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主旨：有關本署擬啟動含Janus kinase(JAK) 抑制劑類成分(tofacitinib、baricitinib、upadacitinib、peficitinib)藥品之臨床效益及安全性再評估一案，詳如說明段，請查照。

說明：

一、含JAK 抑制劑類成分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，為確保民眾用藥安全，本署啟動含JAK 抑制劑類成分藥品之臨床效益及風險再評估。另，美國食品藥物管理局(FDA)亦於110年9月2日發布警訊，限縮該類藥品僅用於病人對一或多項TNF blockers療效不佳或無法耐受時使用，並修訂其仿單「加框警語」以包含嚴重心臟相關事件、癌症、血栓及死亡的風險資訊(警訊內容如附件)。

二、為進行含JAK 抑制劑類成分藥品之臨床效益及風險再評估，貴公司倘有相關意見或下列相關研究文獻等資料，請於110年12月31日前檢送至本署，逾期未提具資料者，視同

無意見：

(一)請針對旨揭藥品之嚴重心臟相關事件（如心臟病、中風等）、血栓、惡性腫瘤和死亡風險提供風險效益分析報告(請依不同適應症分述之)。

(二)請提供旨揭藥品近五年之銷售紀錄（請依年度及醫院、診所、藥局分列之）。

(三)倘有提供予國外主管機關進行安全性再評估之相關資料，亦請提供本署參考。

(四)其他意見或建議。

正本：輝瑞大藥廠股份有限公司、台灣安斯泰來製藥股份有限公司、台灣禮來股份有限公司

副本：中華民國藥劑生公會全國聯合會、台灣製藥工業同業公會、中華民國西藥商業同業公會全國聯合會、社團法人中華民國學名藥協會、台灣研發型生技新藥發展協會、全國藥物不良反應通報中心、中華民國製藥發展協會、台北市西藥代理商業同業公會、中華民國西藥代理商業同業公會、中華民國開發性製藥研究協會、台灣藥品行銷暨管理協會、台灣藥物臨床研究協會 電子公文交換章 2021/11/30 10:49:42

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

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/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.