

▼ Xeljanz (tofacitinib): increased risk of major adverse cardiovascular events and malignancies with use of tofacitinib relative to TNF-alpha inhibitors

Dear Healthcare Professional,

Pfizer Europe MA EEIG in agreement with the European Medicines Agency (EMA) and the <National Competent Authority> would like to inform you of the following:

Summary

- **In the completed clinical trial (A3921133) in patients with rheumatoid arthritis (RA) who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarction was observed with tofacitinib compared to TNF-alpha inhibitors.**
- **The study also showed an increased incidence of malignancies excluding NMSC, particularly lung cancer and lymphoma, with tofacitinib compared to TNF-alpha inhibitors.**
- **Tofacitinib should only be used in patients over 65 years of age, in patients who are current or past smokers, patients with other cardiovascular risk factors, and patients with other malignancy risk factors if no suitable treatment alternatives are available.**
- **Prescribers should discuss with the patients the risks associated with the use of Xeljanz, including myocardial infarction, lung cancer and lymphoma.**

Background on the safety concern

Tofacitinib is a JAK-inhibitor and indicated as treatment for

- adult patients with moderate to severe rheumatoid arthritis (RA) or active psoriatic arthritis (PsA) in patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs.
- adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

In March 2021, a communication was sent to healthcare professionals in writing, informing them that data from a completed clinical trial (A3921133) in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, suggest a higher risk of major adverse cardiovascular events (MACE) and malignancies (excluding non-melanoma skin cancer (NMSC)) with tofacitinib as compared to patients treated with a TNF-alpha inhibitor.

Following the finalization of a review procedure of these data by EMA, recommendations have been adopted as specified in the "summary" above. The product information of Xeljanz and the educational materials for healthcare professional and patients will be updated accordingly.

Long-term safety study A3921133 in patients with RA

Study ORAL Surveillance (A3921133) was a large (N=4,362) randomized active-controlled clinical trial to evaluate the safety of tofacitinib at two doses (5 mg twice daily and 10 mg twice daily) versus a tumour necrosis factor alpha inhibitor (TNF-alpha inhibitors) in subjects with RA who were 50 years of age or older and had at least one additional cardiovascular risk factor (defined in the protocol as current cigarette smoker, high blood pressure, high-density lipoprotein [HDL] <40 mg/dL, diabetes mellitus, history of coronary artery disease, family history of premature coronary heart disease, extraarticular RA disease), some of which are also known risk factors for malignancy.

The co-primary endpoints of this study were adjudicated MACE and adjudicated malignancies (excluding NMSC). The study was an event-powered study that also required at least 1500 patients to be followed for 3 years. Prespecified non-inferiority criteria were not met for these co-primary endpoints and the clinical trial could not demonstrate tofacitinib is non-inferior to ("not worse than") TNF-alpha inhibitors. Results suggest that these risks are associated with both approved dosage/dosing regimens (5 mg twice daily, and 10 mg twice daily which is approved only in UC).

MACE (including myocardial infarction)

An increase in non-fatal myocardial infarction was observed in patients treated with tofacitinib compared to TNF-alpha inhibitor.

Incidence rate and hazard ratio for MACE and myocardial infarction

	Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily^a	All Tofacitinib^b	TNF inhibitor
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)	

^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.

Abbreviations: MACE = major adverse cardiovascular events, MI = myocardial infarction, 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 \geq 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).

Malignancies excluding NMSC (including lung cancer and lymphoma)

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

Incidence rate and hazard ratio for malignancies excluding NMSC^a

	Tofacitinib 5 mg twice daily	Tofacitinib 10 mg twice daily^b	All Tofacitinib^c	TNF inhibitor
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)	

^a Based on events occurring on treatment or after treatment discontinuation up to the end of the study. ^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 \geq 65 years and current or past smoking.

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	XELJANZ/tofacitinib 5 mg film-coated tablets XELJANZ/tofacitinib 10 mg film-coated tablets XELJANZ/tofacitinib 11 mg prolonged-release tablets
Marketing authorisation holder(s)	Pfizer Europe MA EEIG
Safety concern and purpose of the communication	Increased risk of MACE (including myocardial infarction) and malignancies (excluding NMSC), including lung cancer and lymphoma, with use of tofacitinib relative to TNF-alpha inhibitor
DHPC recipients	Rheumatologists and Gastroenterologists Additional healthcare professionals such as internists, orthopaedics, specialized primary care physicians and hospital pharmacists may also be notified in individual Member States during national implementation depending on health care systems.
Member States where the DHPC will be distributed	All EU Member States where Xeljanz is marketed.
Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	Thu 10 Jun 2021
DHPC and communication plan (in English) agreed by CHMP	Thu 24 Jun 2021
Submission of translated DHPCs to the national competent authorities for review	Tue 29 Jun 2021
Agreement of translations by national competent authorities	Thu 01 Jul 2021
Dissemination of DHPC	Tue 06 Jul 2021