# Important Safety Update on XELJANZ® / XELJANZ® XR (tofacitinib) – Risk of Thrombosis

2019/12/02

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

**Key messages**

- **An increased incidence rate of thrombosis, including pulmonary embolism, deep vein thrombosis, and arterial thrombosis was observed in patients treated with XELJANZ (tofacitinib) in a large, ongoing post-marketing study.**
- **The study showed that patients with rheumatoid arthritis and at least one cardiovascular risk factor should not have their dose doubled given the risk of thrombosis.**
- **Healthcare professionals are advised to:**
  - **Avoid XELJANZ / XELJANZ XR in patients at risk of thrombosis.**
  - **Use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve / maintain therapeutic response in patients with ulcerative colitis (UC).**
  - **Use XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily for the treatment of rheumatoid arthritis (RA), and XELJANZ 5 mg twice daily for the treatment of psoriatic arthritis (PsA).**
  - **Monitor for signs and symptoms of thrombosis including deep vein thrombosis, arterial thrombosis, and pulmonary embolism in patients who are taking XELJANZ / XELJANZ XR. If symptoms of these conditions develop, discontinue XELJANZ / XELJANZ XR and promptly evaluate the patient.**
- **The Canadian Product Monograph (CPM) for XELJANZ / XELJANZ XR has been updated to include this new warning with regards to thrombosis under *Serious Warnings and Precautions*.**

**Issue**
An increased incidence of thrombosis, including pulmonary embolism, deep venous thrombosis, and arterial thrombosis, was observed in patients treated with XELJANZ in a large, ongoing post-marketing study. The Canadian Product Monograph (CPM)

of XELJANZ/XELJANZ XR has recently been updated regarding the risks of thrombosis and the use of XELJANZ/XELJANZ XR.

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

**Background information**
In a large, ongoing post-marketing study (Study A3921133), thrombosis, including pulmonary embolism, deep vein thrombosis and arterial thrombosis, was observed at an increased incidence in patients with rheumatoid arthritis. The study showed that rheumatoid arthritis patients aged 50 years or older with at least one cardiovascular (CV) risk factor had a higher rate of all-cause mortality, including sudden CV death, and thrombosis when a 10 mg twice daily dose of XELJANZ was used compared to those treated with XELJANZ 5 mg given twice a day or TNF blockers.

On March 15, 2019, Health Canada announced that it was conducting a safety review after issues were discovered during this ongoing clinical trial. Health Canada has reviewed interim data from this study. To address this safety concern, Health Canada has worked with Pfizer Canada ULC to update the XELJANZ/XELJANZ XR Canadian Product Monograph (CPM). The increased risk of thrombosis has been included in the *Serious Warnings and Precautions Box* of the XELJANZ/XELJANZ XR CPM. The *Adverse Reactions* and *Consumer Information* sections in the CPM have also been updated in relation to this issue.

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

***Rheumatoid Arthritis***
XELJANZ/XELJANZ XR, in combination with methotrexate (MTX), is indicated for reducing the signs and symptoms of rheumatoid arthritis (RA) in adult patients with moderately to severely active RA who have had an inadequate response to MTX. In cases of intolerance to MTX, physicians may consider the use of XELJANZ/XELJANZ XR as monotherapy.

***Psoriatic Arthritis***
XELJANZ, in combination with methotrexate (MTX) or another conventional synthetic disease-modifying antirheumatic drug (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 biological disease-modifying anti-rheumatic drugs (bDMARDs) or 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.

Blood clots in the veins of the legs or arms (deep vein thrombosis, or DVT), arteries (arterial thrombosis) or lungs (pulmonary embolism, PE) have been reported in patients taking XELJANZ/XELJANZ XR. This may be life-threatening and may cause death.

Before taking XELJANZ/XELJANZ XR, patients should tell their healthcare professional if they:

- have had blood clots in the legs (deep vein thrombosis) or lungs (pulmonary embolism) or have been told they are at risk of blood clots;
- have problems with their blood clotting (thrombophilia);
- have chest pain (angina pectoris); or
- have heart failure or any heart problems.

Patients taking XELJANZ or XELJANZ XR who develop any signs or symptoms of a blood clot in their leg (such as swelling, pain or tenderness in legs) or in their lung (such as sudden unexplained chest pain or shortness of breath) should stop taking the medication and seek immediate medical help.

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

**Information for healthcare professionals**

Healthcare professionals are advised to:

- Avoid XELJANZ/XELJANZ XR in patients at risk of thrombosis.
- Use XELJANZ at the lowest effective dose and for the shortest duration needed to achieve/maintain therapeutic response in patients with ulcerative colitis (UC).
- Use XELJANZ 5 mg twice daily or XELJANZ XR 11 mg once daily for the treatment of rheumatoid arthritis (RA), and XELJANZ 5 mg twice daily for the treatment of psoriatic arthritis (PsA).
- Monitor for signs and symptoms of thrombosis including deep vein thrombosis, arterial thrombosis, and pulmonary embolism in patients who are taking XELJANZ/XELJANZ XR. If symptoms of deep vein thrombosis, arterial thrombosis, or pulmonary embolism develop, discontinue XELJANZ/XELJANZ XR and promptly evaluate the patient.
- Inform patients about the thrombosis risk with XELJANZ/XELJANZ XR and advise them to seek medical attention immediately if they experience the symptoms listed above.

**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 (https://healthycanadians.gc.ca/recall-alert-rappel-avis/index-eng.php). 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

**To correct your mailing address or fax number, contact Pfizer Canada.**

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@canada.ca
Telephone: 613-954-6522
Fax: 613-952-7738

Sincerely,

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