Important Safety Information on Janus Kinase Inhibitors [CIBINQO® (abrocitinib), INREBIC® (fedratinib), JAKAVI® (ruxolitinib), OLUMIANT® (baricitinib), RINVOQ® (upadacitinib), XELJANZ®/XELJANZ XR® (tofacitinib)] and the Risk of Major Adverse Cardiovascular Events, Thrombosis (Including Fatal Events) and Malignancy

2022/11/01

Audience

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

Key messages

- **Health Canada, in collaboration with Pfizer Canada ULC, previously communicated on the risks of major adverse cardiovascular events (MACE), thrombosis, malignancy, fatal events and serious infections with the Janus Kinase (JAK) inhibitor, XELJANZ/XELJANZ XR. The Canadian Product Monograph (CPM) for XELJANZ/XELJANZ XR was updated to reflect these risks.**
- **Preliminary results from a retrospective observational study suggest increased risks of MACE and thrombosis in patients with rheumatoid arthritis (RA) treated with OLUMIANT compared to tumour necrosis factor inhibitors (TNFi).**
- **Based on these safety findings and similar mechanisms of action, Health Canada cannot rule out the risks of MACE, thrombosis (including fatal events) and malignancies for other JAK inhibitors (CIBINQO, INREBIC, JAKAVI, OLUMIANT, and RINVOQ).**
- **As a precautionary measure, Health Canada is working with the manufacturers to update and align the information about these risks in the CPMs for JAK inhibitors.**
- **Healthcare professionals are advised to:**
  - **Consult the safety information in the CPM prior to initiating, or continuing, therapy with a JAK inhibitor.**
  - **Consider the benefits and risks of JAK inhibitors for the individual patient, particularly for geriatric patients (above 65 years of age), patients who are current or past smokers, patients with other cardiovascular (CV) or malignancy risk factors, patients with an underlying malignancy or those who develop a malignancy, and patients who may be at increased risk of thrombosis.**

Issue

The final results of a clinical trial conducted with XELJANZ showed higher risks of MACE, thrombosis, malignancy, serious infections and fatal events, compared to TNFi, a group of medicines that suppress the body's natural response to tumor necrosis factor (TNF), in RA patients. Furthermore, preliminary results from a retrospective observational study suggest OLUMIANT is associated with higher risks of MACE and thrombosis when compared to TNFi in RA patients.

Based on these safety findings and similar mechanisms of action, Health Canada cannot rule out the risks of MACE, thrombosis (including fatal events) and malignancies, for other JAK inhibitors (CIBINQO, INREBIC, JAKAVI, OLUMIANT, and RINVOQ).

As a precautionary measure, Health Canada is working with the manufacturers to update and align these risks in the CPMs for JAK inhibitors.

Products affected

Brand Name	Medicinal Ingredients	Available Formulations
CIBINQO	abrocitinib	50 mg, 100 mg, and 200 mg tablets
INREBIC	fedratinib	100 mg capsules
JAKAVI	ruxolitinib	5 mg, 10 mg, 15 mg and 20 mg tablets
OLUMIANT	baricitinib	2 mg tablets
RINVOQ	upadacitinib	15 mg and 30 mg extended-release tablets
XELJANZ/ XELJANZ XR	tofacitinib	5 mg and 10 mg tablets 11 mg extended-release tablets

Background information

There are several JAK inhibitors authorized in Canada for various indications including RA, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, atopic dermatitis, graft-versus-host disease, as well as certain myeloproliferative diseases.

As communicated on January 12, 2022, Health Canada reviewed the final results from clinical trial A3921133. This review found that patients treated with XELJANZ (5 mg BID or 10 mg BID), had an increased risk of MACE and malignancy compared to TNFi. 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. The CPM for XELJANZ/XELJANZ XR was updated to include these risks. In addition, the indication for RA was revised.

Based on findings from that review, Health Canada assessed whether these risks apply to other JAK inhibitors (OLUMIANT and RINVOQ), indicated for inflammatory conditions, in order to determine whether additional warnings or actions were

required. Health Canada reviewed preliminary results from a retrospective observational study, B023, which compared the incidence of MACE, venous thromboembolism and serious infections in RA patients treated with 2 mg and 4 mg OLUMIANT to those treated with TNFi. Preliminary results from this study suggested an increased incidence of MACE and thrombosis in RA patients treated with OLUMIANT versus TNFi. This study did not evaluate malignancies.

Based on these safety findings and similar mechanisms of action for these drugs, Health Canada cannot rule out the risks of MACE, thrombosis (including fatal events) and malignancies for other JAK inhibitors (CIBINQO, INREBIC, JAKAVI, OLUMIANT, and RINVOQ). As a precautionary measure, Health Canada is working with the manufacturers to update and align the warnings of MACE, thrombosis (including fatal events) and malignancies in the CPMs for JAK inhibitors.

Information for consumers

JAK inhibitors are prescription drugs authorized for sale in Canada for various conditions including certain chronic inflammatory diseases.

Health Canada cannot rule out the risks of serious heart-related problems, blood clots (including fatal blood clots) and cancer for JAK inhibitors.

Consumers are advised to:

- Talk to their healthcare professional about possible heart disease risk factors before they start taking a JAK inhibitor.
- Contact their healthcare professional immediately and stop taking their JAK inhibitor if they develop 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 their healthcare professional if they have or have had any type of cancer before taking a JAK inhibitor.
- Talk to their healthcare professional if they are a current or past smoker.
- Be aware that blood clots in the veins of the arms or legs (deep vein thrombosis), arteries (arterial thrombosis) or lungs (pulmonary embolism) can happen in some patients taking a JAK inhibitor. This may be life-threatening and can cause death.
- Stop taking their JAK inhibitor and seek immediate medical help if they develop any symptoms of a blood clot in their arms or legs (such as swelling, pain or tenderness in the arm or leg), or lungs (such as sudden unexplained chest pain or shortness of breath).

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

Information for healthcare professionals

Healthcare professionals are advised to:

- Consult the safety information in the CPM. Consider the benefits and risks for the individual patient prior to initiating, or continuing, therapy with a JAK inhibitor, particularly in geriatric patients, in patients who are current or past smokers, those with other CV or malignancy risk factors, in patients with an underlying malignancy or those who develop a malignancy, and in patients who may be at increased risk of thrombosis.
- Inform patients that JAK inhibitors may increase their risk of MACE, including non-fatal myocardial infarction. Instruct all patients, especially geriatric patients, current and past smokers, and patients with other CV risk factors, to be alert for the symptoms of stroke and CV events. Advise patients to stop taking their JAK inhibitor and seek immediate medical help if they develop symptoms of a heart problem.
- Inform patients that JAK inhibitors may increase their risk for certain cancers, such as lung cancer and lymphoma. Instruct patients to inform their healthcare provider if they have a history of any type of cancer.
- Advise patients to stop taking their JAK inhibitor and to seek immediate medical help if they experience any symptoms of thrombosis.

Action taken by Health Canada

Health Canada is working with the manufacturers to update and align the risks of MACE, thrombosis (including fatal events) and malignancy in the CPMs for JAK inhibitors. 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 JAK inhibitors should be reported to their respective market authorization holder or to Health Canada.

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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 Products Directorate
E-mail: mhpd-dpsc@hc-sc.gc.ca
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Sincerely,

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