SAFETY ALERT

DRAP SAFTEY ALERT NO. 33

Safety alert of risk of serious heart-related events, blood clots, cancer and death with Xeljanz (Tofacitinib)

Date: 11th of April, 2023.

Target Audience:

- Manufacturers and importers of Tofacitinib;
- Healthcare Professionals; and
- Patients, consumers or caregivers.

Background:

Health Canada in September 2022 announced that the product safety information for Janus kinase (JAK) inhibitors (including tofacitinib (Xeljanz®), baricitinib (Olumiant®), upadacitinib (Rinvoq®), abrocitinib (Cibinqo®), *ruxolitinib* (Jakavi®) and fedratinib (Inrebic®)) have been or will be updated to include the risk of serious heart-related problems, blood clots, cancer and death. Health Canada reviewed the final findings from the clinical research study from 2019 which linked tofacitinib to higher risks of serious heart-related problems, cancer and death, and confirmed the initial findings of an increased risk of blood clots. Health Canada also reviewed the interim findings from a 2021 observational study with baricitinib (Olumiant®), which showed increased rates of serious heart-related problems and blood clots with its use. Given the similar mechanisms of action and indications, Health Canada's review concluded that a drug class effect for the risks of serious heart-related problems, blood clots, cancer and death cannot be excluded with JAK inhibitors used for the treatment of chronic inflammatory diseases, including upadacitinib, abrocitinib, ruxolitinib and fedratinib in addition to tofacitinib and baricitinib.

Back in October, 2021, the Medicine and Health Product Regulatory Agency (MHRA) of the United

Kingdom announced that the product information for tofacitinib will be updated with the information that tofacitinib should not be used in patients older than 65 years of age, people who are current or past smokers, or individuals with other cardiovascular (e.g., diabetes or coronary artery disease) or malignancy risk factors unless there are no suitable alternative treatments. The MHRA reviewed the results of a clinical safety trial (ORAL Surveillance) to evaluate the safety of tofacitinib compared with TNF blockers and identified these risk factors. In 2021, the final results from this study showed tofacitinib to be associated with an increased incidence of non-fatal myocardial infarction and malignancies, particularly lung cancer and lymphoma.

Likewise**,** the Ministry of Health Labour and Welfare (MHLW) and Pharmaceutical and Medical Device Agency (PMDA) of Japan had also in October 2021 announced that the package inserts for tofacitinib should be revised to include the risk of cardiovascular events, such as myocardial infarction. The MHLW and the PMDA also reviewed the results of a clinical safety trial to evaluate the safety of tofacitinib compared with TNF blockers and identified.

Similarly, the United States Food and Drug Administration (US-FDA) on 1st September 2021 through a Drug Safety Communication announced that based on a review of a large randomized safety clinical trial, the agency concluded that there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death with arthritis and ulcerative colitis medicines Xeljanz (tofacitinib). This trial compared Xeljanz with another type of medicine used to treat arthritis called tumour 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. FDA recommended revisions to the *Boxed Warning*, FDA's most prominent warning, for Xeljanz to include information about the risks of serious heart-related events, cancer, blood clots, and death.

Previously, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in June, 2021 recommended an update to the product information for tofacitinib

(Xeljanz®) to include a new recommendation for its use due to the risk of cardiovascular events and cancer. The PRAC reviewed the data from a study conducted in patients who were 50 years of age or older with at least one additional cardiovascular risk factor and advised healthcare professionals that tofacitinib should only be used in patients over 65 years old, patients who are current or past smokers, patients with other cardiovascular risk factors and patients with other malignancy risk factors if no suitable treatment alternative is available.

Action in Pakistan:

The National Pharmacovigilance Centre (NPC) of the Drug Regulatory Authority of Pakistan had already issued Safety Alert No. 16, dated 10th September 2021, titled "Risk *of serious heart-related events, cancer, blood clots, and death with Tofacitinib*" in light of US-FDA drug safety communication. As other stringent regulatory authorities have also updated their label/product information, therefore, the case was again submitted to Pharmacovigilance Risk Assessment Expert Committee (PRAEC).

Accordingly, the case of the potential risk of serious heart-related events, cancer, blood clots, and death with Tofacitinib was discussed in the 2nd meeting of the Pharmacovigilance Risk Assessment Expert Committee (PRAEC) of the National Pharmacovigilance Centre (NPC), Division of Pharmacy Services, Drug Regulatory Authority of Pakistan (DRAP), which decided as per Rule 10 (1) (h) (iv) and (vi) of Pharmacovigilance Rules, to update the prescribing information/safety specification of Tofacitinib containing medicines by including information related to heart attack or stroke, cancer, blood clots, and death in the warning and precaution section and to create a Boxed warning as per FDA format.

Therapeutic Goods Affected.

Name: **Xeljanz (tofacitinib)**

Xeljanz (tofacitinib) is used to treat certain serious, chronic, and progressive inflammatory conditions. It is 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 works 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.

Advice for patients.

Those patients who are taking Xeljanz should tell their healthcare professionals if they are current or past smokers, or have had a heart attack, other heart problems, stroke, or blood clots in the past as these may put them at higher risk for serious problems with the medicine. Patients starting this medicine should also tell their healthcare professionals about these risk factors. Patients should seek emergency help right away if they have any symptoms that may signal a heart attack, stroke, or blood clot, including:

- Discomfort in the centre 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 discoloured skin in the painful or swollen leg or arm.

Treatment with this medicine is associated with an increased risk of certain cancers including lymphoma and lung cancer, so patients should inform their healthcare professional if they experience signs and symptoms such as swelling of lymph nodes in the neck, armpits, or groin; constantly feeling tired; fever; night sweats; persistent or worsening cough; difficulty breathing; hoarseness or wheezing; or unexplained weight loss.

Advice for healthcare professionals.

Healthcare professionals should consider the benefits and risks for the individual patient before initiating or continuing therapy with tofacitinib (Xeljanz®). This is particularly the case in patients who are current or past smokers, those with other cardiovascular risk factors, or those who develop a malignancy, and those with a known malignancy other than a successfully treated non-melanoma skin cancer. Reserve this medicine 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.

Guidelines for reporting Adverse Drug Reactions (ADRs):

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction (ADRs) with tofacitinib (Xeljanz®) to the National Pharmacovigilance Centre, Drug Regulatory Authority of Pakistan through the Med Vigilance E-Reporting System available on the DRAP website.

Similarly, ADRs can also be reported through Med Safety App which is available for download from the App Store (for iOS devices) and Google Play (for Android devices).

References:

1. Minutes of 2nd meeting of Pharmacovigilance Risk Assessment Expert Committee.