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A21020000I_1121406938A_doc3_Attach2.pdf、
A21020000I_1121406938A_doc3_Attach3.pdf)

主旨：有關本署擬啟動Janus kinase (JAK)抑制劑類藥品(包含tofacitinib、baricitinib、upadacitinib、peficitinib、filgotinib、ruxolitinib、abrocitinib、fedratinib)之臨床效益及風險再評估一案，詳如說明段，請查照。

說明：

一、JAK抑制劑類藥品可能具有增加嚴重心臟相關事件(如心臟病或中風)、癌症、血栓及死亡之風險，經檢視各國針對該類藥品之管理措施，如美國食品藥物管理局限縮用於慢性發炎性疾病的JAK抑制劑類藥品，為僅用於病人對於一或多項TNF blockers療效不佳或無法耐受時使用，並更新仿單「加框警語」以包含嚴重心臟相關事件、癌症、血栓及死亡之風險(如附件1)；歐洲藥品管理局更新用於慢性發炎性疾病的JAK抑制劑類藥品仿單以包含新的使用建議和警語，

包括65歲以上、具有重大心血管風險、目前吸煙或長期吸煙，以及具有癌症風險等族群之病人，於沒有其他適合的治療方案下才能使用之使用建議，以及嚴重心臟相關事件、癌症、血栓及死亡之風險等警語(如附件2)；加拿大衛生部更新該類藥品之仿單以包含嚴重心臟相關事件、癌症、血栓及死亡之風險資訊(如附件3)，為確保民眾用藥安全，本署啟動該類藥品之臨床效益及風險再評估。

二、為進行JAK抑制劑類藥品之臨床效益及風險再評估，貴會倘有相關意見或下列相關研究文獻資料，請於112年9月15日前檢送至本署，逾期未提具資料者，視同無意見：

(一)針對治療慢性發炎性疾病的JAK抑制劑類藥品(包含tofacitinib、baricitinib、upadacitinib、peficitinib、filgotinib、abrocitinib)：

1、請就該類藥品使用於「65歲以上老年病人、具有動脈粥狀硬化心血管疾病或其他心血管風險因子(如目前吸菸或過去長期吸菸)的病人、具有惡性腫瘤風險因子(如現正患有惡性腫瘤或具有惡性腫瘤病史)的病人」等高風險族群之風險效益比提供臨床見解。

2、請就倘限縮該類藥品用於其核准之適應症(如類風濕性關節炎、乾癬性關節炎、僵直性脊椎炎、潰瘍性結腸炎等)治療時，應保留至使用腫瘤壞死因子抑制劑(TNF blocker)療效不佳或無法耐受之患者提供相關意見。

3、請就倘於「特殊警語」處增列第1項所描述之高風險族群應於沒有其他適當替代療法時才能使用提供相關意

見。

4、請就倘於「用法用量」處增列「65歲以上族群及具有較高重大心血管事件、血栓、惡性腫瘤風險的病人建議採用較低劑量」等安全性資訊提供相關意見。

(二)針對治療血液性疾病的JAK抑制劑類藥品(包含ruxolitinib、fedratinib)：請就倘將重大心血管事件、血栓、次發性惡性腫瘤風險增列於「警語及注意事項」提供相關意見。

(三)其他意見或建議。

正本：中華民國風濕病醫學會、中華民國免疫學會、台灣消化系醫學會、中華民國醫師公會全國聯合會、台灣內科醫學會、臺灣醫學會、社團法人臺灣臨床藥學會、台灣皮膚科醫學會、中華民國癌症醫學會、台灣臨床腫瘤醫學會、中華民國血液病學會、台灣家庭醫學醫學會、中華民國藥師公會全國聯合會

副本：全國藥物不良反應通報中心 電子公文交換章 2023/08/18 10:52:58

FDA requires warnings about increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors that treat certain chronic inflammatory conditions

Approved uses also being limited to certain patients

12/2021 Update: The issues described below have been addressed in product labeling. Health care professionals and patients can access the approval letters and latest prescribing information in Drugs@FDA: Xeljanz (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=203214), Xeljanz XR (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=208246), Olumiant (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=207924), Rinvoq (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=211675)

This information is an update to the FDA Drug Safety Communication issued on February 4, 2021 (/drugs/drug-safety-and-availability/initial-safety-trial-results-find-increased-risk-serious-heart-related-problems-and-cancer-arthritis). FDA also previously communicated about the safety clinical trial with Xeljanz, Xeljanz XR (tofacitinib) in February 2019 (/drugs/drug-safety-and-availability/safety-trial-finds-risk-blood-clots-lungs-and-death-higher-dose-tofacitinib-xeljanz-xeljanz-xr) and July 2019 (/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and).

en Español (/drugs/drug-safety-and-availability/la-fda-exige-la-inclusion-de-advertencias-sobre-un-riesgo-mayor-de-sufrir-efectos-cardiovasculares)

FDA 药品安全通讯 FDA 要求对于治疗某些慢性炎症的 JAK 抑制剂引起严重心脏相关事件、癌症、血栓和死亡风险增加发出警告 批准的用途也仅限于某些患者群体 (/drugs/drug-safety-and-availability/fda-yaopinanquantongxun-fda-yaoqiuduiyuzhiliaomouxiemanxingyanzhengde-jak)

Drug Safety Communication (/media/151936/download) (PDF - 255 KB)

09-01-2021 FDA Drug Safety Communication

What safety concern is FDA announcing?

Based on a completed U.S. Food and Drug Administration (FDA) review of a large randomized safety clinical trial, we have concluded there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with the arthritis and ulcerative colitis medicines Xeljanz and Xeljanz XR (tofacitinib). This trial compared Xeljanz with another type of medicine used to treat arthritis called tumor necrosis factor (TNF) blockers in patients with rheumatoid arthritis. The trial's final results also showed an increased risk of blood clots and death with the lower dose of Xeljanz. A prior DSC (/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and) based upon earlier results from this trial, reported an increased risk of blood clots and death only seen at the higher dose.

We are requiring new and updated warnings for two other arthritis medicines in the same drug class as Xeljanz, called Janus kinase (JAK) inhibitors, Olumiant (baricitinib) and Rinvoq (upadacitinib). Olumiant and Rinvoq have not been studied in trials similar to the large safety clinical trial with Xeljanz, so the risks have not been adequately evaluated. However, since they share mechanisms of action withXeljanz, FDA considers that these medicines may have similar risks as seen in the Xeljanz safety trial.

Two other JAK inhibitors, Jakafi (ruxolitinib) and Inrebic (fedratinib), are not indicated for the treatment of arthritis and other inflammatory conditions and so are not a part of the updates being required to the prescribing information for Xeljanz, Xeljanz XR, Olumiant, and Rinvoq. Jakafi and Inrebic are used to treat blood disorders and require different updates to their prescribing information. If FDA becomes aware of any additional safety information or data that warrants updates to the prescribing information for these medicines, we may take further action and will alert the public.

What is FDA doing?

We are requiring revisions to the Boxed Warning, FDA's most prominent warning, for Xeljanz/Xeljanz XR, Olumiant, and Rinvoq to include information about the risks of serious heart-related events, cancer, blood clots, and death. Recommendations for health care professionals will include consideration of the benefits and risks for the individual patient prior to initiating or continuing therapy. In addition, to ensure the benefits of these three medicines outweigh the risks in patients who receive them, we are limiting all approved uses to certain patients who have not responded or cannot tolerate one or more TNF blockers. Changes will also be made to several sections of the

prescribing information and to the patient Medication Guide (/drugs/drug-safety-and-availability/medication-guides).

What are Xeljanz/Xeljanz XR, Olumiant, and Rinvoq and how can they help me?

Xeljanz/Xeljanz XR, Olumiant, and Rinvoq are used to treat certain serious, chronic, and progressive inflammatory conditions. Xeljanz was the first to be approved in 2012. All three medicines are approved to be used alone or with other drugs to treat rheumatoid arthritis (RA), a condition in which the body attacks its own joints, causing pain, swelling, joint damage, and loss of function. Xeljanz is also approved to treat psoriatic arthritis, a condition that causes joint pain and swelling; ulcerative colitis, which is a chronic, inflammatory disease affecting the colon; and polyarticular course juvenile idiopathic arthritis, a type of childhood arthritis. Xeljanz/Xeljanz XR, Olumiant, and Rinvoq work by decreasing the activity of the immune system; an overactive immune system contributes to RA, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis.

What should patients do?

Those taking Xeljanz/Xeljanz XR, Olumiant, or Rinvoq should tell your health care professional if you are a current or past smoker, or have had a heart attack, other heart problems, stroke, or blood clots in the past as these may put you at higher risk for serious problems with the medicines. Patients starting these medicines should also tell your health care professional about these risk factors. Seek emergency help right away if you have any symptoms that may signal a heart attack, stroke, or blood clot, including:

- Discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- Severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- Unusual pain or discomfort in your arms, back, neck, jaw, or stomach
- Shortness of breath with or without chest discomfort
- Breaking out in a cold sweat
- Nausea or vomiting
- Feeling lightheaded
- Weakness in one part or on one side of your body
- Slurred speech
- Drooping on one side of your mouth
- Swelling of a leg or arm

- Leg pain or tenderness, or red or discolored skin in the painful or swollen leg or arm

Treatment with these medicines is associated with an increased risk of certain cancers including lymphoma and lung cancer, so inform your health care professional if you experience signs and symptoms such as swelling of lymph nodes in your neck, armpits, or groin; constantly feeling tired; fever; night sweats; persistent or worsening cough; difficulty breathing; hoarseness or wheezing; or unexplained weight loss. Talk to your health care professional if you have any questions or concerns.

What should health care professionals do?

Health care professionals should consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Xeljanz/Xeljanz XR, Olumiant, or Rinvoq. This is particularly the case in patients who are current or past smokers, those with other cardiovascular risk factors, those who develop a malignancy, and those with a known malignancy other than a successfully treated nonmelanoma skin cancer. Reserve these medicines for patients who have had an inadequate response or intolerance to one or more TNF blockers. Counsel patients about the benefits and risks of these medicines and advise them to seek emergency medical attention if they experience signs and symptoms of a heart attack, stroke, or blood clot.

What did FDA find?

When FDA first approved Xeljanz, we required the manufacturer, Pfizer, to conduct a safety clinical trial in patients with RA who were taking methotrexate to evaluate the risk of serious heart-related events, cancer, and infections. The trial studied two doses of Xeljanz (5 mg twice daily, which is the approved dosage for RA, and a higher 10 mg twice daily dosage) in comparison to a TNF blocker also used to treat the condition. Patients in the trial were required to be at least 50 years old and have at least one risk factor for heart disease.

Our review of the final trial results showed a higher rate of serious heart-related events such as heart attack and stroke, cancer, blood clots, and death in patients treated with both doses of Xeljanz compared to those treated with TNF blockers. Importantly, a higher rate of blood clots and death was seen with both doses of Xeljanz compared to TNF blockers, whereas previous interim results (/drugs/drug-safety-and-availability/fda-approves-boxed-warning-about-increased-risk-blood-clots-and-death-higher-dose-arthritis-and) showed the risk only with the higher dose. For cancers, a higher rate of lymphomas was observed in patients treated with Xeljanz compared to those treated with TNF blockers. A higher rate of lung cancers was observed in current

or past smokers treated with Xeljanz compared to those treated with TNF blockers. Current or past smokers had an additional increased risk of overall cancers (See Data Summary).

Other JAK inhibitors have not been studied in similar large safety clinical trials, so the risk with these medicines has not been evaluated. However, since they share mechanisms of action with Xeljanz, FDA considers that these medicines may have similar risks as seen in the safety trial with Xeljanz.

What is my risk?

All medicines have side effects even when used correctly as prescribed, but in general the benefits of taking a medicine outweigh these risks. It is important to know that people respond differently to all medicines depending on their health, other medicines they are taking, the diseases they have, genetic factors, and many other factors. As a result, we cannot determine how likely it is that someone will experience these side effects when taking Xeljanz/Xeljanz XR, Olumiant, or Rinvoq.

However, if you are a current or past smoker, or have had a heart attack, other heart problems, stroke, or blood clots in the past, you should tell your health care professional as these may put you at higher risk for serious problems with these medicines.

How do I report side effects from Xeljanz, Olumiant, or Rinvoq?

To help FDA track safety issues with medicines, we urge patients and health care professionals to report side effects involving Xeljanz/Xeljanz XR, Olumiant, Rinvoq, or other medicines to the FDA MedWatch program, using the information in the “Contact FDA” box at the bottom of the page.

How can I get new safety information on medicines I’m prescribing or taking?

You can sign up for email alerts (https://public.govdelivery.com/accounts/USFDA/subscriber/new) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) about Drug Safety Communications on medicines or medical specialties of interest to you.

Facts about Xeljanz/Xeljanz XR (tofacitinib), Olumiant (baricitinib), and Rinvoq

(upadacitinib)

- These medicines are part of a class called Janus kinase (JAK) inhibitors and are used to treat certain serious, chronic, and progressive inflammatory conditions.
- All three medicines are approved to be used alone or with other medicines to treat rheumatoid arthritis. Xeljanz is also approved to treat psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis.
- These medicines work by decreasing the activity of the immune system.
- These medicines are available to be given orally as immediate-release tablets, extended-release tablets that release the medicine into the body over time, and solution.
- Common side effects of these medicines include upper respiratory tract infections such as the common cold and sinus infections, bronchitis, headache, cough, increased cholesterol levels, high blood pressure, increased muscle enzyme levels, rash, nausea, diarrhea, acne, cold sores, and shingles.

Additional Information for Patients

- FDA is requiring new and updated warnings about an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with the medicines Xeljanz/Xeljanz XR (tofacitinib), Olumiant (baricitinib), and Rinvoq (upadacitinib) used to treat certain serious inflammatory conditions including rheumatoid arthritis (RA) and ulcerative colitis.
- We are also limiting the use of these medicines to certain patients who are not treated effectively or who experience severe side effects with another type of medicine used to treat serious inflammatory conditions called tumor necrosis factor (TNF) blockers.
- If you are taking Xeljanz/Xeljanz XR, Olumiant, or Rinvoq, tell your health care professional if you are a current or past smoker, or have had a heart attack, other heart problems, stroke, or blood clots in the past as these may put you at higher risk for serious problems with the medicines. Before starting these medicines, also tell your health care professional about these risk factors.
- Seek emergency help right away if you have any symptoms that may signal a heart attack, stroke, or blood clot, including:
    - Discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
    - Severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw

    - Pain or discomfort in your arms, back, neck, jaw, or stomach
    - Shortness of breath with or without chest discomfort
    - Breaking out in a cold sweat
    - Nausea or vomiting
    - Feeling lightheaded
    - Weakness in one part or on one side of your body
    - Slurred speech
    - Drooping on one side of your mouth
    - Swelling of a leg or arm
    - Leg pain or tenderness, or red or discolored skin in the painful or swollen leg or arm
- Also inform your health care professionals if you experience signs and symptoms such as:
    - Swelling of lymph nodes in your neck, armpits or groin
    - Constantly feeling tired
    - Fever
    - Night sweats
    - Persistent or worsening cough
    - Difficulty breathing
    - Hoarseness or wheezing
    - Unexplained weight loss.
- Read the patient Medication Guide (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=medguide.page) every time you receive a prescription for Xeljanz/Xeljanz XR, Olumiant, or Rinvoq. The Medication Guide will be updated with this new or other important information about your medicine. It explains the important things that you need to know. These include the side effects, what the medicine is used for, how to take and store it properly, and other things to watch out for when you are taking the medicine.
- Talk to your health care professional if you have any questions or concerns.
- To help FDA track safety issues with medicines, report side effects from Xeljanz, Olumiant, Rinvoq, or other medicines to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of this page.
- You can sign up for email alerts (https://public.govdelivery.com/accounts/USFDA/subscriber/new)

(http://www.fda.gov/about-fda/website-policies/website-disclaimer) about Drug Safety Communications on medicines or medical specialties of interest to you.

Additional Information for Health Care Professionals

- FDA is requiring new and updated warnings about an increased risk of major adverse cardiovascular events, malignancy, thrombosis, and mortality with the Janus kinase (JAK) inhibitors Xeljanz, Xeljanz XR (tofacitinib), Olumiant (baricitinib), and Rinvoq (upadacitinib).
- Reserve these medicines for patients who have had an inadequate response or intolerance to one or more TNF blockers.
- Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with Xeljanz/Xeljanz XR, Olumiant, or Rinvoq, particularly in patients who are current or past smokers, those with other cardiovascular risk factors, those who develop a malignancy, and those with a known malignancy other than a successfully treated nonmelanoma skin cancer.
- Inform patients about the symptoms of serious cardiovascular events and to seek emergency medical attention if they occur.
- Encourage patients to read the Medication Guide (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=medguide.page) they receive with each prescription, which explains the safety risks and provides other important information.
- To help FDA track safety issues with medicines, report adverse events involving Xeljanz/Xeljanz XR, Olumiant, Rinvoq, or other medicines to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of this page.
- You can sign up for email alerts (https://public.govdelivery.com/accounts/USFDA/subscriber/new) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) about Drug Safety Communications on medicines or medical specialties of interest to you.

Data Summary

When FDA first approved Xeljanz (tofacitinib), we required the manufacturer, Pfizer, to conduct a randomized safety clinical trial in patients with rheumatoid arthritis (RA) who were taking methotrexate to evaluate the risk of cardiovascular events, malignancy, and infections. It was a multicenter, randomized, open-label trial to evaluate two doses of Xeljanz (5 mg twice daily (N=1455), which is the approved dosage for RA, and a higher 10 mg twice daily dosage (N=1456)) in comparison to treatment with a tumor necrosis

factor (TNF) blocker (N=1451). Patients in the trial were required to be 50 years of age or older and have at least one cardiovascular risk factor. The co-primary endpoints were major adverse cardiovascular events (MACE), defined as cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke; and malignancy, excluding nonmelanoma skin cancer (NMSC). The trial was designed to exclude a prespecified risk margin of 1.8 for the hazard ratio of combined Xeljanz regimens when compared to the TNF blocker control for each co-primary endpoint. The median on-study follow-up time was 4 years.

The mean age of the population was 61 years and the median age was 60 (range 50-88 years). Most patients were female (78 percent) and Caucasian (77 percent). The noninferiority criterion was not met for the comparison of the combined Xeljanz regimens to TNF blockers for the endpoints of MACE and malignancies since the upper limit of the 95% confidence intervals (CI) for these hazard ratios exceeded the prespecified noninferiority criterion of 1.8. For MACE, the estimated hazard ratio and 95% CI associated with the combined Xeljanz regimens relative to TNF blockers were 1.33 (0.91, 1.94). For malignancies excluding NMSC, the estimated hazard ratio and 95% CI associated with the combined Xeljanz regimens relative to TNF blockers were 1.48 (1.04, 2.09).

There was an increased risk of death, MACE, malignancies, and thrombosis associated with both regimens of Xeljanz. The data showed evidence of a dose-dependent increased risk for MACE, all-cause mortality, and thrombosis at both doses of Xeljanz when compared to treatment with TNF blockers. Additionally, the data showed evidence of a non-dose-dependent increased risk for malignancy excluding NMSC at both doses of Xeljanz when compared to TNF blockers. Lymphomas and lung cancers were observed at a higher rate in patients treated at both doses of Xeljanz compared to those treated with TNF blockers. In particular, a higher rate of lung cancers was observed in current or past smokers treated with Xeljanz. Current or past smokers had an additional increased risk of overall cancers.

Other JAK inhibitors have not been studied in similar large safety clinical trials, so the risk with these medicines has not been evaluated. However, since they share mechanisms of action with Xeljanz, FDA considers that these medicines may have similar risks as seen in the safety clinical trial with Xeljanz.

Related Information

- National Institute of Arthritis and Musculoskeletal and Skin Diseases: Rheumatoid Arthritis (https://www.niams.nih.gov/health-topics/rheumatoid-arthritis)
- National Institute of Arthritis and Musculoskeletal and Skin Diseases: Psoriatic Arthritis (https://www.niams.nih.gov/health-topics/psoriatic-arthritis)
- National Institute of Diabetes and Digestive and Kidney Diseases: Ulcerative Colitis (https://www.niddk.nih.gov/health-information/digestive-diseases/ulcerative-colitis)

- Genetic and Rare Diseases Information Center: Polyarticular onset juvenile idiopathic arthritis (https://rarediseases.info.nih.gov/diseases/10967/polyarticular-onset-juvenile-idiopathic-arthritis)
- National Heart, Lung, and Blood Institute: Heart Attack (https://www.nhlbi.nih.gov/health-topics/heart-attack)
- National Heart, Lung, and Blood Institute: Stroke (https://www.nhlbi.nih.gov/health-topics/stroke)
- National Heart, Lung, and Blood Institute: Venous Thromboembolism (https://www.nhlbi.nih.gov/health-topics/venous-thromboembolism)
- National Cancer Institute (https://www.cancer.gov/)
- FDA: Information on Tumor Necrosis Factor (TNF) Blockers (/drugs/postmarket-drug-safety-information-patients-and-providers/information-tumor-necrosis-factor-tnf-blockers-marketed-remicade-enbrel-humira-cimzia-and-simponi)
- The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective (/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective)
- Think It Through: Managing the Benefits and Risks of Medicines (/drugs/information-consumers-and-patients-drugs/think-it-through-managing-benefits-and-risks-medicines)

Contact FDA

For More Info
855-543-DRUG (3784) and press 4
druginfo@fda.hhs.gov (mailto:druginfo@fda.hhs.gov)

Report a Serious Problem to MedWatch
Complete and submit the report Online (https://www.accessdata.fda.gov/scripts/medwatch/).
Download form (/about-fda/forms/medwatch-consumer-voluntary-reporting-pdf) or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 March 2023
EMA/142279/2023

EMA confirms measures to minimise risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders

On 23 January 2023, EMA's human medicines committee (CHMP) endorsed the measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to minimise the risk of serious side effects with Janus kinase (JAK) inhibitors used to treat several chronic inflammatory disorders. These side effects include cardiovascular conditions, blood clots, cancer and serious infections.

These medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer.

JAK inhibitors should be used with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in patient groups who are at risk of VTE, cancer or major cardiovascular problems, where possible.

The recommendations follow a review of available data, including the final results from a clinical trial[1] of the JAK inhibitor Xeljanz (tofacitinib) and preliminary findings from an observational study involving Olumiant. The review also included advice from an expert group of rheumatologists, dermatologists, gastroenterologists and patient representatives.

The review confirmed Xeljanz increases the risk of major cardiovascular problems, cancer, VTE, serious infections and death due to any cause when compared with medicines belonging to the class of TNF-alpha inhibitors. EMA has now concluded that these safety findings apply to all approved uses of JAK inhibitors in chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata).

The product information for JAK inhibitors used to treat chronic inflammatory disorders will be updated with the new recommendations and warnings. In addition, the educational material for patients and healthcare professionals will be revised accordingly.

[1] Ytterberg SR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *New Engl J Med* 2022;*3*86(4):316-326. doi: 10.1056/NEJMoa2109927

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Information for patients

- Janus kinase (JAK) inhibitors used to treat chronic inflammatory disorders have been found to increase the risk of major cardiovascular problems (such as heart attack or stroke), cancer, blood clots in the lungs and in deep veins, serious infections and death when compared with TNF alpha inhibitors.
- These JAK inhibitors (Xeljanz, Cibinqo, Olumiant, Rinvoq and Jyseleca) are used to treat one or more of the following chronic inflammatory disorders: rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata.
- If you are aged 65 years or above, have an increased risk of major cardiovascular problems or cancer or if you smoke or have done so for a long time in the past, you should only be prescribed these medicines if there are no suitable treatment alternatives for you.
- If you have certain risk factors, your doctor may reduce the dose of your JAK inhibitor or switch treatment depending on your inflammatory disorder and the JAK inhibitor you are taking to treat it.
- If, at any stage during your treatment, you experience chest pain or tightness (which may spread to arms, jaw, neck and back), shortness of breath, cold sweat, light headedness, sudden dizziness, weakness in arms and legs or slurred speech, contact your doctor immediately.
- Examine your skin periodically and let your doctor know if you notice any new growths on the skin.
- If you have any questions about your treatment, speak to your doctor.

Information for healthcare professionals

- An EMA review has found that, compared with TNF-alpha inhibitors, Janus kinase (JAK) inhibitors used to treat chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata) are linked to a higher risk of major adverse cardiovascular events (MACE), venous thromboembolism (VTE), malignancy, serious infections and all-cause mortality.
- The review included the final results from an open-label clinical trial (ORAL Surveillance study)[2] of the JAK inhibitor Xeljanz (tofacitinib) in patients with rheumatoid arthritis and cardiovascular risk factors which found a higher risk of these events with Xeljanz than with TNF-alpha inhibitors.
- Preliminary findings from an observational study (B023) involving another JAK inhibitor, Olumiant (baricitinib), also suggest an increased risk of MACE and VTE in patients with rheumatoid arthritis treated with Olumiant compared with those treated with TNF-alpha inhibitors.
- EMA concluded that the identified risks apply to all JAK inhibitors approved for the treatment of chronic inflammatory disorders.
- These medicines (Xeljanz, Cibinqo, Olumaint, Rinvoq and Jyseleca) should only be used in the following patients if no suitable treatment alternatives are available: those aged 65 years or above, those who are current or past long-time smokers, those with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, or those with other malignancy risk

[2] Ytterberg SR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *New Engl J Med* 2022;*3*86(4):316-326. doi: 10.1056/NEJMoa2109927

factors. Cautious use is also recommended in patients with known risk factors for VTE other than those listed above.

- If JAK inhibitors are needed in patients with these risk factors, a lower dose may be recommended, depending on the medicine, the indication and the specific risk factor.
- Healthcare professionals should discuss the risks associated with JAK inhibitors with their patients.
- It is recommended that healthcare professionals carry out periodic examinations of their patients' skin to check for skin cancer, particularly for patients at risk for skin cancer.
- A letter will be sent to all healthcare professionals expected to prescribe these medicines to inform them of the outcome of the review. Full treatment recommendations will be included in the updated summary of product characteristics and the educational material for the respective products.

More about the medicines

The Janus kinase inhibitors subject to this review are Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib). These medicines are used to treat several chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata). The active substances in these medicines work by blocking the action of enzymes known as Janus kinases. These enzymes play an important role in the process of inflammation that occurs in these disorders. By blocking the enzymes' action, the medicines help reduce the inflammation and other symptoms of these disorders.

Some JAK inhibitors (Jakavi and Inrebic) are used to treat myeloproliferative disorders; the review did not include these medicines. The review also did not cover the use of Olumiant in the short-term treatment of COVID-19, which was under assessment by EMA at the time.

More about the procedure

The review of JAK inhibitors in the treatment of inflammatory disorders was initiated at the request of the European Commission (EC) under Article 20 of Regulation (EC) No 726/2004.

The review was carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations on 27 October 2022. The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which adopted the Agency's opinion. Following further review of its recommendation of October 2022, the PRAC issued an update on 12 January 2023 to further align dosing recommendations for the medicines concerned by the procedure. The PRAC's revised recommendations were sent to the CHMP, which adopted the Agency's opinion. The CHMP's opinion was forwarded to the European Commission, which issued a final legally binding decision applicable in all EU Member States on 10 March 2023.

Health professional risk communication

Janus Kinase Inhibitors and the Risk of Major Adverse Cardiovascular Events, Thrombosis (Including Fatal Events) and Malignancy

Last updated: 2022-10-31

Summary

Product: CIBINQO (abrocitinib), INREBIC (fedratinib), JAKAVI (ruxolitinib), OLUMIANT (baricitinib), RINVOQ (upadacitinib), XELJANZ/XELJANZ XR (tofacitinib)

Issue: Health products - New safety information
Health products - Product safety

What to do: See Key Messages below

Audience: Health professionals

Affected products

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

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.

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.

Background

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 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
Telephone: 613-954-6522
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Sincerely,

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Additional information

▶ Details

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