Direct Healthcare-Professional Communication

31/August /2023

Rinvoq® (upadacitinib): Updated recommendations to minimize the risks of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality with use of Janus kinase inhibitors (JAKi)

Dear Healthcare Professional,
In agreement with the Saudi Food and Drug Authority (SFDA), AbbVie would like to inform you of the following:

Summary

- **In a large, randomized, post-marketing safety study of Xeljanz® (tofacitinib), a JAK inhibitor, in rheumatoid arthritis patients 50 years of age and older with at least one cardiovascular risk factor the following was observed in patients treated with this JAK inhibitor compared to patients treated with Tumor Necrosis Factor (TNF) inhibitors:**
    - **an increased risk of serious infections**
    - **a higher all-cause mortality**
    - **a higher rate of tumor diseases particularly lung cancer, lymphoma, and non-melanoma skin cancer (NMSC)**
    - **an increased incidence of major adverse cardiovascular events (MACE)**
    - **an increased occurrence of pulmonary embolism, venous and arterial thrombosis**
- **Based on these safety findings and similar mechanism of actions, these risks are considered class effects and relevant across all approved indications of JAK inhibitors. These JAK inhibitors should only be used if no suitable treatment alternatives are available in patients:**
    - **65 years of age and older;**
    - **who are current or past long-time smokers;**
    - **With other cardiovascular or malignancy risk factors (i.e. current malignancy or history of malignancy).**
- **JAKi should be used with caution in patients with VTE risk factors other than those listed above.**
- **Dosing recommendations are revised for some patient groups with risk factors.**
- **Periodic skin examination is recommended for all patients.**
- **Prescribers should discuss with patients the benefits and risks associated with the use of JAKi**

Background

- Rinvoq® (upadacitinib) is a Janus kinase (JAK) inhibitor approved for the treatment of several chronic inflammatory disorders (Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, Ulcerative colitis, and Atopic dermatitis).
- Based on the results from the ORAL Surveillance study, a post-marketing safety study of tofacitinib, a different JAK inhibitor, we would like to notify you about updated recommendations to minimize the risks of serious side effects (malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism, and mortality) associated with the use of JAK inhibitors.
- The ORAL Surveillance study was a large, randomized trial designed to assess the safety profile of tofacitinib, at two doses (5 mg twice daily and 10 mg twice daily) versus a tumor necrosis factor (TNF) inhibitor in patients with rheumatoid arthritis. Participants were 50 years of age and older with at least one additional cardiovascular risk factor.
- The study found higher incidence rates of MACE, thromboembolic events, malignancies (particularly lung cancer, lymphoma and non-melanoma skin cancer (NMSC)), serious infections and all-cause mortality in patients treated with tofacitinib compared to those treated with TNF inhibitors.
- The incidence rates of MACE and malignancies were higher with combined tofacitinib doses (5mg and 10mg) than with a TNF inhibitor (Hazard ratio 1.33 [95% CI 0.91 –1.94] and 1.48 [95% CI 1.04 –2.09], respectively). MACE and malignancies were more common in patients 65 years and older and in patients who were current or past long-time smokers. The increase in malignancies was mainly driven by higher rates of lung cancer and lymphoma. Adjudicated venous thromboembolism (VTE), serious infection and death from any cause were more frequent with the combined tofacitinib doses than with a TNF inhibitor.

Further information on the safety concerns and the recommendations

Healthcare professionals are advised to consider the benefits and risks of JAK inhibitors for the individual patient, particularly for elderly patients (above 65 years of age), patients who are current or past long-time smokers, or patients with other cardiovascular (CV) or malignancy risk factors.

The safety updates made to the Summary of Product Characteristics (SmPC) for Rinvoq® (upadacitinib).

Further information

Rinvoq® (upadacitinib) SmPC (to be inserted once SmPC approved by SFDA)

This letter is not intended as a complete description of the benefits and risks related to the use of this product. For further details, please refer to the updated SmPC.

Call for reporting

The SFDA urges both healthcare professionals and patients to report ADRs related to use of any medication to the SFDA using the following contact information:

The National Pharmacovigilance Centre (NPC):

SFDA Call Center: 19999

E-mail: npc.drug@sfda.gov.sa

Website: https://ade.sfda.gov.sa

AbbVie Pharmacovigilance Contacts:

For Adverse Events Reporting: please email PV.MEA@abbvie.com or contact Hotline number: +966 55 828 2010

Company contacts point

Should you have any questions regarding RINVOQ (upadacitinib), please contact AbbVie Medical Information on www.abbviemedinfo.com or email to medinfo_saudi@abbvie.com

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List of references:

1. Ytterberg SR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. New Engl J Med 2022;386(4):316-326. doi:: https://www.nejm.org/doi/full/10.1056/NEJMoa2109927.

2. Updated recommendations to minimise the risks of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality with use of Janus kinase inhibitors (JAKi). EMA. Available at: https://www.ema.europa.eu/en/medicines/dhpc/updated-recommendations-minimise-risks-malignancy-major-adverse-cardiovascular-events-serious