1. NAME OF THE MEDICINAL PRODUCT

XELJANZ 1 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect

Each mL of oral solution contains 2.39 mg propylene glycol.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral solution

Clear, colourless solution.

Patient safety information Card
The marketing of Xeljanz is subject to a risk management plan (RMP) including a 'Patient safety information card'. The 'Patient safety information card', emphasizes important safety information that the patient should be aware of before and during treatment. Please explain to the patient the need to review the card before starting treatment.
Prescriber guide
This Product is marketed with prescriber guide providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS
Patients treated with Xeljanz 1 mg/ml are at increased risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt XELJANZ 1 mg/ml until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for latent tuberculosis before XELJANZ 1 mg/ml use and during therapy. Treatment for latent infection should be initiated prior to XELJANZ 1 mg/ml.**

- **Invasive fungal infections, including cryptococcosis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, including herpes zoster, and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with XELJANZ 1 mg/ml should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with XELJANZ 1 mg/ml, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

MORTALITY
In a large, randomized, postmarketing safety study in rheumatoid arthritis (RA) patients 50 years of age and older with at least one cardiovascular risk factor comparing XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day to tumor necrosis factor (TNF) blockers, a higher rate of all-cause mortality, including sudden cardiovascular death, was observed with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day. A XELJANZ 10 mg twice daily dosage is not recommended for the treatment of RA or PsA.

MALIGNANCIES
Malignancies, including lymphomas and solid tumors, have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. In RA patients, a higher rate of malignancies (excluding NMSC) was observed in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day compared with TNF blockers.

Lymphomas and lung cancers were observed at a higher rate in patients treated with XELJANZ 5 mg twice a day or XELJANZ 10 mg twice a day in RA patients compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk.

Epstein Barr Virus-associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications.

MAJOR ADVERSE CARDIOVASCULAR EVENTS
RA patients 50 years of age and older with at least one cardiovascular risk factor, treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily, had a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke), compared to those treated with TNF blockers. Patients who are current or past smokers are at additional increased risk. Discontinue XELJANZ 1 mg/ml in patients that have experienced a myocardial infarction or stroke.

THROMBOSIS
Thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis have occurred in patients treated with XELJANZ and other Janus kinase inhibitors used to treat inflammatory conditions. Many of these events were serious and some resulted in death. RA patients 50 years of age and older with at least one cardiovascular risk factor treated with XELJANZ 5 mg twice daily or XELJANZ 10 mg twice daily compared to TNF blockers had an observed increase in incidence of these

events. Avoid XELJANZ 1 mg/ml in patients at risk. Discontinue XELJANZ 1 mg/ml and promptly evaluate patients with symptoms of thrombosis.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

XELJANZ 1 MG/ML is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with disease modifying antirheumatic drugs (DMARDs).

XELJANZ 1 MG/ML can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

4.2 Posology and method of administration

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

Posology

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

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

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

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

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

Dose adjustment

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

Dose interruption and discontinuation

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

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

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including lymphopenia, neutropenia, and anaemia. As described in Tables 2, 3 and 4 below,

recommendations for temporary dose interruption or permanent discontinuation of treatment are made according to the severity of laboratory abnormalities (see section 4.4).

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

Table 2: Low absolute lymphocyte count

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

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

Table 3: Low absolute neutrophil count

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

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

Table 4: Low haemoglobin value

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

Interactions

Tofacitinib total daily dose should be reduced to 5 mg film-coated tablet once daily or weight-based equivalent once daily in patients receiving 5 mg film-coated tablets or weight-based equivalent twice daily in patients receiving potent inhibitors of cytochrome P450 (CYP) 3A4 (e.g., ketoconazole) and in patients receiving 1 or more concomitant medicinal products that result in both moderate inhibition of CYP3A4 as well as potent inhibition of CYP2C19 (e.g., fluconazole) (see section 4.5).

Special populations

Elderly

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

Hepatic impairment

Table 5: Dose adjustment for hepatic impairment

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

Renal impairment

Table 6: Dose adjustment for renal impairment

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

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

Method of administration

Oral use.

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

Tofacitinib is given orally with or without food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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

Combination with other therapies

Tofacitinib has not been studied and its use should be avoided in combination with biologics such as TNF antagonists, interleukin (IL)-1R antagonists, IL-6R antagonists, anti-CD20 monoclonal antibodies, IL-17 antagonists, IL-12/IL-23 antagonists, anti-integrins, selective co-stimulation modulators and potent immunosuppressants such as azathioprine, 6-mercaptopurine, ciclosporin and tacrolimus because of the possibility of increased immunosuppression and increased risk of infection.

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

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

Venous thromboembolism (VTE)

Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), have been observed in patients taking tofacitinib. In a randomised post-authorisation safety study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, a dose dependent increased risk for VTE was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1).

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

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

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

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

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

Retinal venous thrombosis

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

Serious infections

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

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

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

- with recurrent infections,

- with a history of a serious or an opportunistic infection,
- who have resided or travelled in areas of endemic mycoses,
- who have underlying conditions that may predispose them to infection.

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

As there is a higher incidence of infections in the elderly and in the diabetic populations in general, caution should be used when treating the elderly and patients with diabetes (see section 4.8). In patients 65 years of age and older, tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1).

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

Tuberculosis

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

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

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

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

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

Viral reactivation

Viral reactivation and cases of herpes virus reactivation (e.g., herpes zoster) have been observed in patients receiving tofacitinib (see section 4.8).

In patients treated with tofacitinib, the incidence of herpes zoster appears to be increased in:

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

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

At least one confirmed case of progressive multifocal leukoencephalopathy (PML) has been reported in RA patients receiving tofacitinib in the post marketing setting. PML can be fatal and should be considered in the differential diagnosis in immunosuppressed patients with new onset or worsening neurological symptoms.

Major adverse cardiovascular events (including myocardial infarction)

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

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

Malignancies and lymphoproliferative disorder

Tofacitinib may affect host defences against malignancies.

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

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

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

In patients 65 years of age and older, patients who are current or past long-time smokers, and patients with other malignancy risk factors (e.g. current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available (see section 5.1). Periodic skin examination is recommended for all patients, particularly those who are at increased risk for skin cancer (see Table 7 in section 4.8).

Interstitial lung disease

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

Gastrointestinal perforations

Events of gastrointestinal perforation have been reported in clinical studies although the role of JAK inhibition in these events is not known. Tofacitinib should be used with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis,

patients with concomitant use of corticosteroids and/or nonsteroidal anti-inflammatory drugs). Patients presenting with new onset abdominal signs and symptoms should be evaluated promptly for early identification of gastrointestinal perforation.

Fractures

Fractures have been observed in patients treated with tofacitinib.

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

Liver enzymes

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

Hypersensitivity

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

Laboratory parameters

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

Neutrophils
Treatment with tofacitinib was associated with an increased incidence of neutropenia (less than 2,000 cells/mm^3) compared to placebo. It is not recommended to initiate tofacitinib treatment in adult patients with an ANC less than 1,000 cells/mm^3 and in paediatric patients with an ANC less than 1,200 cells/mm^3. ANC should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on ANC, see section 4.2.

Haemoglobin
Treatment with tofacitinib has been associated with decreases in haemoglobin levels. It is not recommended to initiate tofacitinib treatment in adult patients with a haemoglobin value less than 9 g/dL and in paediatric patients with haemoglobin value less than 10 g/dL. Haemoglobin should be monitored at baseline and after 4 to 8 weeks of treatment and every 3 months thereafter. For recommended modifications based on haemoglobin level, see section 4.2.

Lipid monitoring
Treatment with tofacitinib was associated with increases in lipid parameters such as total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. Maximum

effects were generally observed within 6 weeks. Assessment of lipid parameters should be performed after 8 weeks following initiation of tofacitinib therapy. Patients should be managed according to clinical guidelines for the management of hyperlipidaemia. Increases in total and LDL cholesterol associated with tofacitinib may be decreased to pretreatment levels with statin therapy.

Hypoglycaemia in patients treated for diabetes

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

Vaccinations

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

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

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

Excipients contents

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

Examples of propylene glycol exposures based on daily doses (see section 4.2) are as follows:
- A dose of 3.2 mg twice daily of XELJANZ 1 mg/mL oral solution administered to a child weighing 10 kg to < 20 kg would result in a propylene glycol exposure of 1.53 mg/kg/day.
- A dose of 4 mg twice daily of XELJANZ 1 mg/mL oral solution administered to a child weighing 20 kg to <40 kg would result in a propylene glycol exposure of 0.96 mg/kg/day.
- A dose of 5 mg twice daily of XELJANZ 1 mg/mL oral solution administered to a child weighing ≥40 kg would result in a propylene glycol exposure of 0.60 mg/kg/day.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

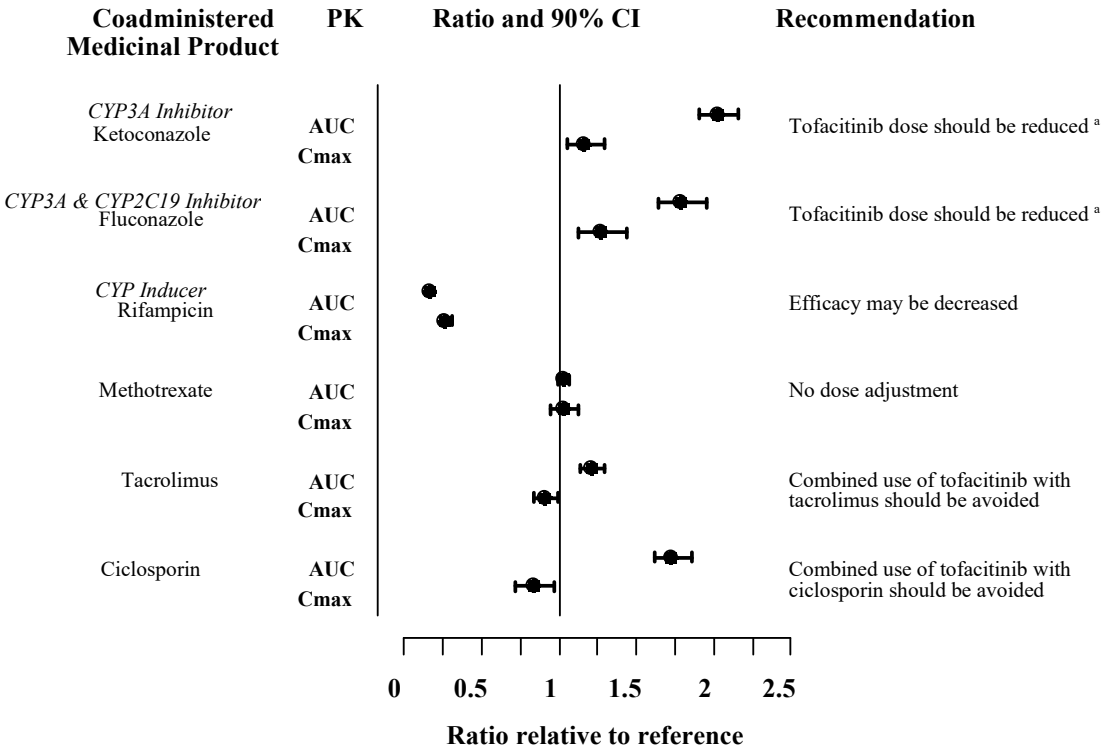
Potential for other medicinal products to influence the pharmacokinetics (PK) of tofacitinib

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

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

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

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



Note: Reference group is administration of tofacitinib alone.

[a] Tofacitinib dose should be reduced to 5 mg film-coated tablet once daily or oral solution weight-based equivalent in patients receiving 5 mg or weight-based equivalent twice daily (see section 4.2).

Potential for tofacitinib to influence the PK of other medicinal products

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

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

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Women of childbearing potential/contraception in females

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Rheumatoid arthritis
The most common serious adverse reactions were serious infections (see section 4.4). In the long-term safety all exposure population, the most common serious infections reported with tofacitinib were pneumonia (1.7%), herpes zoster (0.6%), urinary tract infection (0.4%), cellulitis (0.4%), diverticulitis (0.3%), and appendicitis (0.2%). Among opportunistic infections, TB and other mycobacterial infections, cryptococcus, histoplasmosis, oesophageal candidiasis, multidermatomal herpes zoster, cytomegalovirus infection, BK virus infections and listeriosis were reported with tofacitinib. Some patients have presented with disseminated rather than localised disease. Other serious infections that were not reported in clinical studies may also occur (e.g., coccidioidomycosis).

The most commonly reported adverse reactions during the first 3 months of the double-blind, placebo or MTX controlled clinical studies were headache (3.9%), upper respiratory tract infections (3.8%),

viral upper respiratory tract infection (3.3%), diarrhoea (2.9%), nausea (2.7%), and hypertension (2.2%).

The proportion of patients who discontinued treatment due to adverse reactions during first 3 months of the double-blind, placebo or MTX controlled studies was 3.8% for patients taking tofacitinib. The most common infections resulting in discontinuation of therapy during the first 3 months in controlled clinical studies were herpes zoster (0.19%) and pneumonia (0.15%).

Tabulated list of adverse reactions

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

Table 7: Adverse reactions

System organ class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare <1/10,000	Not known (cannot be estimated from the available data)
Infections and infestations	Pneumonia Influenza Herpes zoster Urinary tract infection Sinusitis Bronchitis Nasopharyngitis Pharyngitis	Tuberculosis Diverticulitis Pyelonephritis Cellulitis Herpes simplex Gastroenteritis viral Viral infection	Sepsis Urosepsis Disseminated TB Bacteraemia *Pneumocystis jirovecii* pneumonia Pneumonia pneumococcal Pneumonia bacterial Cytomegalovirus infection Arthritis bacterial	Tuberculosis of central nervous system Meningitis cryptococcal Necrotizing fasciitis Encephalitis Staphylococcal bacteraemia *Mycobacterium avium* complex infection Atypical mycobacterial infection	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Lung cancer Non-melanoma skin cancers	Lymphoma		
Blood and lymphatic system disorders	Lymphopenia Anaemia	Leukopenia Neutropenia			
Immune system disorders					Hypersensitivity * Angioedema* Urticaria*
Metabolism and nutrition disorders		Dyslipidaemia Hyperlipidaemia Dehydration			
Psychiatric disorders		Insomnia			
Nervous system disorders	Headache	Paraesthesia			
Cardiac disorders		Myocardial infarction			

System organ class	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very rare <1/10,000	Not known (cannot be estimated from the available data)
Vascular disorders	Hypertension	Venous thromboembolism**			
Respiratory, thoracic and mediastinal disorders	Cough	Dyspnoea Sinus congestion			
Gastrointestinal disorders	Abdominal pain Vomiting Diarrhoea Nausea Gastritis Dyspepsia				
Hepatobiliary disorders		Hepatic steatosis Hepatic enzyme increased Transaminases increased Gamma glutamyl-transferase increased	Liver function test abnormal		
Skin and subcutaneous tissue disorders	Rash Acne	Erythema Pruritus			
Musculoskeletal and connective tissue disorders	Arthralgia	Joint swelling Tendonitis	Musculoskeletal pain		
General disorders and administration site conditions	Oedema peripheral	Pyrexia Fatigue			
Investigations	Blood creatine phosphokinase increased	Blood creatinine increased Blood cholesterol increased Low density lipoprotein increased Weight increased			
Injury, poisoning and procedural complications		Ligament sprain Muscle strain			

*Spontaneous reporting data
**Venous thromboembolism includes PE, DVT, and Retinal Venous Thrombosis

Description of selected adverse reactions

Venous thromboembolism

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

Overall infections

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

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

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

Serious infections

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

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

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

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

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

Viral reactivation

Patients treated with tofacitinib who are Japanese or Korean, or patients with long standing RA who have previously received two or more biological DMARDs, or patients with an ALC less

than 1,000 cells/mm^3, or patients treated with 10 mg twice daily may have an increased risk of herpes zoster (see section 4.4).

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

Laboratory tests

Lymphocytes
In the controlled RA clinical studies, confirmed decreases in ALC below 500 cells/mm^3 occurred in 0.3% of patients and for ALC between 500 and 750 cells/mm^3 in 1.9% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

In the RA long-term safety population, confirmed decreases in ALC below 500 cells/mm^3 occurred in 1.3% of patients and for ALC between 500 and 750 cells/mm^3 in 8.4% of patients for the 5 mg twice daily and 10 mg twice daily doses combined.

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

Neutrophils
In the controlled RA clinical studies, confirmed decreases in ANC below 1,000 cells/mm^3 occurred in 0.08% of patients for the 5 mg twice daily and 10 mg twice daily doses combined. There were no confirmed decreases in ANC below 500 cells/mm^3 observed in any treatment group. There was no clear relationship between neutropenia and the occurrence of serious infections.

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

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

In the controlled portion of the RA phase 3 monotherapy study (0-3 months) (study I, see section 5.1), ALT elevations greater than 3x ULN were observed in 1.65%, 0.41%, and 0% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively. In this study, AST elevations greater than 3x ULN were observed in 1.65%, 0.41% and 0% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively.

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

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

studies, AST elevations greater than 3x ULN were observed in 0.72%, 0.5% and 0.31% of patients receiving placebo, tofacitinib 5 mg and 10 mg twice daily, respectively.

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

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

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

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

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

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

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

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

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

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

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

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

Myocardial infarction

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

Malignancies excluding NMSC

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

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

Paediatric population

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

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

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

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

Hepatic events

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

Laboratory tests

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse event should be reported to the Ministry of Health according to the National Regulation by using an online form

https://sideeffects.health.gov.il/

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic groups: Immunosuppressants, Janus-associated kinase (JAK) inhibitors; ATC code: L04AF01

Mechanism of action

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

Pharmacodynamic effects

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

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

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

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

Vaccine studies

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

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

Clinical efficacy and safety

Clinical response

The tofacitinib Phase 3 program for JIA consisted of one completed Phase 3 trial (Study JIA-I [A3921104]) and one ongoing long-term extension (LTE) (A3921145) trial. In these studies the following JIA subgroups were included: patients with either RF+ or RF- polyarthritis, extended oligoarthritis, systemic JIA with active arthritis and no current systemic symptoms (referred as pJIA dataset) and two separate subgroups of patients with juvenile PsA and enthesitis-related arthritis

(ERA). However, the pJIA efficacy population only includes the subgroups with either RF+ or RF- polyarthritis or extended oligoarthritis; inconclusive results have been seen in the subgroup of patients with systemic JIA with active arthritis and no current systemic symptoms. Patients with juvenile PsA are included as separate efficacy subgroup. ERA patients are not included in the efficacy analysis.

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

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

Signs and symptoms
A significantly smaller proportion of patients with pJIA in Study JIA-I treated with tofacitinib 5 mg film-coated tablets twice daily or tofacitinib oral solution weight-based equivalent twice daily flared at Week 44 compared with patients treated with placebo. A significantly greater proportion of patients with pJIA treated with tofacitinib 5 mg film-coated tablets or tofacitinib oral solution achieved JIA ACR30, 50, and 70 responses compared to patients treated with placebo at Week 44 (Table 8).

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

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

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

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

Primary endpoint (Type I error controlled)	**Treatment group**	**Occurrence rate**	**Difference (%) from placebo (95% CI)**
Occurrence of disease flare	Tofacitinib 5 mg Twice Daily (N=67)	28%	-24.7 (-40.8, -8.5)
	Placebo (N=66)	53%	
Secondary endpoints (Type I error controlled)	**Treatment group**	**Response rate**	**Difference (%) from placebo (95% CI)**

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

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

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

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

Long-term controlled safety data in RA

Study ORAL Surveillance (A3921133) was a large (N=4362), randomised active-controlled post-authorisation safety surveillance study of rheumatoid arthritis patients who were 50 years of age and older and had at least one additional cardiovascular risk factor (CV risk factors defined as: current cigarette smoker, diagnosis of hypertension, diabetes mellitus, family history of premature coronary heart disease, history of coronary artery disease including a history of revascularization procedure, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina, acute coronary syndrome, and presence of extra-articular disease associated with RA, e.g. nodules, Sjögren's syndrome, anaemia of chronic disease, pulmonary manifestations). The majority (more than 90%) of tofacitinib patients who were current or past smokers had a smoking duration of more than 10 years and a median of 35.0 and 39.0 smoking years, respectively. Patients were required to be on a stable dose of methotrexate at study entry; dose adjustment was permitted during the study.

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

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

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

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

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

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

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

[c] Based on events occurring on treatment or within 60 days of treatment discontinuation.
[d] Based on events occurring on treatment or within 28 days of treatment discontinuation.
Abbreviations: MACE = major adverse cardiovascular events, MI = myocardial infarction, VTE = venous thromboembolism, PE = pulmonary embolism, DVT = deep vein thrombosis, TNF = tumour necrosis factor, IR = incidence rate, HR = hazard ratio, CI = confidence interval, PY = patient years, Inf = infinity

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

Malignancies

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

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

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

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

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

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

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

	Tofacitinib 5 mg twice daily	**Tofacitinib 10 mg twice daily[b]**	**All Tofacitinib[c]**	**TNF inhibitor (TNFi)**
Mortality (all cause)				
IR (95% CI) per 100 PY	0.50 (0.33, 0.74)	0.80 (0.57, 1.09)	0.65 (0.50, 0.82)	0.34 (0.20, 0.54)
HR (95% CI) vs TNFi	1.49 (0.81, 2.74)	2.37 (1.34, 4.18)	1.91 (1.12, 3.27)	

Fatal infections				
IR (95% CI) per 100 PY	0.08 (0.02, 0.20)	0.18 (0.08, 0.35)	0.13 (0.07, 0.22)	0.06 (0.01, 0.17)
HR (95% CI) vs TNFi	1.30 (0.29, 5.79)	3.10 (0.84, 11.45)	2.17 (0.62, 7.62)	
Fatal CV events				
IR (95% CI) per 100 PY	0.25 (0.13, 0.43)	0.41 (0.25, 0.63)	0.33 (0.23, 0.46)	0.20 (0.10, 0.36)
HR (95% CI) vs TNFi	1.26 (0.55, 2.88)	2.05 (0.96, 4.39)	1.65 (0.81, 3.34)	
Fatal Malignancies				
IR (95% CI) per 100 PY	0.10 (0.03, 0.23)	0.00 (0.00, 0.08)	0.05 (0.02, 0.12)	0.02 (0.00, 0.11)
HR (95% CI) vs TNFi	4.88 (0.57, 41.74)	0 (0.00, Inf)	2.53 (0.30, 21.64)	

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

5.2 Pharmacokinetic properties

The PK profile of tofacitinib is characterised by rapid absorption (peak plasma concentrations are reached within 0.5-1 hour), rapid elimination (half-life of ~3 hours) and dose-proportional increases in systemic exposure. Steady state concentrations are achieved in 24-48 hours with negligible accumulation after twice daily administration.

Absorption and distribution

Tofacitinib is well-absorbed, with an oral bioavailability of 74%. Coadministration of tofacitinib with a high-fat meal resulted in no changes in AUC while C_{max} was reduced by 32%. In clinical studies, tofacitinib was administered without regard to meal.

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

Biotransformation and elimination

Clearance mechanisms for tofacitinib are approximately 70% hepatic metabolism and 30% renal excretion of the parent drug. The metabolism of tofacitinib is primarily mediated by CYP3A4 with minor contribution from CYP2C19. In a human radiolabelled study, more than 65% of the total circulating radioactivity was accounted for by unchanged active substance, with the remaining 35% attributed to 8 metabolites, each accounting for less than 8% of total radioactivity. All metabolites have been observed in animal species and are predicted to have less than 10-fold potency than tofacitinib for JAK1/3 inhibition. No evidence of stereo conversion in human samples was detected. The pharmacologic activity of tofacitinib is attributed to the parent molecule. *In vitro*, tofacitinib is a substrate for MDR1, but not for breast cancer resistance protein (BCRP), OATP1B1/1B3, or OCT1/2.

Renal impairment

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

Hepatic impairment

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

Interactions

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

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

5.3 Preclinical safety data

In non-clinical studies, effects were observed on the immune and haematopoietic systems that were attributed to the pharmacological properties (JAK inhibition) of tofacitinib. Secondary effects from immunosuppression, such as bacterial and viral infections and lymphoma were observed at clinically relevant doses. Lymphoma was observed in 3 of 8 adult monkeys at 6 or 3 times the clinical tofacitinib exposure level (unbound AUC in humans at a dose of 5 mg or 10 mg twice daily), and 0 of 14 juvenile monkeys at 5 or 2.5 times the clinical exposure level of 5 mg or 10 mg twice daily. Exposure in monkeys at the no observed adverse effect level (NOAEL) for the lymphomas was approximately 1 or 0.5 times the clinical exposure level of 5 mg or 10 mg twice daily. Other findings at doses exceeding human exposures included effects on the hepatic and gastrointestinal systems.

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

The carcinogenic potential of tofacitinib was assessed in 6-month rasH2 transgenic mouse carcinogenicity and 2-year rat carcinogenicity studies. Tofacitinib was not carcinogenic in mice at exposures up to 38 or 19 times the clinical exposure level at 5 mg or 10 mg twice daily. Benign testicular interstitial (Leydig) cell tumours were observed in rats: benign Leydig cell tumours in rats are not associated with a risk of Leydig cell tumours in humans. Hibernomas (malignancy of brown adipose tissue) were observed in female rats at exposures greater than or equal to 83 or 41 times the clinical exposure level at 5 mg or 10 mg twice daily. Benign thymomas were observed in female rats at 187 or 94 times the clinical exposure level at 5 mg or 10 mg twice daily.

Tofacitinib was shown to be teratogenic in rats and rabbits, and have effects in rats on female fertility (decreased pregnancy rate; decreases in the numbers of corpora lutea, implantation sites, and viable foetuses; and an increase in early resorptions), parturition, and peri/postnatal development. Tofacitinib had no effects on male fertility, sperm motility or sperm concentration. Tofacitinib was secreted in milk of lactating rats at concentrations approximately 2-fold those in serum from 1 to 8 hours postdose. In studies conducted in juvenile rats and monkeys, there were no tofacitinib-related effects on bone development in males or females, at exposures similar to those achieved at approved doses in humans.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Purified water
Xylitol (E967)
Grape flavour [containing propylene glycol (E1520), glycerol (E422), ethanol and other components
Lactic acid (E270)
Sucralose (E955)
Sodium benzoate (E211)
Hydrochloric acid

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

Shelf life after first opening

Should be discarded after 60 days of first opening.
Storage after first opening: Store at 25°C

6.4 Special precautions for storage

Store at 25°C in the original bottle and carton to protect from light.

6.5 Nature and contents of container

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

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

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

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Pfizer Pharmaceuticals Israel Ltd
9 Shenkar St Herzliya Pituach
Israel

8. MARKETING AUTHORISATION NUMBER(S)

176-47-37836-99

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