February 24, 2021

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

Audience

Healthcare professionals including rheumatologists, internists, gastroenterologists, dermatologists, family physicians, general practitioners, and pharmacists.

Dear Health Care Professionals,

The purpose of this letter is to inform you of important safety information for:

- XELJANZ and XELJANZ XR (tofacitinib) approved for adults with moderately to severely active rheumatoid arthritis (RA),
  and
- XELJANZ approved for active psoriatic arthritis (PsA) and moderately to severely active ulcerative colitis (UC)

Please refer to the current approved Product Monograph for complete information on INDICATIONS AND CLINICAL USE.

Information regarding 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

On January 27, 2021, Pfizer announced co-primary endpoint results from ORAL Surveillance; please see press release at www.pfizer.com/news/press-release/press-release-detail/pfizer-shares-co-primary-endpoint-results-post-marketing. 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 XELJANZ is non-inferior to ("not worse than") TNFi. Topline 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.

On February 4, 2021, the United States Food and Drug Administration (FDA) issued a Drug Safety Communication (DSC) about these preliminary results; please see DSC at www.fda.gov/drugs/drug-safety-and-availability/initial-safety-trial-results-find-increased-risk-serious-heart-related-problems-and-cancer-arthritis. In its announcement, FDA noted:

> The U.S. Food and Drug Administration (FDA) is alerting the public that preliminary results from a safety clinical trial show an increased risk of serious heart-related problems and cancer with the arthritis and ulcerative colitis medicine Xeljanz, Xeljanz XR (tofacitinib) compared to another type of medicine called tumor necrosis factor (TNF) inhibitors. FDA required the safety trial, which also investigated other potential risks including blood clots in the lungs and death. Those final results are not yet available.
>
> We will evaluate the clinical trial results we have received to date and will work with the drug manufacturer to obtain further information as soon as possible. We will communicate our final conclusions and recommendations when we have completed our review or have more information to share.
>
> Patients should not stop taking tofacitinib without first consulting with your health care professionals, as doing so may worsen your condition. Talk to your health care professionals if you have any questions or concerns.
>
> Health care professionals should consider the benefits and risks of tofacitinib when deciding whether to prescribe or continue patients on the medicine. Continue to follow the recommendations in the tofacitinib prescribing information.

Pfizer is working with the FDA, Health Canada, 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.

Information for 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 Product Monograph.

This letter is not intended as a complete description of the benefits and risks of XELJANZ/XELJANZ XR. The Product Monograph and the Consumer Information should be consulted for further information. It is available at https://www.pfizer.ca/xeljanz-tofacitinib.

Patient safety is of the utmost importance to Pfizer and the company continually monitors the safety of its medicines. We wanted you to be aware of this important safety information so that you can consider it when counseling your patients on the use of XELJANZ/XELJANZ XR.

Report health or safety concerns:

Managing marketed health product-related side effects depends on health care professionals and consumers reporting them. Any case of serious or unexpected side effects in patients receiving XELJANZ/XELJANZ XR should be reported to Pfizer Canada ULC or Health Canada.

Pfizer Canada ULC
17300 Trans-Canada Highway
Kirkland, QC
H9J 2M5
Telephone: 1-866-723-7111
Fax: 1-855-242-5652

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Calling toll-free at 1-866-234-2345; or
- Visiting MedEffect™ Canada's Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax.

If you have any questions or would like additional information, please call Pfizer Medical Information at 1-800-463-6001.

Sincerely,

DocuSigned by:
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Vratislav Hadrava M.D., Ph.D.
Vice President & Medical Director
Pfizer Canada ULC