PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

XELJANZ (Tofacitinib)

Marketing Authorization Number 62630

Film-coated tablets, 5 mg; 10 mg

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LIST OF ABBREVIATIONS

EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
PL	Package leaflet
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics (Europe)

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OVERVIEW

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary for Xeljanz is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss marketing authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Xeljanz in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Pfizer is fully responsible for the accuracy and correctness of the content of the published RMP summary of Xeljanz.

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1. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Xeljanz (Tofacitinib)

This is a summary of the RMP for XELJANZ. The RMP details important risks of XELJANZ, how these risks can be minimised, and how more information will be obtained about XELJANZ's risks and uncertainties (missing information).

XELJANZ's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how XELJANZ should be used.

This summary of the RMP for XELJANZ should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of XELJANZ's RMP.

I. The Medicine and What It Is Used For

XELJANZ is authorised for the treatment of adults with moderate to severe active rheumatoid arthritis, active psoriatic arthritis, moderately to severely active ulcerative colitis, active polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis, and ankylosing spondylitis (see SmPC for the full indication). It contains Tofacitinib citrate as the active substance and it is given by oral route of administration.

Further information about the evaluation of XELJANZ's benefits can be found in XELJANZ's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/xeljanz

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of XELJANZ, together with measures to minimise such risks and the proposed studies for learning more about XELJANZ's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine's legal status — the way a medicine is supplied to the public (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

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In the case of XELJANZ, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of XELJANZ is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of XELJANZ are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of XELJANZ. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 1. List of Important Risks and Missing Information

Important identified risks	Venous thromboembolic events (DVT/PE)
	Serious and other important infections
	HZ reactivation
	Lung cancer
	Lymphoma
	Myocardial infarction
	Decrease in Hgb levels and anaemia
	NMSC
	Transaminase elevation and potential for DILI
	Higher incidence and severity of AEs in the elderly
Important potential risks	Malignancy
	Cardiovascular risk (excl MI)
	GI perforation
	ILD
	PML
	All-cause mortality
	Fractures
	Increased risk of AEs when Tofacitinib is administered in combination with MTX in RA or PsA patients
	Primary viral infection following live vaccination
Missing information	Effects on pregnancy and the foetus
	Use in breastfeeding
	Effect on vaccination efficacy and the use of live/attenuated vaccines
	Use in patients with mild, moderate, or severe hepatic impairment
	Use in patients with moderate or severe renal impairment
	Use in patients with evidence of hepatitis B or hepatitis C infection
	Use in patients with malignancy
	Long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)

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Table 1. List of Important Risks and Missing Information

AE = adverse event; DILI = drug-induced liver injury; DVT = deep vein thrombosis; Excl = excluding; GI = gastrointestinal; Hgb = haemoglobin; HZ = herpes zoster; IBD = inflammatory bowel disease; ILD = interstitial lung disease; JIA = juvenile idiopathic arthritis; MI = myocardial infarction; MTX = methotrexate; NMSC = non-melanoma skin cancer; pJIA = polyarticular juvenile idiopathic arthritis; PE = pulmonary embolism; PML = progressive multifocal leukoencephalopathy; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RMP = risk management plan

II.B. Summary of Important Risks and Missing Information

Table 2. Summary of Important Risks and Missing Information

Important Identified Risk: Venous thromboembolic events (DVT/PE)	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Venous thromboembolism was observed at an increased and dose-dependent incidence in patients treated with Tofacitinib compared to TNF inhibitors in Study A3921133 (patients with RA aged 50 years and older with at least one CV risk factor). No differential risk factors were identified for the increased risk relative to TNF inhibitors. Numerous VTE risk factors are known in the general population. These known VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (body mass index [BMI] ≥30), diabetes, hypertension, smoking status should also be considered. Pediatric JIA patients can experience many of the risk factors seen in adults. In a review article it is noted that in children aged 2 to <18 years with JIA, cardiovascular risk factors including hypertension, dyslipidaemia and being less physically active are more frequent than in their healthy peers. JIA patients may also have other cardiovascular risk factors seen in adult RA such as obesity, diabetes, and smoking. JIA patients potentially could have other risk factors (e.g., adolescent contraceptive hormone use, major surgeries, immobilization, congenital and acquired thrombophilias), which may increase their risk of such events. Published literature suggest a higher prevalence of anticardiolipin antibodies positive, or elevated levels of coagulation factors in JIA patients compared with non-JIA patients; however, these findings were not correlated with clinical features such as abnormal clotting test or anticardiolipin antibody syndrome. Data also suggest an increased risk of malignancy among JIA patients compared with non-JIA patients. In a retrospective cohort study based in the Swedish Cancer Register, the HR (95% CI) for all pediatric malignancies in JIA vs the general population was 1.43 (0.71-2.88). Summary of results from the US Corrona RA Registry A3921205: The overall number of VTE events in the Tofacitinib group with moderate-to-severe disease was small and the rate [0.18 (0.04, 0.51)] was similar to the bDMARD group [0.32 (0.20, 0.47)]. The risk factors associated with VTE were generally similar between Tofacitinib and bDMARD groups and were consistent with the known risk factors for VTE (e.g., advanced age). In patients with moderate-to-severe disease aged 50 years and older with at least one CV risk factor, the crude incidence rate (95% CI) was 0.22 (0.03, 0.78) in Tofacitinib initiators compared with 0.51 (0.31, 0.80) for bDMARDs initiators.
Risk minimisation measures	<u>Routine risk communication:</u> SmPC Sections 4.4, 4.8, and 5.1 <u>Additional risk minimisation measures:</u>

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Table 2. Summary of Important Risks and Missing Information

	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and within the Juvenile Arthritis Methotrexate/Biologics long-term Observation (JuMBO) Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC) •A3921403: A drug utilisation study using French claims database (SNDS)
Important Identified Risk: Serious and other important infections	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Risk factors/groups for serious infections include patients who are elderly or diabetic, patients that use drugs along with Tofacitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts in their blood, and patients from certain Asian countries. Summary of results from the US Corrona RA Registry A3921205: The risk factors associated with serious infection events were similar between Tofacitinib and bDMARD groups in patients with moderate-to-severe disease (such as history of hypertension, history of diabetes mellitus, age 70+, age 60+). The rates of serious infection events were higher without overlapping 95% CI in patients 65 and older than in patients younger than 65 in both Tofacitinib initiators [<65 years: 2.03 (1.35, 2.94); ≥65 years: 5.1 (3.57, 7.06)] and bDMARD initiators [<65 years: 2.15 (1.8, 2.54); ≥65 years: 4.54 (3.85, 5.33)]. The 95% CI overlapped between the Tofacitinib group ≥65 years and bDMARD group ≥65 years.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, 4.8, and 5.1 Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry

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Table 2. Summary of Important Risks and Missing Information

	•A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Identified Risk: HZ reactivation	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	There is a higher rate of herpes zoster in Japanese and Korean patients. Patients who have had rheumatoid arthritis for many years, were elderly or have previously used two or more medicines that depress the immune system, including so called targeted biologic (antibody) therapies, such as those that inhibit tumour necrosis factor, and corticosteroids also have an increased risk. Patients with a low white blood cell (lymphocyte) count may have an increased risk of herpes zoster.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Identified Risk: Lung cancer	
Evidence for linking the risk to the medicine	Clinical trial data (A3921133)
Risk factors and risk groups	Patients with RA may be at higher risk than the general population for the development of lung cancer. In Study A3921133, 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 excluding NMSC, particularly lung cancer, lymphoma, and an increase in NMSC was observed with Tofacitinib compared to TNF inhibitors.

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Table 2. Summary of Important Risks and Missing Information

	Summary of Study A3921133 results: an increase in malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed in patients treated with Tofacitinib compared to TNF inhibitor. The IRs of lung cancer per 100 PY (95% CI) (based on total time) for the Tofacitinib 5 mg BID, Tofacitinib 10 mg BID, All Tofacitinib, and TNFi groups, respectively, were 0.23 (0.12, 0.40), 0.32 (0.18, 0.51), 0.28 (0.19, 0.39), 0.13 (0.05, 0.26).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Identified Risk: Lymphoma	
Evidence for linking the risk to the medicine	Clinical trial data (A3921133)
Risk factors and risk groups	Patients with RA, particularly those with highly active disease, may be at higher risk (up to several fold) than general population for the development of lymphoma. In Study A3921133, 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 excluding NMSC, particularly lung cancer, lymphoma, and an increase in NMSC was observed with Tofacitinib compared to TNF inhibitors. Summary of Study A3921133 results: an increase in malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed in patients treated with Tofacitinib compared to TNF inhibitor. The IRs of lymphoma per 100 PY (95% CI) (based on total time) for the Tofacitinib 5 mg BID, Tofacitinib 10 mg BID, All Tofacitinib, and TNFi groups, respectively, were 0.07 (0.02, 0.18), 0.11 (0.04, 0.24), 0.09 (0.04, 0.17), 0.02 (0.00, 0.10).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties

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Table 2. Summary of Important Risks and Missing Information

	Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Identified Risk: Myocardial infarction	
Evidence for linking the risk to the medicine	Clinical trial data (A3921133)
Risk factors and risk groups	In Study A3921133, a large, randomised active-controlled post authorisation safety surveillance study of RA patients who were 50 years of age and older and had at least one additional cardiovascular risk factor, 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). Summary of Study A3921133 results: an increase in incidence of non-fatal MI was observed with Tofacitinib compared to TNFi. The IRs of adjudicated non-fatal MI per 100 PY (95% CI) (based on 60 days risk period) for the Tofacitinib 5 mg BID, Tofacitinib 10 mg BID, All Tofacitinib, and TNFi groups, respectively, were 0.37 (0.22, 0.57), 0.33 (0.19, 0.53), 0.35 (0.24, 0.48), 0.16 (0.07, 0.31). The IRs of adjudicated fatal MI per 100 PY (95% CI) (based on 60 days risk period) for the Tofacitinib 5 mg BID, Tofacitinib 10 mg BID, All Tofacitinib, and TNFi groups, respectively, were 0.00 (0.00, 0.07), 0.06 (0.01, 0.18), 0.03 (0.01, 0.09), 0.06 (0.01, 0.17).
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Special warnings and precautions for use SmPC Section 4.8 Undesirable effects SmPC Section 5.1 Pharmacodynamic properties Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).

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Table 2. Summary of Important Risks and Missing Information

Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC) •A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •A3921403: A drug utilisation study using French claims database (SNDS)
Important Identified Risk: Decrease in Hgb levels and anaemia	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	No risk groups have been identified.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, and 4.8. Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	None.
Important Identified Risk: NMSC	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	In the RA programme, NMSC primarily occurred in sun-exposed areas of the body including the face/head and hands. The commonly reported risk factors of NMSC include sun exposure (i.e., ultraviolet), medications that suppress the immune system, light therapy, virus infections (eg, human papilloma virus), age, and certain types of radiation. In Study A3921133, 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 excluding NMSC, particularly lung cancer, lymphoma, and an increase in NMSC was observed with Tofacitinib compared to TNF inhibitors.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8. Additional risk minimisation measures:

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Table 2. Summary of Important Risks and Missing Information

	Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
Important Identified Risk: Transaminase elevation and potential for DILI	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Use of other medications (called DMARDs) to treat RA or to treat PsA at the same time as Tofacitinib.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	None
Important Identified Risk: Higher incidence and severity of AEs in the elderly	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	In Study A3921133, 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, patients 65 years of age and older had an increased risk of serious infections, MI, malignancies, and all-cause mortality with Tofacitinib.
Risk minimisation measures	Routine risk communication: SmPC Sections 4.2, 4.4, 4.8, and 5.1. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years (incidence only for ARTIS, BIOBADASER, BSRBR)

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Table 2. Summary of Important Risks and Missing Information

	•Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years (incidence only).
Important Potential Risk: Malignancy	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	The risk of malignancy (cancer) in general is increased in the elderly population. 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. 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. Summary of results from the US Corrona RA Registry A3921205: The rates of malignancy excluding NMSC were higher without overlapping 95% CI in patients 65 and older than in patients younger than 65 in both Tofacitinib and bDMARD initiator groups. The rate of malignancy excluding NMSC in patients 65 and older in Tofacitinib initiators was 1.77 (95%CI=1.17, 2.57) and the rate in bDMARD initiators was 1.22 (95% CI=0.95, 1.55); the 95% CI overlapped. Summary of Study A3921133 results: an increase in malignancies (excluding NMSC), particularly lymphoma and lung cancer, was observed with Tofacitinib compared to TNFi. This increased risk was predominantly observed in older patients and in patients who are current or past smokers. The IR per 100 PY (95% CI) (based on total time) of adjudicated malignancies (excluding NMSC) in adults aged ≥65 years or who had ever smoked for the Tofacitinib 5 mg BID, Tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 1.38 (1.01, 1.82), 1.59 (1.19, 2.07), 1.48 (1.21, 1.80), and 0.96 (0.66, 1.34). In patients who were less than 65 years of age and had never smoked, the IR per 100 PY (95% CI) (based on total time) for malignancies excluding NMSC for Tofacitinib 5 mg BID, Tofacitinib 10 mg BID, All Tofa, and TNFi groups, respectively, were 0.70 (0.38, 1.17), 0.31 (0.12, 0.68), 0.51 (0.31, 0.79), and 0.44 (0.20, 0.84).
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.4. SmPC Section 5.1. <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry

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Table 2. Summary of Important Risks and Missing Information

	•Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Potential Risk: Cardiovascular risk (excl MI)	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Patients with autoimmune diseases have an increased risk for cardiovascular disorders. The risk of cardiovascular events in general is increased in the elderly population. Tofacitinib has been associated with increased cholesterol, high blood pressure (hypertension), and weight gain, which are known risk factors for cardiovascular events. In Study A3921133, 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 MACE was observed with Tofacitinib compared to TNF inhibitors. Summary of results from the US Corrona RA Registry A3921205: The rates of MACE were higher in patients 65 and older than in patients younger than 65 in both Tofacitinib and bDMARD initiator groups, with overlapping 95% CIs. The rate of MACE in patients 65 and older in Tofacitinib initiators was 1.23 (95%CI=0.56, 2.34) and the rate in bDMARD initiators was 1.43 (95% CI=1.06, 1.89); the 95% CI overlapped.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Section 4.4. SmPC Section 5.1. <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)

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Table 2. Summary of Important Risks and Missing Information

Important Potential Risk: GI perforation	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Patients with painful inflammation of small pockets in the lining of the intestine (diverticulitis) or patients who also take nonsteroidal anti-inflammatory drugs or corticosteroids (eg, prednisone) may be at higher risk.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years. •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Potential Risk: ILD	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Patients living in Asian countries.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register

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Table 2. Summary of Important Risks and Missing Information

Important Potential Risk: PML	
Evidence for linking the risk to the medicine	PML has been reported in some patients taking other medications that depress the immune system.
Risk factors and risk groups	Patients taking other medications along with Tofacitinib that also depress the immune system.
Risk minimisation measures	Routine risk communication: Not applicable Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years.
Important Potential Risk: All-cause mortality	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Mortality in patients treated with Tofacitinib was mainly due to cardiovascular events, infections, and malignancies. Risk factors/groups for serious infections include patients who are elderly or diabetic, patients that use drugs along with Tofacitinib that suppress the immune system (including corticosteroids), patients with low absolute lymphocyte counts, and patients from certain Asian countries. The risk of cardiovascular events in general is increased in the elderly population. Tofacitinib has been associated with increased cholesterol, high blood pressure (hypertension), and weight gain, which are known risk factors for cardiovascular events. The risk of malignancy (cancer) in general is increased in the elderly population. There are no known Tofacitinib-associated risk factors for malignancy (cancer). In Study A3921133, 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 increase in non-fatal MI, lung cancer, lymphoma, VTE, and NMSC was observed in patients treated with Tofacitinib compared to TNF inhibitor. Summary of results from the US Corrona RA Registry A3921205: The risk factors found to be associated with an increased risk of mortality events were in general similar among Tofacitinib initiators and bDMARD initiators with moderate-to-severe disease (such as history of hypertension, history of coronary artery disease, history of VTE, age 70+, age 60+). In patients aged 50 years and older with moderate-to-severe disease with at least one CV risk factor, the incidence rates (95% CI) were comparable among Tofacitinib initiators and bDMARD initiators.
Risk minimisation measures	Routine risk communication SmPC Section 4.4

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Table 2. Summary of Important Risks and Missing Information

	SmPC Section 5.1 <u>Additional risk minimisation measures:</u> Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (SWIBREG [A3921344] and UR-CARE [A3921352]) over 5 years •A3921347: A drug utilisation and active surveillance, post-authorisation study in the US using data from an administrative healthcare claims database (UC)
Important Potential Risk: Fractures	
Evidence for linking the risk to the medicine	Corrona RA registry Study A3921205 and Study A3921133
Risk factors and risk groups	Elderly patients, female patients, and patients with corticosteroid use.
Risk minimisation measures	<u>Routine risk communication</u> SmPC Section 4.4. <u>Additional risk minimisation measures:</u> None.
Additional pharmacovigilance activities	•Prospective, non-interventional active surveillance safety study using 4 European RA registries (ARTIS [A3921314], BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years. •Prospective, non-interventional active surveillance study using 2 European UC registries (Swedish National Quality Registry for Inflammatory Bowel Disease [SWIBREG] – A3921344, and the United Registries for Clinical Assessment and Research [UR-CARE] – A3921352), over 5 years. •A3921347: A drug utilization and active surveillance post-authorisation study in the US using data from an administrative health claims database (UC) •A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry •A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers •A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry

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Table 2. Summary of Important Risks and Missing Information

Important Potential Risk: Increased risk of AEs when Tofacitinib is administered in combination with MTX in RA or PsA patients	
Evidence for linking the risk to the medicine	Clinical trial data and post-marketing data.
Risk factors and risk groups	Subjects on Tofacitinib and methotrexate together may be at higher risk of developing adverse events.
Risk minimisation measures	Routine risk communication: SmPC Section 4.4. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Prescriber Brochure).
Additional pharmacovigilance activities	•Prospective, non-interventional active surveillance safety study using 3 European RA registries (BIOBADASER [A3921316], BSRBR [A3921312], and RABBIT [A3921317]) over at least 5 years (RA only).
Important Potential Risk: Primary viral infection following live vaccination	
Evidence for linking the risk to the medicine	A3921237 study report.
Risk factors and risk groups	In general, patients treated with medications that depress the immune system are at an increased risk of developing a viral infection after getting a live vaccine. This is possible when there is not enough time between live vaccination and starting the medication that depresses the immune system or with zoster vaccination, where the patients have not had chicken pox in the past.
Risk minimisation measures	Routine risk communication: SmPC Section 4.4. Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921427: Observational Study of Effectiveness and Safety of Recombinant Zoster Vaccine (Shingrix) in Moderately-to-Severely Active UC or RA Patients Treated with Tofacitinib (Xeljanz) in Real-World Clinical Care Settings
Missing Information: Effects on pregnancy and the foetus	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.3 and 4.6. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	None
Missing Information: Use in breastfeeding	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.3 and 4.6. Additional risk minimisation measures: Development of an educational programme including additional communication to both patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	None

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Table 2. Summary of Important Risks and Missing Information

Missing Information: Effect on vaccination efficacy and the use of live/attenuated vaccines	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. Additional risk minimisation measures: Development of an educational programme including additional communication to patients (Patient Alert Card) and prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	None
Missing Information: Use in patients with mild, moderate, or severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, and 5.2. Additional risk minimisation measures: Development of an educational programme including additional communication to prescribers (including Treatment Checklists, Prescriber Brochure).
Additional pharmacovigilance activities	•A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •A3921403: A drug utilisation study using French claims database (SNDS)
Missing Information: Use in patients with moderate or severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2 and 5.2. Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	None
Missing Information: Use in patients with evidence of hepatitis B or hepatitis C infection	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4. Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	None
Missing Information: Use in patients with malignancy	
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.4 Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	•A3921321: An EU-based drug utilisation study using electronic health care records (aRMM effectiveness assessment) •A3921403: A drug utilisation study using French claims database (SNDS)c
Missing Information: Long-term safety in pJIA patients and juvenile PsA patients (e.g., growth or development disturbances)	
Risk minimisation measures	Routine risk minimisation measures: None Additional risk minimisation measures: None proposed
Additional pharmacovigilance activities	•A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within BIKER and within the JuMBO Registry

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Table 2. Summary of Important Risks and Missing Information

	•A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register •A3921371: An Active Surveillance PASS of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the CARRA Registry •Study A3921145: A Long Term, Open Label Follow Up Study of Tofacitinib for Treatment of JIA

ARTIS = Anti-rheumatic Therapies in Sweden; BID = twice daily; BIKER = German Biologics in Pediatric Rheumatology Registry; BIOBADASER = Registro Español De Acontecimientos Adversos De Terapias Biológicas En Enfermedades Reumáticas; BSRBR = British Society for Rheumatology Biologics Register; CARRA = Childhood Arthritis and Rheumatology Research Alliance; CI = confidence interval; CV = cardiovascular; DMARD = disease-modifying anti-rheumatic drug; EU = European Union; Excl = excluding; IR = incidence rate; JIA = juvenile idiopathic arthritis; JuMBO = Juvenile Arthritis Methotrexate/Biologics long-term Observation; MI = myocardial infarction; NMSC = non-melanoma skin cancer; OI = opportunistic infection; PASS = post-authorisation safety studies; PE = pulmonary embolism; pJIA = polyarticular juvenile idiopathic arthritis; PML = progressive multifocal leukoencephalopathy; PRAC = Pharmacovigilance Risk Assessment Committee; PsA = psoriatic arthritis; RA = rheumatoid arthritis; RABBIT = Rheumatoide Arthritis: Beobachtung der Biologika-Therapie; RMM = risk minimisation measure; RMP = Risk Management Plan; SmPC = summary of product characteristics; SWIBREG = Swedish National Quality Registry for Inflammatory Bowel Disease; TNF = tumour necrosis factor; UC = ulcerative colitis; UR-CARE = United Registries for Clinical Assessment and Research; US = United States

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Tofacitinib.

II.C.2. Other Studies in Post-Authorisation Development Plan

- Category 3 (required additional pharmacovigilance activities): 17

  - Study A3921321 is an EU-based drug utilisation study using electronic health care records. The research question is: Is there evidence that prescribers in the EU are compliant with the recommendations and limitations for use described in the Tofacitinib aRMM materials? The primary objectives include 1. Describe the characteristics of patients treated with Tofacitinib, stratified by study country (i.e., Sweden, Hungary, the Netherlands and Germany) and indication (i.e., RA, PsA, and UC; off-label indications), in terms of demographics (e.g., age, sex) and comorbidities and prior and current medication use. 2. Evaluate prescribers' adherence to the Tofacitinib aRMMs, specifically compliance to the recommended posology per indication (average daily dose) and duration of use; compliance to patient screening and laboratory monitoring prior to and during Tofacitinib treatment; and compliance to recommendations for limitations of use, including use in patients with VTE risk factors, use in patients aged 65 years and older, use in patients with CV risk factors, use in patients with malignancy risk factors, contraindicated use, and use with concomitant medications not compatible with Tofacitinib. The secondary objectives are to 1. Describe prescribing patterns over time; and 2. To describe changes in the utilisation of Tofacitinib following the updated recommendations and limitations for use implemented after the 2019 Article 20 referral and the 2021 signal evaluation procedure, specifically: use in

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patients with VTE risk factors; use in the elderly (patients aged 65 years and older), use in patients with CV risk factors, and use in patients with malignancy risk factors.

- Study A3921314 is a prospective, non-interventional active surveillance study embedded within the ARTIS registry. This study is being conducted to describe safety outcomes among RA patients treated with Tofacitinib and other new advanced targeted therapies in real-world clinical use in ARTIS (Sweden). It will address the concerns of venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk (excl MI) [specifically MACE], MI, GI perforation, PML, all-cause mortality, fractures, higher incidence of AEs in elderly patients (≥65 years) including infections.

- Study A3921312 is a prospective, non-interventional active surveillance study embedded within the BSRBR registry. This study is being conducted to describe safety outcomes among RA patients treated with Tofacitinib versus other new advanced targeted therapies in real-wold clinical use in BSRBR (UK). It will address the concerns of venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk (excl MI) [specifically MACE], MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with Tofacitinib in combination use of MTX, higher incidence of AEs in elderly patients (≥65 years) including infections.

- Study A3921317 is a prospective, non-interventional active surveillance study embedded within the RABBIT registry. This study is being conducted to describe safety outcomes among RA patients treated with Tofacitinib versus other new advanced targeted therapies in real-wold clinical use in RABBIT (German). It will address the concerns of venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk (excl MI) [specifically MACE], MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with Tofacitinib in combination use of MTX, higher incidence and severity of AEs in elderly patients (≥65 years) including infections.

- Study A3921316 is a prospective, non-interventional active surveillance study embedded within the BIOBADASER registry. This study is being conducted to describe safety outcomes among RA patients treated with Tofacitinib versus other new advanced targeted therapies in real-wold clinical use in BIOBADASER (Spain). It will address the concerns of venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), CV risk (excl MI) [specifically MACE], MI, GI perforation, PML, all-cause mortality, fractures, increased risk of AEs in patients treated with Tofacitinib in combination use of MTX, higher incidence of AEs in elderly patients (≥65 years) including infections.

- Study A3921344 and Study A3921352 are prospective, non-interventional active surveillance studies in 2 European UC registries (SWIBREG and UR-CARE, respectively) over at least 5 years to further understand and characterise the safety profile of Tofacitinib within the clinical practice setting. Safety concerns addressed

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include venous thromboembolism (deep vein thrombosis and pulmonary embolism), serious infections, HZ reactivation, NMSC, malignancy (including lymphoma and lung cancer), cardiovascular risk (excl MI) [specifically MACE], MI, GI perforation, PML, all-cause mortality, fractures, higher incidence and severity of adverse events in elderly patients (≥65 years) including infections. Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.

- Study A3921347 is a drug utilisation and active surveillance, post-authorisation study in the US, to assess Tofacitinib utilisation patterns in the US and to characterise the safety of Tofacitinib use in patients with moderately to severely active UC in the real-world setting using data from a US administrative healthcare claims database. Safety concerns for the active surveillance portion of the study include venous thromboembolism (deep vein thrombosis and pulmonary embolism), in-hospital mortality, fractures, malignancies (including lymphoma and lung cancer), opportunistic and serious infections, herpes zoster, major adverse cardiovascular endpoints, MI, and gastrointestinal perforations. Safety outcomes with 10 mg BID dose during maintenance will be evaluated in a separate sub-analysis.

- A3921427: Observational Study of Effectiveness and Safety of Recombinant Zoster Vaccine (Shingrix) in Moderately-to-Severely Active UC or RA Patients Treated with Tofacitinib (Xeljanz) in Real-World Clinical Care Settings. This study will address safety outcomes following vaccination with recombinant adjuvanted zoster vaccine. .

- Study A3921407: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the German Biologics in Pediatric Rheumatology Registry (BIKER) and the Juvenile Arthritis Methotrexate/Biologics long-term Observation [JuMBO] registryA3921407. This study is a planned study in the EU that will help to contextualise the rates of safety events [venous thromboembolism, serious infections and other important infections (including opportunistic infection, tuberculosis and vaccine preventable infections), all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer, GI perforations, major adverse cardiac events (including MI), long-term safety in pJIA patients and juvenile PsA patients (for example, growth or development disturbances), PML, hypersensitivity, all-cause mortality, fractures, HZ reactivation, NMSC, and ILD observed among Tofacitinib-treated pJIA patients and juvenile PsA patients. To assess long-term safety, a minimum of 5 years follow-up is planned.

- Study A3921408: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA Using Nationwide Swedish HealthCare Registers. This study will help to contextualise the rates of safety events [venous thromboembolism, serious infections and other important infections (including opportunistic infection, tuberculosis), all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer, GI perforations, major cardiac adverse events (including MI), long-term safety in pJIA patients and juvenile PsA patients [PML, all-cause mortality, fractures, HZ reactivation, NMSC, and ILD] observed among Tofacitinib-

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treated pJIA patients and juvenile PsA patients. To assess long-term safety, a minimum of 5 years follow-up is planned.

- Study A3921409: Post-Authorisation Active Safety Surveillance Program Among Patients Treated with Tofacitinib for Polyarticular Juvenile Idiopathic Arthritis and Juvenile PsA within the UK JIA Biologics Register. This study will help to contextualise the rates of safety events [venous thromboembolism, serious infections and other important infections (including opportunistic infections, tuberculosis and vaccine preventable infections), all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer, GI perforations, major cardiac adverse events (including MI), long-term safety in pJIA patients and juvenile PsA patients [for example, growth or development disturbances], hypersensitivity, PML, all-cause mortality, fractures, HZ reactivation, NMSC, and ILD observed among Tofacitinib-treated pJIA patients and juvenile PsA patients. To assess long-term safety, a minimum of 5 years follow-up is planned.

- Study A3921371: An Active Surveillance Post-Authorisation Safety Study (PASS) of Safety Events of Special Interest Among Patients in the United States Treated with Tofacitinib for Juvenile Idiopathic Arthritis Within the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry: this planned study is a long-term observational safety study to evaluate the risk of all malignancies combined (excluding nonmelanoma skin cancer), lymphoma, lung cancer, major cardiac adverse events (including MI), serious infections (including opportunistic infections), venous thromboembolism, fractures, and long-term safety in pJIA patients (for example, growth or development disturbances) in the US.

- Study A3921145 (A Long Term, Open Label Follow Up Study of Tofacitinib for Treatment of JIA) is an on-going Phase 2/3 study being conducted to address long-term safety and tolerability in pJIA and juvenile PsA patients (e.g., growth or development disturbances). This study will also evaluate the persistence of efficacy of Tofacitinib for treatment of the signs and symptoms of JIA.

- Study A3921403: A Post-Authorisation Safety Study of the Utilisation and Prescribing Patterns of Xeljanz (Tofacitinib) Using an Administrative Healthcare Database in France. This is a drug utilisation study that complements Study A3921321 to assess the effectiveness of aRMMs using secondary data. Safety concerns include venous thromboembolic events (eg, use of Tofacitinib in patients with VTE risk factors), patients with mild, moderate, or severe hepatic impairment, MI (eg, use of Tofacitinib patients with cardiovascular risk factors), and use in patients with malignancy risk factors.

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