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2 Sep 2021

Dear Healthcare Professionals,

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

Your attention is drawn to the United States Food and Drug Administration's (FDA) announcement that, based on a completed FDA review of a large randomized safety clinical trial, it has 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 Drug Safety Communication based upon earlier results from this trial, reported an increased risk of blood clots and death only seen at the higher dose.

FDA is 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 with Xeljanz, 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, FDA may take further action and will alert the public.

FDA is 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.

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.

Please refer to the following website in FDA for details:
https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-warnings-about-increased-risk-serious-heart-related-events-cancer-blood-clots-and-death

In Hong Kong, there are 3 registered pharmaceutical products containing tofacitinib, namely Xeljanz Tablets 5mg (HK-63303), Xeljanz XR Extended Release Tablets 11mg (HK-66141) and Xeljanz Tablets 10mg (HK-66833) which are registered by Pfizer Corporation Hong Kong Limited; 2 products containing baricitinib, namely Olumiant Tablets 2mg (HK-65663) and Olumiant Tablets 4mg (HK-65664) which are registered by Eli Lilly Asia, Inc.; and one product containing upadacitinib, namely Rinvoq Prolonged-Release Tablets 15mg (HK-66872) which is registered by Abbvie Limited. All products are prescription-only medicines.

So far, the Department of Health (DH) has received 8 cases of adverse drug reaction related to tofacitinib (of which one case is lung cancer and 3 cases are deep vein thrombosis); 3 cases related to baricitinib (of which one case is deep vein thrombosis); and 4 cases related to upadacitinib.

Related news on the risk of blood clots and death of tofacitinib was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 26 Feb 2019, with the latest update posted on 5 Feb 2021. Letters to inform local healthcare professionals were issued by the DH on 29 Jul 2019 and 19 Jun 2020. In Dec 2019, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that the sales pack or package insert of tofacitinib products should include safety information about increased risk of blood clots and death with higher dose (10 mg twice daily).

Related news on the risk of blood clots of baricitinib was previously issued by the United Kingdom Medicines and Healthcare products Regulatory Agency and Health Canada, and was posted on the Drug Office website on 19 Mar 2020 and 19 Jun 2020. Letters to inform local healthcare professionals were issued by the DH on 19 Jun 2020. The current local product inserts already contain safety information on the risk of venous thromboembolism.

Related news on the risk of serious heart-related problems and cancer of tofacitinib was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 5 Feb 2021, with the latest update posted on 12 Jun 2021. Letters to inform local healthcare professionals were issued by the DH on 15 Jun 2021.

In light of the above FDA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Adverse Drug Reaction Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

(Ling PANG)
for Assistant Director (Drug)