SAFETY ALERT

DRAP SAFTEY ALERT NO. 16

RISK OF SERIOUS HEART-RELATED EVENTS, CANCER, BLOOD CLOTS, AND DEATH WITH TOFACITINIB.

UPDATE FROM US-FDA

Date: 10th of September, 2021

Target Audience:

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

Problem or Issue:

I. European Medicines Agency (EMA).

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 that 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.

II. The United States Food and Drug Administration (US-FDA).

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, they have concluded 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 is requiring 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. Recommendations for healthcare professionals will include consideration of the

benefits and risks for the individual patient before initiating or continuing therapy. In addition, to ensure the benefits of this medicine outweigh the risks in patients who receive them. It was also informed that FDA is limiting all approved uses to certain patients who have not responded or cannot tolerate one or more TNF blockers.

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 professional 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 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 of Adverse Drug Reactions (ADRs):

Both healthcare professionals and patients are requested to report any suspected adverse drug reaction with Xeljanz (tofacitinib) to **Pakistan National Pharmacovigilance Centre,** Drug Regulatory Authority of Pakistan through **DRAP Med Vigilance e-reporting system** https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=PK or at npc@dra.gov.pk

Similarly, ADRs can also be reported through MedSafety Mobile Application (available on android and the ioS platform.

References:

1. https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death

2. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-7-10-june-2021