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SAUDI ARABIA

Direct Healthcare Professional Communication (DHPC)

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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), which is approved for adults with moderately to severely active rheumatoid arthritis (RA), active psoriatic arthritis (PsA), and moderately to severely active ulcerative colitis (UC).

Summary:

Based on co-primary endpoint results from the recently completed post-marketing required safety clinical trial ORAL Surveillance (A3921133; NCT02092467), major adverse cardiovascular events (MACE) has been identified as a new important potential risk and malignancies (excluding non-melanoma skin cancer (NMSC)) remains an important potential risk.

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

Background on the safety concern:

ORAL Surveillance (A3921133) is a randomized active-controlled clinical trial. The primary objective of this clinical trial was to evaluate the safety of XELJANZ at two doses (5 mg twice daily and 10 mg twice daily) versus a tumor necrosis factor inhibitor (TNFi) in subjects with rheumatoid arthritis 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). Results showed for these co-primary endpoints, prespecified non-inferiority criteria were not met, and the clinical trial could not demonstrate tofacitinib is non-inferior to ("not worse than") TNFi. 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).

This clinical trial required at least 1500 subjects to be followed for three years and a targeted number of MACE and malignancies (excluding NMSC) to be observed before it could be declared complete. In total, 4,362 subjects received study treatments. The primary analyses included 135 subjects with adjudicated MACE and 164 subjects with adjudicated malignancies (excluding NMSC). For tofacitinib, MACE has been identified as a new important potential risk.

The most frequently reported MACE was myocardial infarction. Malignancies (excluding NMSC) remains an important potential risk. The most frequently reported malignancy (excluding NMSC) was lung cancer. In those subjects with a higher prevalence of known risk factors for MACE and malignancy (e.g., older age, smoking), a higher occurrence of events was seen across all treatment groups.

*Adjudicated MACE**

	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID****	**Tofacitinib Doses Combined**	**TNFi**
Total number of subjects	1455	1456	2911	1451
Number of subjects with first event within the risk period*** (%)	47 (3.23)	51 (3.50)	98 (3.37)	37 (2.55)
Person-years	5166.32	4871.96	10038.28	5045.27
IR (95% CI) (number of subjects with event/100 person-years)	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) for tofacitinib vs TNFi	1.24 (0.81, 1.91)	1.43 (0.94, 2.18)	1.33 (0.91, 1.94)****	

(*) Based on Cox proportional hazard model
(**)The 10 mg BID treatment group includes patients that were switched from 10 mg BID to 5 mg BID as a result of a study modification in February 2019.
(***) The risk period was from start of therapy up to 60 days past last dose.
(****) The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNFi since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8, ie, 1.94 >1.8.

*Adjudicated Malignancies Excluding NMSC**

	Tofacitinib 5 mg BID	**Tofacitinib 10 mg BID****	**Tofacitinib Doses Combined**	**TNFi**
Total number of subjects	1455	1456	2911	1451
Number of subjects with first event within the risk period*** (%)	62 (4.26)	60 (4.12)	122 (4.19)	42 (2.89)
Person-years	5491.48	5311.71	10803.19	5482.30
IR (95% CI) (number of subjects with event/100 person-years)	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) for tofacitinib vs TNFi	1.47 (1.00, 2.18)	1.48 (1.00, 2.19)	1.48 (1.04, 2.09)****	

(*) Based on Cox proportional hazard model
(**)The 10 mg BID treatment group includes patients that were switched from 10 mg BID to 5 mg BID as a result of a study modification in February 2019.
(***) The risk period included all available follow-up regardless of treatment exposure.
(****) The non-inferiority criterion was not met for the primary comparison of the combined tofacitinib doses to TNFi since the upper limit of the 95% CI exceeded the pre-specified non-inferiority criterion of 1.8, ie, 2.09 >1.8.

Pfizer is working with the SFDA and other regulatory agencies to review the full results and analyses as they become available. In addition, Pfizer is conducting additional analyses to further identify any risk factors that might have contributed to the increased risk, which will inform the need for any additional risk mitigation measures.

Recommendations to Healthcare Professionals

- Consider the benefits and risks of XELJANZ/XELJANZ XR when deciding whether to prescribe or continue patients on the medicine.
- Counsel patients about the risks and benefits of XELJANZ/XELJANZ XR.
- Advise patients that they should not stop taking XELJANZ/XELJANZ XR without first consulting their healthcare professional and to talk to their healthcare professional if they have questions or concerns.
- Continue to follow the recommendations in the XELJANZ/XELJANZ XR prescribing information.

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,

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Pfizer Saudi Limited