)11 320 6000 / 0860 734 937 (toll free South Africa)

8. REGISTRATION NUMBERS

XELJANZ® 5 mg film-coated tablets: 47/3.1/1156

XELJANZ® 10 mg film-coated tablets: 47/3.1/1157

9. DATE OF FIRST AUTHORISATION

27 October 2020

10. DATE OF REVISION OF THE TEXT

BOTSWANA: S2

Xeljanz 5 mg:

60 tablets in HDPE bottle- Reg. No.: BOT1502686

180 tablets in HDPE bottle- Reg. No.: BOT1502686A

56 (4x14) in blisters- Reg. No.: BOT1502686B
Xeljanz 10 mg: 60 tablets in HDPE bottle- Reg. No.: BOT1502687 180 tablets in HDPE bottle- Reg. No.: BOT1502687A 56 (4x14) in blisters- Reg. No.: BOT1502687B

ZIMBABWE: PP **Xeljanz 5 mg:** 2014/3.3/4956