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SAUDI ARABIA

Direct Healthcare Professional Communication (DHPC)

March 07, 2022

IMPORTANT DRUG WARNING - Risk of Major Adverse Cardiovascular Events and Malignancies (Excluding NMSC) with Use of XELJANZ/XELJANZ XR (tofacitinib) Relative to TNFi Therapy

Dear Healthcare Provider,
Pfizer in agreement with the Saudi Food and Drug Authority would like to inform you of important safety information for XELJANZ/XELJANZ XR (tofacitinib).

Summary:

- Healthcare providers should consider the benefits and risks of Xeljanz when deciding whether to prescribe or continue patients on Xeljanz.
- 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 MACE particularly 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 active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.
- 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.
- 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 DMARDs.

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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.

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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 ≥ 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.

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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				
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 ≥ 65 years and current or past smoking.

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Reporting Adverse Events

Healthcare providers and patients are encouraged to report adverse events in patients taking XELJANZ/XELJANZ XR to:

The National Pharmacovigilance Centre (NPC) at Saudi Food and Drug Authority (SFDA)
SFDA Call Center: 19999
Toll Free Phone: 8002490000
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa/

Pharmacovigilance Department in the company
E-mail: SAU.AEReporting@pfizer.com

This letter is not intended as a complete description of the benefits and risks of XELJANZ/XELJANZ XR. The full Prescribing Information and Medication Guide should be consulted for further information.
For more information, please see the Xeljanz local full prescribing information enclosed or contact Pfizer Medical Information via: MedInfoMEandAfrica@pfizer.com
https://pmiform.com/HCP/MID-EAST

Sincerely,

Bayan Darwesh, SMM
Senior Medical Manager ,Inflammation and Immunology

Pfizer Saudi Limited

Bayan Darwesh