Important Safety Update on XELJANZ®/XELJANZ® XR (tofacitinib) – Risk of Major Adverse Cardiovascular Events, Malignancy, Thrombosis and Infection

2022/01/12

Audience
Healthcare professionals including rheumatologists, internists, gastroenterologists, dermatologists, cardiologists, oncologists, family physicians, general practitioners, allergists/immunologists, and pharmacists.

Key messages

- **In a post-authorization safety study, major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, were observed more frequently with XELJANZ (tofacitinib) (5 mg BID or 10 mg BID) compared to tumour necrosis factor inhibitors (TNFi) in rheumatoid arthritis (RA) patients who were 50 years of age or older with at least one additional cardiovascular (CV) risk factor.**
- **The safety study also observed malignancies, including lung cancer and lymphoma, more frequently with XELJANZ (5 mg BID or 10 mg BID) compared with TNFi in RA patients who were 50 years of age or older with at least one additional CV risk factor.**
- **Patients treated with XELJANZ 10 mg BID also had a higher rate of all-cause mortality including sudden CV death, thrombosis and serious infections, compared to those treated with XELJANZ 5 mg given BID or TNFi.**
- **Healthcare professionals are advised to:**
  - **Avoid XELJANZ/XELJANZ XR in patients who may be at increased risk of thrombosis.**
  - **Use XELJANZ/XELJANZ XR with caution in older patients, especially geriatric patients (above 65 years of age), patients who are current or past smokers, and patients with other CV or malignancy risk factors.**
  - **Use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response in patients with ulcerative colitis (UC).**
  - **Closely monitor patients for signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR.**
- **To ensure the benefits outweigh the risks in patients receiving XELJANZ/XELJANZ XR, the approved use in RA is now limited to**

certain patients who have had an inadequate response or intolerance to methotrexate (MTX) and one or more disease-modifying anti-rheumatic drugs (DMARDs). The Canadian Product Monograph (CPM) for XELJANZ/XELJANZ XR has been updated to include the risks of MACE and malignancies under the *Serious Warnings and Precautions* section.

Issue
A post-authorization safety study in RA patients 50 years of age or older with at least one additional CV risk factor showed an increased risk of MACE and malignancy in patients treated with XELJANZ (5 mg BID or 10 mg BID) in comparison to TNFi. An increased risk of thrombosis was observed with XELJANZ 10 mg BID compared to TNFi.

Products affected
XELJANZ (tofacitinib), 5 mg and 10 mg tablets
XELJANZ XR (tofacitinib), 11 mg extended-release tablets

Background information
On April 6, 2021, Health Canada announced that it was conducting a safety review of XELJANZ/XELJANZ XR after an increased risk of MACE and malignancy was discovered during the post-authorization clinical trial A3921133. This clinical trial investigated the long-term safety of XELJANZ at 2 doses (5 mg twice a day and 10 mg twice a day) in patients with RA, who were 50 years of age or older and had at least one additional CV risk factor.

Health Canada has completed the safety review of this data and found that patients treated with XELJANZ (5 mg BID or 10 mg BID), compared to TNFi, had an increased risk of MACE and malignancy. In addition, patients who were treated with XELJANZ 10 mg BID had a higher rate of all-cause mortality including sudden CV death, thrombosis and serious infections, compared to those treated with XELJANZ 5 mg BID or TNFi. To address these safety concerns, Health Canada has worked with Pfizer Canada ULC to update the XELJANZ/XELJANZ XR CPM to include these risks. As well, the indication for RA has been revised (see bolded, updated text below).

XELJANZ/XELJANZ XR has received market authorization in Canada for the following indications :

Rheumatoid Arthritis
XELJANZ/XELJANZ XR, in combination with MTX, is indicated for reducing the signs and symptoms of RA in adult patients with moderately to severely active RA who have had an inadequate response to MTX **and to one or more DMARDs**. In cases of intolerance to MTX **and other DMARDs**, physicians may consider the use of XELJANZ/XELJANZ XR as monotherapy. The use of XELJANZ/XELJANZ XR in combination with biological DMARDs (bDMARDs) or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Psoriatic Arthritis
XELJANZ, in combination with MTX or another conventional synthetic DMARD, is indicated for reducing the signs and symptoms of psoriatic arthritis (PsA) in adult patients with active PsA when the response to previous DMARD therapy has been inadequate. The use of XELJANZ in combination with bDMARDs or potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Ulcerative Colitis
XELJANZ is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) with an inadequate response, loss of response or intolerance to either conventional UC therapy or a tumor necrosis factor alpha inhibitor. The use of XELJANZ in combination with biological UC therapies or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

Information for consumers
XELJANZ/XELJANZ XR (tofacitinib) is used to treat adults with moderate to severe active inflammation of the joints (rheumatoid arthritis), active inflammation of the joints with scaly dry patches formed on the skin (psoriatic arthritis), or moderate to severe active inflammation of the colon and rectum (ulcerative colitis), when other medicines do not work. It is generally prescribed in combination with other drugs, such as methotrexate.

Serious heart-related problems (heart attack, stroke or cardiovascular death) and cancer have been reported in rheumatoid arthritis patients treated with XELJANZ/XELJANZ XR.

Consumers are advised to:

- Talk to your healthcare professional about possible heart disease risk factors before you take XELJANZ/XELJANZ XR.
- Contact your healthcare professional right away and stop taking XELJANZ/XELJANZ XR if you develop signs and symptoms of a heart problem. Symptoms may include:
    - new or worsening chest pain;
    - shortness of breath;
    - irregular heartbeats; or
    - swelling of the legs.
- Talk to your healthcare professional if you have or had any type of cancer before you take XELJANZ/XELJANZ XR.
- Be aware that blood clots in the veins of your legs or arms (deep vein thrombosis, DVT), arteries (arterial thrombosis) or lungs (pulmonary embolism, PE) can happen in some people taking XELJANZ/XELJANZ XR. This may be life-threatening and cause death.
- Stop taking XELJANZ/XELJANZ XR and seek immediate medical help if you develop any signs or symptoms of a blood clot in your leg or arm (such as swelling, pain or tenderness in the leg or arm) or in your lung (such as sudden unexplained chest pain or shortness of breath).

- Contact your healthcare professional if you have any signs or symptoms of an infection (such as fever, sweating, chills, cough, etc.). If a serious infection develops, stop taking XELJANZ/XELJANZ XR and contact your healthcare professional right away.

Patients should contact their healthcare professional for more details on this new safety information.

Information for healthcare professionals
Healthcare professionals are advised to:

- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with XELJANZ/XELJANZ XR, particularly in geriatric patients, in patients who are current or past smokers, those with other cardiovascular or malignancy risk factors, those who develop a malignancy, and those with a known malignancy.
- Inform patients that XELJANZ/XELJANZ XR may increase their risk of MACE including non-fatal myocardial infarction. Instruct all patients, especially geriatric patients, current or past smokers, or patients with other cardiovascular risk factors, to be alert for signs and symptoms of cardiovascular events.
- Inform patients that XELJANZ/XELJANZ XR may increase their risk of certain cancers, and that lung cancer, lymphoma and other cancers have been observed in patients taking XELJANZ. Instruct patients to inform their healthcare provider if they have ever had any type of cancer.
- Advise patients to stop taking XELJANZ/XELJANZ XR and to call their healthcare provider right away if they experience any symptoms of thrombosis (sudden shortness of breath, chest pain worsened with breathing, swelling of leg or arm, leg pain or tenderness, red or discoloured skin in the affected leg or arm). Avoid XELJANZ/XELJANZ XR in patients who may be at increased risk of thrombosis.
- Use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response in patients with UC.
- Use XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily for the treatment of RA and XELJANZ 5 mg twice daily for the treatment of PsA.
- Closely monitor patients for signs and symptoms of infection during and after treatment with XELJANZ/XELJANZ XR. XELJANZ/XELJANZ XR should be interrupted if a patient develops a serious infection, an opportunistic infection, or sepsis. If a patient develops a new infection during treatment with XELJANZ/XELJANZ XR, they should undergo prompt and complete diagnostic testing appropriate for an immunocompromised patient, and appropriate antimicrobial therapy should be initiated**.**
- Ensure the benefits outweigh the risks in patients taking XELJANZ/XELJANZ XR. The approved use in RA is now limited to certain patients who have had an inadequate response or intolerance to MTX and one or more DMARDs.

Action taken by Health Canada
Health Canada has worked with Pfizer Canada ULC to update the Canadian Product Monograph (CPM) for XELJANZ/ XELJANZ XR. Health Canada is communicating this important safety information to healthcare professionals and Canadians via the Recalls and Safety Alerts Database on the Healthy Canadians Web Site. This communication update will be further distributed through the MedEffect™ e-Notice email notification system, as well as through social media channels, including LinkedIn and Twitter.

Report health or safety concerns
Health Canada's ability to monitor the safety of marketed health products depends on healthcare professionals and consumers reporting adverse reactions and medical device incidents. 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.

For other health product inquiries related to this communication, contact Health Canada at:

Marketed Health Product Directorate
E-mail: hc.mhpd-dpsc.sc@hc-sc.gc.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Sincerely,

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Pfizer Canada ULC